

MCM-BP as a Novel Nanomagnetic Reusable Basic Catalyst for the one Pot Solvent- Free Synthesis of Dihydropyridine, Polyhydroquinoline and Polyhydroacridine Derivatives via Hantzsch Multicomponent Condensation Reaction

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ABSTRACT: By the immobilization of bipyridinium chloride onto mesoporous MCM-41 encapsulated Fe_3O_4 nanoparticles via a simple post-synthesis method, a totally new organic–inorganic hybrid nanocomposite was formulated. The heterogeneous hybrid nanomagnetic composite was characterized by Fourier Transform InfraRed (FT-IR), X-Ray powder Diffraction (XRD), Scanning Electron Microscope (SEM), Transmission Electron Microscope (TEM), Vibrating Sample Magnetometer (VSM) and Thermal Gravimetric Analytical (TGA). The potential applications of this novel nanomagnetic and recyclable basic nanocomposite, $Fe_3O_4@MCM-BP$, were also investigated for solvent-free synthesis of 1,4-dihydropyridine, polyhydroquinoline and polyhydroacridine derivatives via Hantzsch multicomponent condensation reaction. High isolated yields, operational simplicity, clean reaction conditions and minimum pollution of the environment, makes the procedure a useful and appealing process in organic transformation.

KEYWORDS: Hantzsch reaction; $Fe_3O_4@MCM-BP$; Magnetic nanocatalyst; Dihydropyridine; polyhydroquinoline; Polyhydroacridine.

INTRODUCTION

Research in recent decades has paid proliferating attention to the design and development of mesoporous and nanostructures silica based heterogeneous catalysts. Among these materials, ordered xerogel mesoporous

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silicas such as MCM-41 and its functionalized family have received considerable interest because of their intriguing advantages including controlled size and morphology, tunable pore size, as well as dual-functional surface (external and internal) [1,2].

Taking into account the basic principles of green chemistry, the use of regenerable catalysis is a major tool in green synthesis. In this context, magnetic-nanoparticle-supported catalysts, particularly iron oxide nanoparticles such as magnetite, Fe_3O_4 , have gained an increased attention in recent years. Due to the feasibility to combine the enormous functional group along with the adventary of magnetically property of MNPs and thermally stable and robust inorganic substrate, the amalgamation of the properties of MNPs and mesoporous materials within a single material is particularly glamorous from the perspective of catalysis technique [1,3].

On the other hands, 4-aryl-1,4-dihydropyridine (DHP) derivatives have found widespread applications as pharmaceuticals and industrial compounds and shown a broad spectrum of biological activities such as vasodilator, antitumor, bronchodilator, antiatherosclerotic, geroprotective, nefedipine, heldipin and heaptoprotective activity [4-10]. Due to the bulk of interest in dihydropyridine, polyhydroquinoline and polyhydroacridine derivatives, and in concomitance with ongoing work on the synthesis of novel heterogeneous hybrid nanomagnetic catalysts in our laboratory, we strive to describe the preparation of a new organic-inorganic hybrid nanocomposite, bipyridinium chloride functionalized Fe_3O_4 @MCM-41, as an efficient, green, and heterogeneous catalyst for the Hantzsch multicomponent condensation reaction under solvent free thermal conditions (Scheme 1). As described here, a variety of Hantzsch derivative products can be synthesized in atom economical manner under mild and non-toxic conditions.

EXPERIMENTAL SECTION

General

Bipyridine, cetyltrimethyl ammonium bromide (CTAB), aldehydes and other chemicals were purchased from Fluka and Merck companies. The purity determination of the products and reaction monitoring were accomplished by TLC on silica gel. Products were characterized by comparison of their physical data, IR,

