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Synthesis of Pyridopyrimidine-Indole Hybrids Using γ-Fe_2O_3@HAp@PBABMD@Cu as Efficient Magnetic Nanocatalyst

N. Haghgoo, M. Mamaghani*, E. Saberikhah and R. Hossein Nia
Department of Chemistry, Faculty of Sciences, University of Guilan, P. O. Box: 41335-1914, Rasht, Iran
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A novel and practical method for the synthesis of pyridopyrimidine-indole hybrids, using a three-component reaction of thiouracil or 6-amino-*N*,*N*-dimethyluracil, various aryl aldehydes and 3-cyanoacetyl indole in the presence of a green heterogeneous nano-catalyst γ-Fe_2O_3@HAp@PBABMD@Cu was developed. This protocol furnished the desired products in high yields (82-95%) and lower reaction times (18-40 min).

Keywords: Pyridopyrimidine, 3-Cyanoacetylindole, 6-Amino-*N*,*N*-dimethyluracil, Aanocatalyst, γ-Fe_2O_3@HAp@PBABMD@Cu

INTRODUCTION

Hybrid heterocycles play an important role in bioactive compounds and drugs. pyridopyrimidines, in particular pyrido[2,3-*d*]pyrimidines, are the most important heterocycles that play a special role in many drugs and bioactive compounds. Figure 1 shows some examples of bioactive piridopyrimidines. Many of these compounds display anti-inflammatory [1], antibacterial [2], antiviral [3], diuretic, analgesic [4], anticonvulsive [5,6], antipyretic [7], antitumoral [8], cardiotonic [9,10], antihistaminic [11], bronchiodilator [12] and bactericidal [13] activities, and also act as a cyclin-dependent kinase 4 inhibitor [14]. A number of multi-component methods have been reported for the synthesis of pyridopyrimidines especially pyrido[2,3-*d*]pyrimidines in our recent review[15]. The indole nucleus is also a known heterocycle with biological and medicinal properties [16]. Compounds containing indole show antibacterial and antifungal activity [17]. Therefore, it would be useful to design a system that combines bio-labilenuclei such as indole and pyridopyrimidine in a molecular framework.

On the other hand, the catalyzed reactions of transition metals are the most attractive protocols for the synthesis of heterocycles. Among the transition metal catalysts, nano particles of magnetic iron oxide (Fe_3O_4 and γ-Fe_2O_3) have been found to be effective and attracted much interest because of their unique properties, such as high surface-to-volume ratio, superparamagnetic, greater surface area, sizes, shapes, sustainable nature, nontoxicity, inexpensive, environmentally benign and simple separation methodology [18-23]. The most common surface modification method to conjugate the organic or inorganic materials onto the surface of iron oxide nanoparticles is coating method. This protocol prevents the oxidation and agglomeration of iron oxide nanoparticles and allows for further functionalization [24]. The physicochemical properties of iron oxide nanoparticles are improved by functionalization, and they become ideal candidates for the field of biomedicine and catalysis.