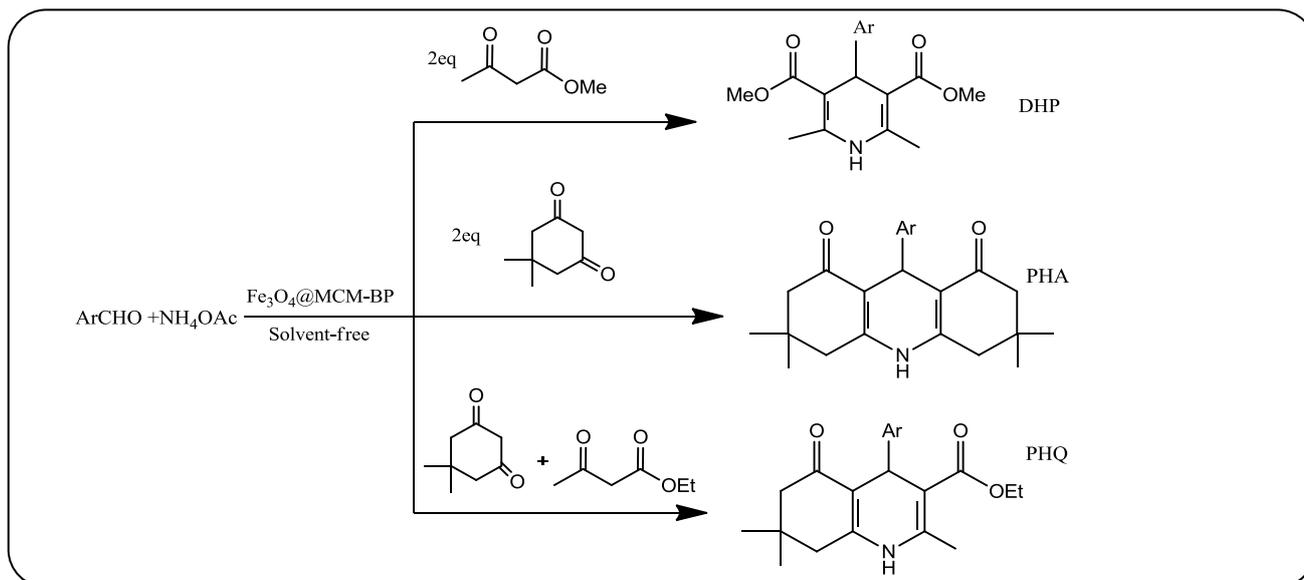
NMR spectra with known samples. NMR spectra were recorded on a Bruker Advance DPX 400 MHz instrument spectrometer using TMS as internal standard. IR spectra were recorded on a BOMEM MB-Series 1998 FT-IR spectrometer. Transmission Electron Microscope (TEM) images were obtained using Zeiss – EM10C – 80 kV instrument. The SEM analyze was carried out using a LEO 1455VP Scanning Electron Microscope, operating from 1 to 30 kV. Thermal stability of the supported catalyst was examined using Thermo-Gravimetric Analyzer (TGA) at a heating rate of 10 °C/min over the temperature range from 40 to 950 °C. The magnetic properties of the nanocomposite was detected at room temperature using a vibrating sample magnetometer (VSM, Meghnatis Kavir Kashan Co., Kashan, Iran).

Preparation of magnetite Fe_3O_4 nano particles (MNPs)

The magnetite Fe_3O_4 was prepared via an improved chemical coprecipitation method [11]. Briefly, $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (7.57 g, 28 mmol) and $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$ (3.1736 g, 16 mmol) were completely dissolved in 320 mL of deionized water under N_2 atmosphere at 90 °C with vigorous mechanical stirring. After 1h, ammonia solution 25% (40 ml) was added drop-wise to the solution until the brown color solution turned to black. After approximately 1h, the reaction mixture was cooled to room temperature and black precipitated particles were washed five times with hot water and separated by magnetic decantation. Finally, nano- Fe_3O_4 was dried under vacuum at 60 °C for 12 h.

Preparation of Fe_3O_4 @MCM-41

The mesoporous Fe_3O_4 @MCM-41 has been synthesized using an earlier procedure with suitable adaptation [12]. In a typical synthesis, CTAB (4.6 mmol, 1.67 g) was dissolved in 33 mL of deionized water at room temperature with vigorous mechanical stirring. To the reaction mixture was added 11.34g (140 mmol) ammonia solution 25% and absolute ethanol (37 mL) and stirred for 20 min. 0.5 g of synthesized Fe_3O_4 nano particles and 3.41 g of tetraorthosilicate (TEOS) (15 mmol) was added to the homogenous solution with constant stirring at room temperature for 2 h. The solid product was filtered off, washed with sufficient amount of water followed by ethanol and dried. The surfactant (CTAB) was removed by calcinations at 540 °C for 4h



Scheme 1: One-pot synthesis of DHP, PHQ and PHA derivatives catalyzed by bipyridinium chloride functionalized $Fe_3O_4@MCM-41$ under solvent free thermal conditions

to give the $Fe_3O_4@MCM-41$. The surfactant removed $Fe_3O_4@MCM-41$ was separated by magnetic decantation and washed with ethanol, and then dried under vacuum at 60 °C.

Preparation of chloropropyl-grafted $Fe_3O_4@MCM-41$, $Fe_3O_4@MCM-Cl$

2g of the synthesized $Fe_3O_4@MCM-41$ and n-chloro propyltriethoxysilane (4 ml) were dispersed in 30 mL of dry toluene and the continuously refluxed at 110 °C for 24 h. The $Fe_3O_4@MCM-Cl$ nanocomposite was washed with toluene, water and ethanol and separated by magnetic decantation. Finally, the solid was dried in vacuum at 100 °C for 6 h.

Synthesis of bipyridinium chloride functionalized $Fe_3O_4@MCM-41$, $Fe_3O_4@MCM-BP$

2g of $Fe_3O_4@MCM-41-Cl$ nanocomposite and Bipyridine (1.8 mmol) were dispersed in 30 ml of dry toluene and the continuously refluxed at 110 °C for 24 h. The $Fe_3O_4@MCM-BP$ nanocomposite was magnetically separated and washed with toluene and then dried in vacuum at 50 °C for 6 h.

Typical procedure for the preparation of 1,4-DHPs derivatives

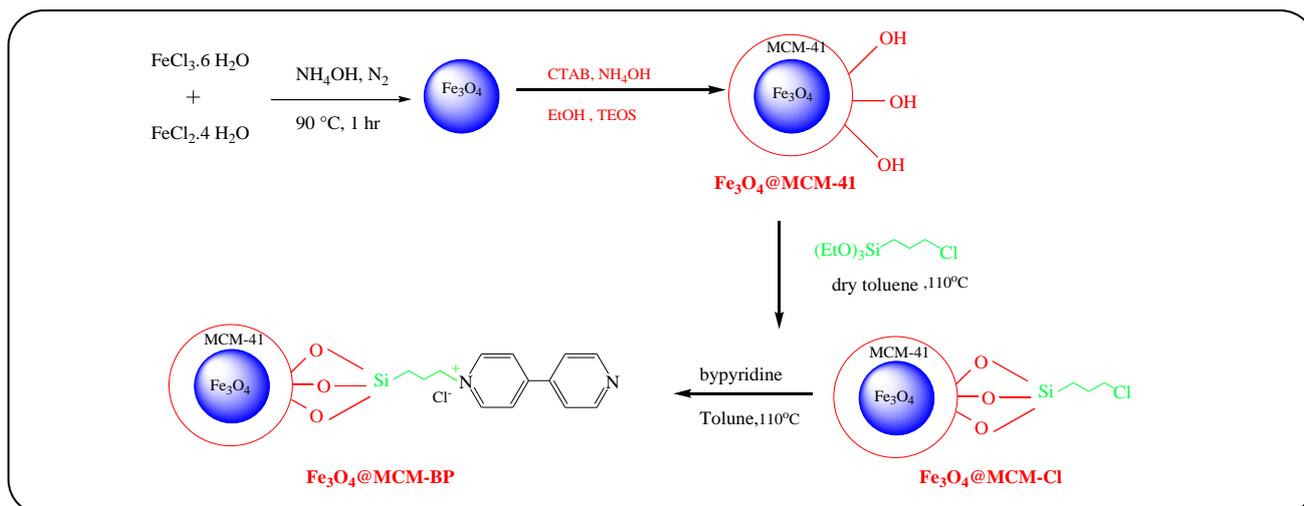
A mixture of aromatic aldehyde (1 mmol), β -dicarbonyl compound (2 mmol), ammonium acetate (1.5 mmol), and $Fe_3O_4@MCM-BP$ (0.005 g) was heated

at 80 °C for appropriate time. After satisfactory completion of the reaction (monitored by TLC), the catalyst was removed by an external magnet and the crude product was extracted by ether. The organic solvent was removed by simple evaporation and finally crude product recrystallized from EtOH/H₂O to afford pure corresponding 1,4-dihydropyridine derivatives in high yields.

RESULTS AND DISCUSSION

Research in recent decades has paid proliferating attention to the design and development of organized magnetic hybrid xerogel mesoporous materials, where the organic component is bonded to a polymeric silica framework.

The systematic steps of bipyridinium chloride functionalized $Fe_3O_4@MCM-41$ preparation was shown in Scheme 2. Firstly, Fe_3O_4 nanoparticles were prepared by coprecipitation of ferrous and ferric ions in a basic aqueous solution followed by thermal treatment. Because of the sensitivity of the Fe_3O_4 , its surface was coated with mesoporous MCM-41 through the hydrolysis of TEOS in the present of CTAB. The obtained $Fe_3O_4@MCM-41$ nanocomposite was then conjugated with 3-chloropropyltrimethoxysilane. Subsequently, the target nanocomposite, $Fe_3O_4@MCM-BP$, was synthesized by the grafting of bipyridine into the surface by simple nucleophilic substitution reaction.



Scheme 2: Schematic diagram for the synthesis of $\text{Fe}_3\text{O}_4@\text{MCM-BP}$.