We have recently reported efficient and eco-friendly

*Corresponding author. E-mail: m-chem41@guilan.ac.ir

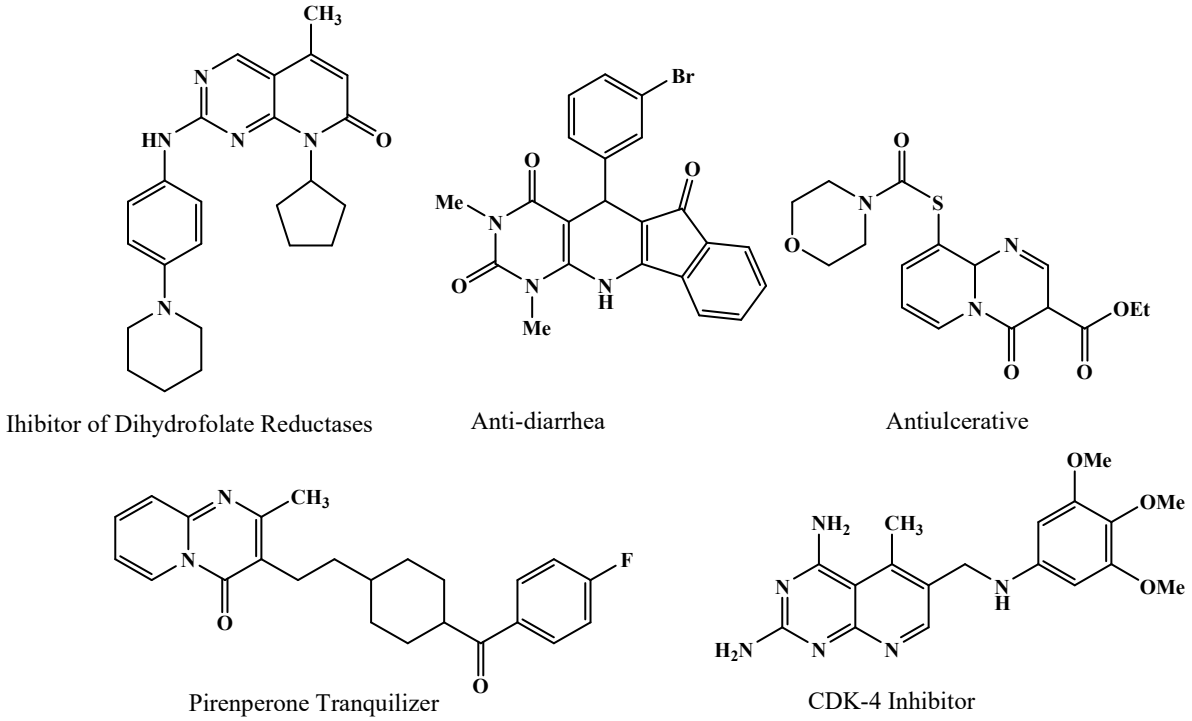


Fig. 1. Some bioactive piridopyrimidines.

procedures for the preparation of indole-pyrido[2,3-*d*]pyrimidines using Nickel-incorporated fluorapatite encapsulated iron oxide nanocatalyst (Fe_3O_4@FAp@Ni) and evaluated their antibacterial activities [25]. In the present study, based on our ongoing experience in synthesizing the biologically active compound [26-29], we decided to investigate the synthesis of some indole-pyrido[2,3-*d*]pyrimidine hybrids by using γ-Fe_2O_3@HAp@PBABMD@Cu as magnetically separable nanocatalyst.

Recently, in our laboratory, Copper(II) complex covalently anchoring 3,3'-((1E,1'E)-(1,2-phenylenebis(azanylylidene))bis(methanylylidene))-di-phenol) (PBABMD) on HAp coated magnetite particles as heterogeneous magnetic nanocatalyst (γ-Fe_2O_3@HAp@PBABMD@Cu) (Fig. 2) was prepared, identified and applied to synthesize of pyrrole-pyrido[2,3-*d*]pyrimidines [29]. The high efficiency of this green and recyclable nanocatalyst encouraged us to use this catalyst for the synthesis of pyridopyrimidine-indole hybrids.

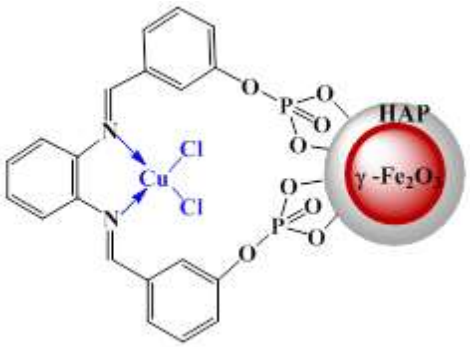


Fig. 2. γ-Fe2O3@HAp@PBABMD@Cu magnetic nanocatalyst.

EXPRIMENTAL

An electrothermal 9100 device was applied for measuring melting points. Carlo-Erba EA1110CNNO-S analyzer was used for elemental analysis and approved with the calculated

values. Fourier transform-infrared (FT-IR) spectra were recorded by a VERTEX 70 Brucker spectrometer, mixed with KBr, and pressed into pellets, scanning from 4000 to 400 cm^{-1}. The ^1H NMR and ^{13}C NMR spectra were run on a Bruker DRX-300 spectrometer operating at 300 and 75 MHz in DMSO-d6 as solvent and TMS as an internal standard. Chemical shifts for ^1H and ^{13}C NMR were expressed in ppm downfield from tetramethylsilane. All solvents, reagents and chemicals used in this research were purchased from Merck and were used without any more refinement.