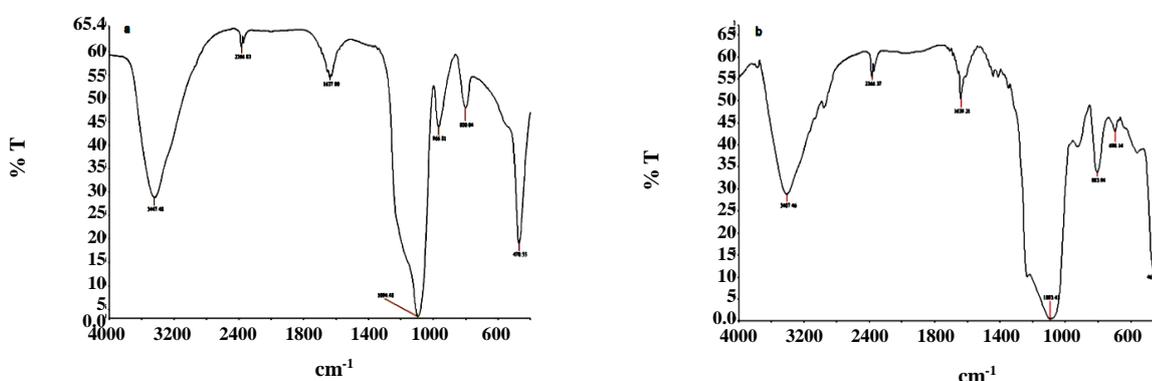


Fig. 1: FT-IR spectra of (a) $\text{Fe}_3\text{O}_4@\text{MCM-41}$ and (b) $\text{Fe}_3\text{O}_4@\text{MCM-BP}$ in the range of $400\text{--}4000\text{ cm}^{-1}$.

This charged hybrid organic–inorganic magnetic mesoporous silica has been characterized by Fourier Transform Infrared (FT-IR) spectroscopy, X-Ray powder Diffraction (XRD), Scanning Electron Microscope (SEM), Transmission Electron Microscope (TEM), Vibrating Sample Magnetometer (VSM) and Thermal Gravimetric Analytical (TGA).

FT-IR spectroscopy was utilized, to determine the properties of the catalyst, and to confirm the immobilization of the active components on the pore surface. Fig. 1 depicts the FT-IR spectra of $\text{Fe}_3\text{O}_4@\text{MCM-41}$ and $\text{Fe}_3\text{O}_4@\text{MCM-BP}$. As shown, the typical Si–O–Si bands around 1220 , 1093 , 803 and 462 cm^{-1} associated with the formation of a condensed silica network are present; however, weak peaks associated with noncondensed Si–OH groups in the range of $940\text{--}960\text{ cm}^{-1}$ were also present. The peaks around 580 and

1639 cm^{-1} are mainly from the bending vibration of Fe–O and adsorbed H_2O respectively [13]. In addition, the FT-IR spectra of the $\text{Fe}_3\text{O}_4@\text{MCM-BP}$ showed two new peaks display at 1640 , 1660 cm^{-1} which were designated to C=C, C=N bands of the bipyridinium units, respectively, and a new peak at 3010 cm^{-1} corresponded to stretch vibrating mode of aromatic C–H.

The thermal stability of the functionalized $\text{Fe}_3\text{O}_4@\text{MCM-BP}$ was examined by thermo-gravimetric analysis. The TGA thermogram (Fig. 2) presents the initial weight loss below $200\text{ }^\circ\text{C}$ which can be pertained to the desorption of physically adsorbed water and also dehydration of the surface –OH groups. The decomposition of organic groups is probably the reason for nearly 20% weight loss from 200 to $700\text{ }^\circ\text{C}$, while relatively slow weight loss at elevated temperatures can be associated to the decomposition of the silica shell.

Hence, the TGA curves confirm the grafting of organic groups onto the surface of silica.

Fig. 3 presents the low-angle XRD pattern of the $\text{Fe}_3\text{O}_4@\text{MCM-BP}$. Diffractogram has only one peak at $2\theta = 2.7^\circ$, corresponding to the (100) plane, which is the feature of a hexagonal pore system. The absence of peaks for (110) and (200) reflections suggests that the material has a disoriented unidirectional structure, as previously described in the literature [14].

For practical utilizations, it is quintessential that the nanocomposite should possess sufficient magnetic and super-paramagnetic properties. As it is shown in Fig. 4, the hysteresis loops that are characteristic of superparamagnetic behavior can be clearly observed for $\text{Fe}_3\text{O}_4@\text{MCM-BP}$ nanocomposite. From M versus H curves, the saturation magnetization value (M_s) was found to be 2.1 emu/g that is lower than that of uncoated Fe_3O_4 [7]. This is mainly attributed to the existence of nonmagnetic materials on the surface of the nanoparticles.

The morphology and particle size distribution of $\text{Fe}_3\text{O}_4@\text{MCM-BP}$ nanocomposite was examined by SEM and TEM photographs. Fig. 5 reveals that nanocomposite has spherical shape and core-shell structured magnetic silica microspheres with nano dimension ranging under 300 nm.

To evaluate the catalytic activity of $\text{Fe}_3\text{O}_4@\text{MCM-BP}$ nanocomposite as a magnetic powerful basic nanocatalyst and with an aim to develop a simple practical method for the synthesis of a large range of 1,4-dihydropyridines, through multicomponent reaction, initially, three-component coupling reaction of methyl acetoacetate and benzaldehyde with ammonium acetate in a 2:1:1.5 ratios as a Hantzsch model reaction (Scheme 2) was examined to address the optimized conditions and to identify whether or not the use of it was efficient.

After doing some experiments, it was revealed that in order to have an efficient coupling reaction, the best condition is the presence of 0.005 of catalyst under solvent-free conditions at 80 °C (8 min, 90 %). Using lower amounts of catalyst, the corresponding DHP was produced in lower yield, whereas higher amounts of catalyst have no significant impact on the reaction time and yield as well. Furthermore, a similar reaction in the absence of the catalyst was examined to show the role of the catalyst. After a long reaction time, the reaction,

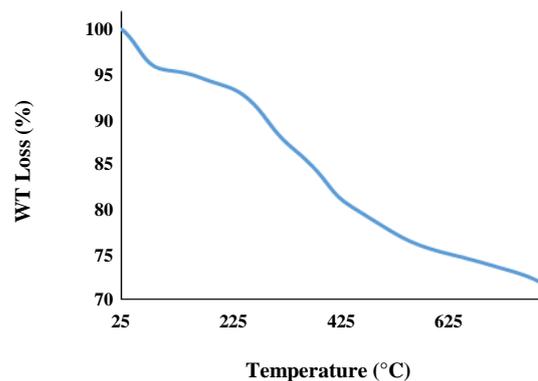


Fig. 2: TGA analysis of $\text{Fe}_3\text{O}_4@\text{MCM-BP}$ at a heating rate of $10\text{ }^\circ\text{C}\cdot\text{min}^{-1}$ over the temperature range 40-950 °C.

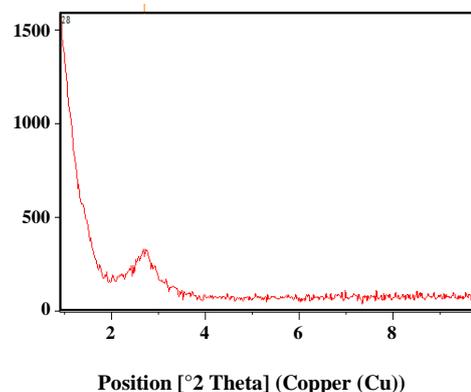


Fig. 3: The low-angle XRD pattern of the $\text{Fe}_3\text{O}_4@\text{MCM-BP}$.

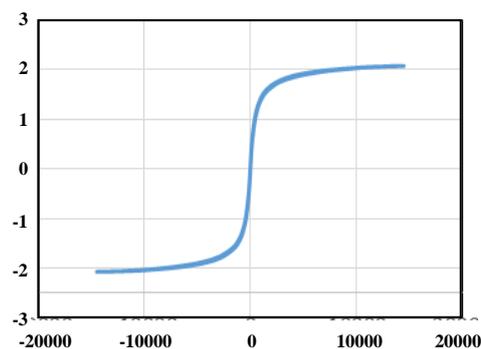


Fig. 4: VSM curve of $\text{Fe}_3\text{O}_4@\text{MCM-BP}$ nanocomposite at room temperature.

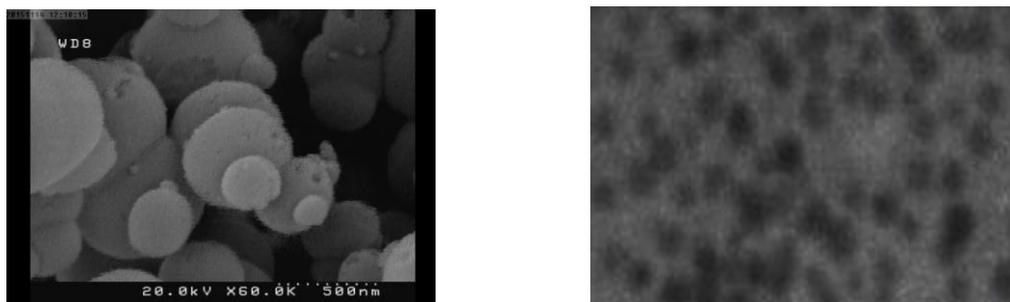


Fig. 5: SEM (a) and TEM (b) photographs of $Fe_3O_4@MCM-BP$.

under this condition, led to the formation of the covet product in low yield.

Subsequently, with optimal conditions in hand, 1:2:1.5 molar ratios of aryl aldehyde, methyl acetoacetate and ammonium acetate and 0.005 g of $Fe_3O_4@MCM-BP$ at 80 °C under solvent-free conditions, the generality and synthetic scope of this coupling protocol were demonstrated by synthesizing a series of DHPs having different steric and electronic properties. As Table 1 shows, yields are good to excellent in most cases.

With such a auspicious result in hand, in order to evaluate the generality as well as the synthetic scope of this coupling protocol, a series of polyhydroquinoline derivatives was also prepared under the optimized reaction conditions through one-pot four-component coupling reaction of ethyl acetoacetate, dimedone and benzaldehyde with ammonium acetate in 1:1:1:1.5 ratios (Table 2). The whole process contains the Knoevenagel condensation of dimedone with aryl aldehydes, coming after in situ Michael addition of ethyl acetoacetate in a single operation.