General Procedure for the Preparation of Indole-pyrido[2,3-*d*]pyrimidine Derivatives

An equimolar amount of thiouracil or 6-amino-*N*,*N*-dimethyluracile (1) (1.0 mmol), aromatic aldehyde (2) (1.0 mmol), 3-cyanoacetylindole (3) (1.0 mmol), and γ-Fe_2O_3@HAp@PBABMD@Cu MNPs (20 mg) was stirred in refluxing EtOH (5 ml) until disappearance of the starting materials (monitored by TLC (petroleum ether:EtOAc: MeOH, 8:4:1)). After completion of the reaction, the catalyst was separated by applying an external magnet. The reaction mixture was cooled to room temperature and added 4 ml of distilled water to the reaction mixture, the reaction mixture was filtered and the resulting solid recrystallized from EtOH to furnish the desired pure product.

Spectra Data of New Products

1,2,3,4-Tetrahydro-7-(1*H*-indol-3-yl)-5-(3-nitro-phenyl)-4-oxo-2-thioxopyrido[2,3-*d*]pyrimidine-6-carbo-nitrile (4a). Orange-yellow powder; FT-IR (KBr): ν (cm^{-1}) 3440, 3400, 3100, 2208, 1656, 1525, 1423, 1346, 858, 804, 756 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ (ppm) 7.24-7.34 (m, 2H, Ar-H), 7.56 (d, *J* = 7.2, 1H, Ar-H), 7.80-7.86 (m, 1H, Ar-H), 7.94 (d, *J* = 7.8 Hz, 1H, Ar-H), 8.38-840 (m, 2H, Ar-H), 8.68 (d, *J* = 3.3 Hz, 1H, =CH-NH), 9.02 (d, *J* = 7.2, 1H), 12.13 (d, *J* = 3.3 Hz, 1H, NH), 12.55 (s, 1H, NH), 13.64 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 100.9, 106.3, 112.5, 112.6, 118.3, 122.1, 123.7, 123.7, 124.0, 124.6, 126.5, 130.1, 131.7, 135.3, 136.9, 138.3, 147.8, 153.4, 156.0, 158.3, 159.8, 176.8. Anal. Calcd. for $C_{22}H_{12}N_6O_3S$ (440.43): C, 59.99; H, 2.75; N, 19.08. Found: C, 59.86; H, 2.67; N, 19.22.

1,2,3,4-Tetrahydro-7-(1*H*-indol-3-yl)-5-(2-nitro-phenyl)-4-oxo-2-thioxopyrido[2,3-*d*]pyrimidine-6-carbo-nitrile (4b). Orange-Yellow powder, FT-IR (KBr): ν (cm^{-1}) 3447, 2930, 2209, 1646, 1516, 1429, 1340, 747 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ (ppm) 7.28-7.33 (m, 2H, Ar-H), 7.57-7.60 (m, 1H, Ar-H), 7.69-7.75 (m, 1H, Ar-H), 7.86 (t, *J* = 8.25 Hz, 1H, Ar-H), 8.10 (d, *J* = 8.4 Hz, 2H, Ar-H), 8.20-8.22 (m, 1H, Ar-H), 8.45 (d, *J* = 2.1 Hz, 1H, =CH-NH), 12.31 (s, 1H, NH), 12.06 (s, 1H, NH),13.52 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 98.0, 111.7, 112.9, 114.9, 116.9, 119.8, 121.8, 122.1, 123.8, 125.6, 128.2, 129.1, 129.9, 130.8, 135.3, 137.1, 154.8, 151.7, 157.3, 162.8, 165.5, 175.1. Anal. Calcd. for $C_{22}H_{12}N_6O_3S$ (440.43): C, 59.99; H, 2.75; N, 19.08. Found: C, 59.84; H, 2.69; N, 18.92.