Moreover, a series of polyhydroacridine derivatives were prepared by one-pot three-component coupling reaction of aryl aldehydes and dimedone with ammonium acetate in 1:2:1.5 ratios (Table 3).

As shown in Tables 1-3, in all cases, aromatic aldehydes carrying either electron-donating or electron-withdrawing groups reacted successfully and gave the expected products in good to excellent yields and short reaction times.

In order to check the overall utility of the current methodology, we contrasted our results with those of the other methodologies reported for the synthesis of PHQ.

This comparison is shown in Table 4. As can be comprehended, in addition to the general advantages ascribed to the magnetic property of nanocomposite, $Fe_3O_4@MCM-BP$ is an equally or more profitable in the Hantzsch multicomponent condensation reaction.

The reusability of the catalyst was also tested. For this gold, after completion of the condensation reaction, the $Fe_3O_4@MCM-BP$ was easily separated from the reaction mixture by means of an external magnetic field and washed with water and diethyl ether and then dried and reused for four times under one constant set of operating conditions (benzaldehyde / methyl acetoacetate/ ammonium acetate: 1: 2: 1.5, temperature: 80 °C, time: 8 min). The average chemical yield for four consecutive runs was 88% which clearly demonstrates the practical recyclability of this catalyst.

CONCLUSIONS

In conclusion, using the immobilization of Bipyridine on mesoporous MCM-41 encapsulated Fe_3O_4 nanoparticles, a magnetically separable basic nanocatalyst was successfully prepared and was characterized by FT-IR, SEM, TGA, TEM, VSM and XRD. Under solvent-free thermal conditions, the catalytic activity of $Fe_3O_4@MCM-BP$ was investigated through one-pot synthesis of 1,4-dihydropyridines, polyhydroquinoline and polyhydroacridine derivatives through Hantzsch condensation reaction. The nanocatalyst can be easily isolated from the reaction mixture by using a magnetic field and directly used in the next reaction cycles without a significant loss of its activity. Some of another advantages offered by the procedure include: operational simplicity, clean reaction

Table 1: Preparation of 1,4-dihydropyridine derivatives catalyzed by $Fe_3O_4@MCM-BP$.

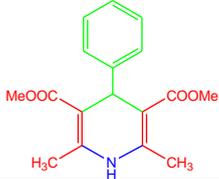
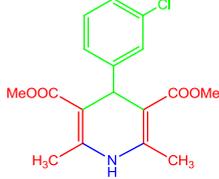
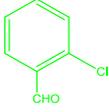
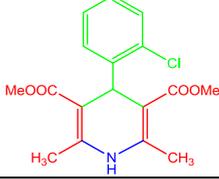
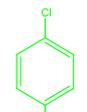
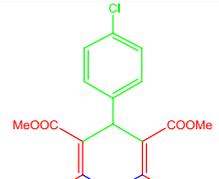
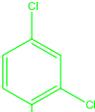
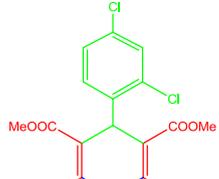
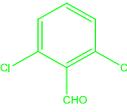
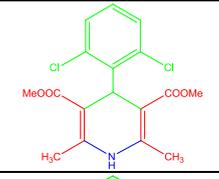
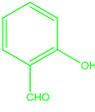
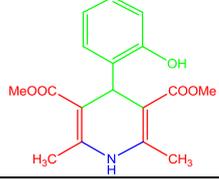
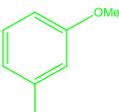
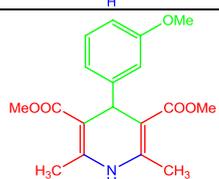
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					Observed	Reported	Ref
1			8	90	115-116	116-118	[15]
2			5	92	188-189	191-192	[15]
3			10	90	153-155	-	-
4			12	96	194-196	196-198	[15]
5			10	96	189-190	190-192	[15]
6			8	85	150-153	-	-
7			15	86	Oil	Oil	-
8			25	88	Oil	NR	-

Table 1: Preparation of 1,4-dihydropyridine derivatives catalyzed by $Fe_3O_4@MCM-BP$.

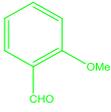
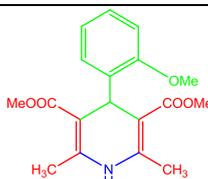
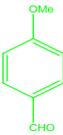
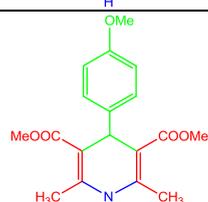
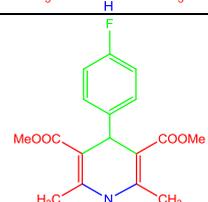
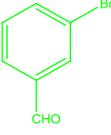
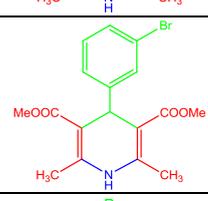
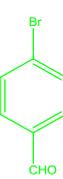
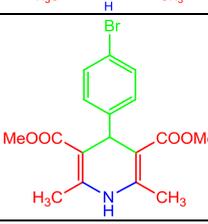
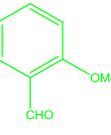
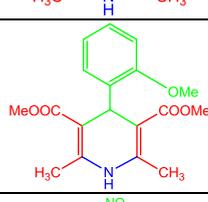
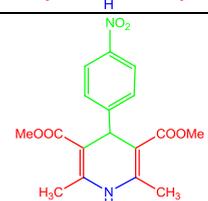
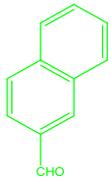
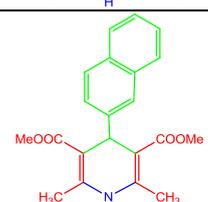
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					Observed	Reported	Ref
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10			30	85	182-185	186-188	[15]
11			10	90	174-175	171-172	[16]
12			10	90	170-173	NR	-
13			20	98	195-196	200-202	[15]
14			10	80	Oil	NR	-
15			10	90	168-170	166-168	[15]
16			30	85	Oil	NR	-

Table 2: Preparation of polyhydroquinoline derivatives catalyzed by $Fe_3O_4@MCM-BP$.

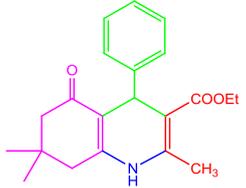
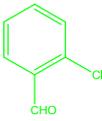
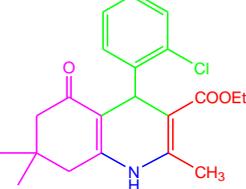
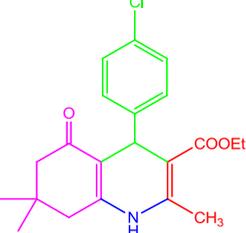
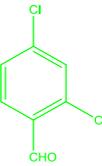
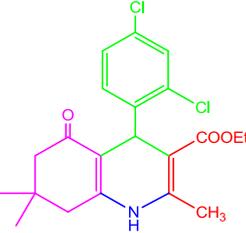
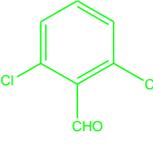
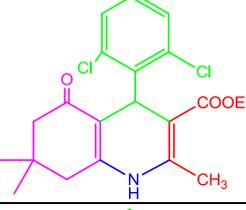
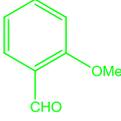
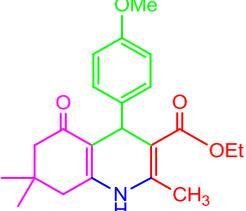
Entry	Aldehyde	Product	Time (min)	Yield (%)	M.P.°C		
					Observed	Reported	Ref
1			5	80	201-203	202-204	[17]
2			10	85	208-210	206-208	[17]
3			5	90	244-245	245-247	[17]
4			5	95	241-242	241-244	[18]
5			7	85	238-240	241-244	[19]
6			4	85	250-253	251-254	[17]
7			3	91	250-255	255-257	[17]

Table 2: Preparation of polyhydroquinoline derivatives catalyzed by $Fe_3O_4@MCM-BP$.

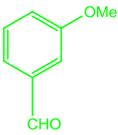
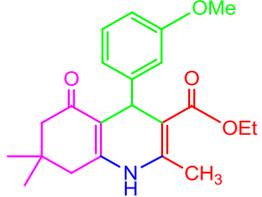
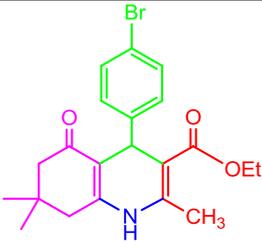
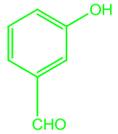
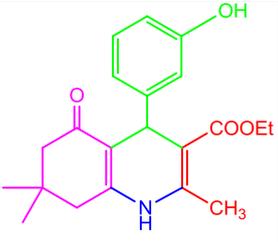
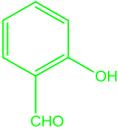
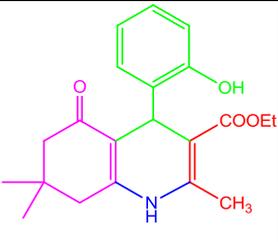
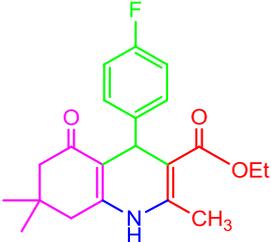
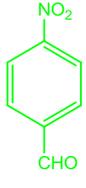
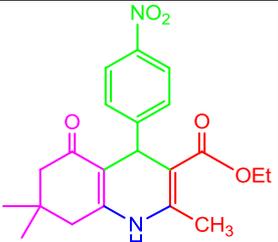
Entry	Aldehyde	Product	Time (min)	Yield (%)	M.P.°C		
					Observed	Reported	Ref
8			3	80	256-258	NR	
9			5	90	240-245	252-255	[17]
10			8	80	235-237	218-220	[17]
11			10	88	220-221	NR	-
12			4	82	181-182	184-186	[15]
13			5	90	241-242	244-246	[17]

Table 3: Preparation of polyhydroacridinederivatives catalyzed by $Fe_3O_4@MCM-BP$.

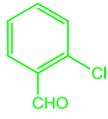
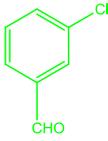
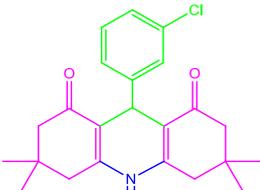
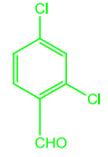
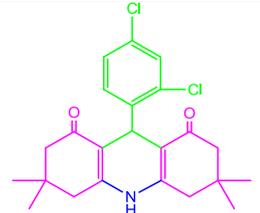
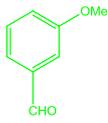
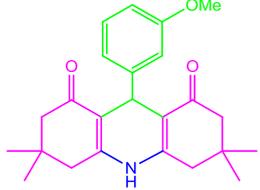
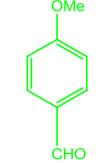
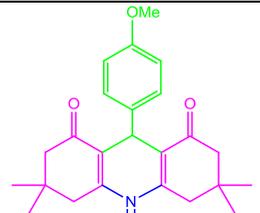
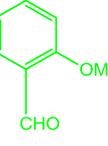
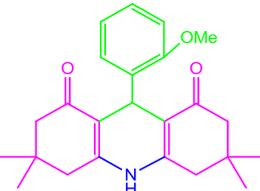
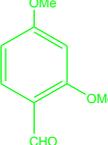
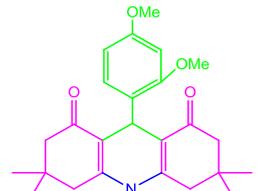
Entry	Aldehyde	Product	Time (min)	Yield (%)	M.P.°C		
					Observed	Reported	Ref
1			8	85	259-260	221-225	[20]
2			4	88	283-285	281-282	[21]
3			4	85	308-310	NR	-
4			3	88	294-296	NR	-
5			3	90	275-277	266-269	[21]
6			4	85	259-261	247-249	[22]
7			4	85	Oil	NR	-

Table 3: Preparation of polyhydroacridinederivatives catalyzed by Fe₃O₄@MCM-BP.

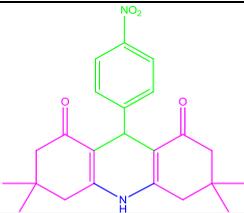
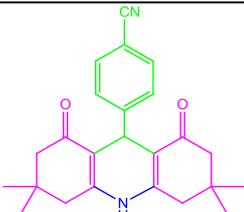
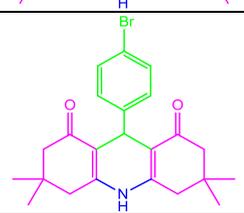
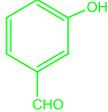
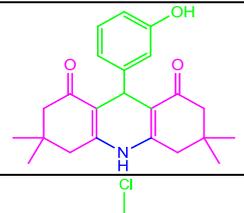
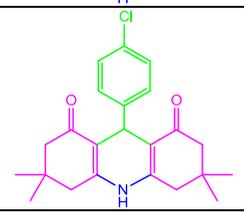
Entry	Aldehyde	Product	Time (min)	Yield (%)	M.P.°C		
					Observed	Reported	Ref
8			2	88	258-260	261-262	[23]
9			4	88	315-320	328-330	[24]
10			4	85	310-315	330-332	[24]
11			3	85	301-305	302	[24]
12			3	91	296-299	>300	[23]

Table 4: Comparison of various catalysts for the synthesis of PHQ.

Entry	Catalyst	Conditions ^a	Time (Min)	Yield (%)	Refs.
1	L-proline (10 mol%)	EtOH/r.t	210	92	[25]
2	(NH ₄) ₂ Ce(NO ₃) ₆ (10 mol%)	EtOH/ r.t	120	94	[26]
3	CTAB (1 mol%)	Water- reflux	90	85	[27]
4	PTSA (10 mol%)	EtOH /r.t	120	93	[28]
5	Co NPs (10 mol %)	Solvent free/r.t	60	95	[29]
6	Fe ₃ O ₄ @MCM-BP (0.005 g)	Solvent free/ 80°	5	80	This work

A) Benzaldehyde was used as aromatic aldehyde

conditions and minimum pollution of the environment, which makes the procedure a useful and appealing process to synthesize Hantzsch derivatives.

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