5-(3-Chlorophenyl)-1,2,3,4-tetrahydro-7-(1*H*-indol-3-yl)-4-oxo-2-thioxopyrido[2,3-*d*]pyrimidine-6-carbonitrile (4d). Pale yellow powder, FT-IR (KBr): ν (cm^{-1}) 3249, 3213, 2287, 2192, 1645, 1571, 1510, 1442, 1097, 1008, 838, 798 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ (ppm) 7.12-7.29 (m, 3H, Ar-H), 7.37-7.47 (m, 2H, Ar-H), 7.50-7.59 (m, 1H, Ar-H), 8.08-8.14 (m, 1H, Ar-H), 8.23 (d, *J* = 1.5 Hz, 1H, =CH-NH), 9.14(s, 1H, Ar-H), 12.17 (s, 1H, NH), 12.70 (s, 1H, NH), 13.21 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 93.2, 112.6, 107.3, 116.6, 116.7, 121.8, 122.0, 123.4, 125.4, 126.7, 127.8, 128.6, 129.9, 131.1, 133.7, 136.6, 144.9, 151.2, 152.8, 161.5, 163.6, 172.7. Anal. Calcd. for $C_{22}H_{12}ClN_5OS$ (429.88): C, 61.47; H, 2.81; N, 16.29. Found: C, 61.58; H, 2.72; N, 16.12.

5-(2-Chlorophenyl)-1,2,3,4-tetrahydro-7-(1*H*-indol-3-yl)-4-oxo-2-thioxopyrido[2,3-*d*]pyrimidine-6-carbonitrile (4e). Yellow powder, FT-IR (KBr): ν (cm^{-1}) 3232, 2248, 1641, 1564, 1523, 1438, 1093, 1004, 873, 790, 752 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ (ppm) 7.16-7.31 (m, 4H, Ar-H), 7.50-7.54 (m, 2H, Ar-H), 8.14-8.17 (m, 1H, Ar-H), 8.39 (d, *J* = 2.1 Hz, 1H, =CH-NH), 9.14 (s, 1H, Ar-H), 12.20 (s, 1H, NH), 12.92 (s, 1H, NH), 13.70 (s, 1H, NH). ^{13}C NMR

(75 MHz, DMSO-d_6): δ (ppm) 78.7, 108.1, 112.6, 112.9, 114.9, 116.9, 121.5, 122.1, 122.8, 123.8, 125.6, 126.7, 129.9, 136.0, 136.6, 137.1, 143.0, 151.2, 154.8, 162.1, 166.2, 175.1. Anal. Calcd. for $C_{22}H_{12}ClN_5OS$ (429.88): C, 61.47; H, 2.81; N, 16.29. Found: C, 61.32; H, 2.93; N, 16.13.

1,2,3,4-Tetrahydro-7-(1*H*-indol-3-yl)-1,3-dimethyl-2,4-dioxo-5-phenylpyrido[2,3-*d*]pyrimidine-6-carbonitrile (4p). Yellow powder, FT-IR (KBr): ν (cm^{-1}) 3317, 3104, 2929, 2198, 1647, 1500, 1428, 833, 749 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 3.16 (s, 3H, CH_3), 3.55 (s, 3H, CH_3), 7.14-7.23 (m, 2H, Ar-H), 7.26-7.33 (m, 2H, Ar-H), 7.38-7.40 (m, 3H, Ar-H), 7.50-7.55 (m, 1H, Ar-H), 7.61 (d, *J* = 8.7 Hz, 1H, Ar-H), 7.93 (d, *J* = 3.0, 1H, =CH-NH), 11.88 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) δ_C; 28.2, 30.6, 89.0, 107.7, 112.8, 112.8, 120.2, 120.8, 121.1, 122.2, 122.7, 125.7, 127.5, 127.5, 127.6, 128.0, 128.4, 129.1, 129.3, 136.6, 144.7, 145.7, 151.3, 161.2. Anal. Calcd. for $C_{24}H_{17}N_5O_2$ (407.42): C, 70.75; H, 4.21; N, 17.19. Found: C, 70.61; H, 4.10; N, 17.08.

RESULTS AND DISCUSSION

The catalyst γ-Fe_2O_3@HAp@PBABMD@Cu was synthesized and characterized by FT-IR, SEM and ICP analysises which matched with our previously reported data [29]. The FT-IR spectra for γ-Fe_2O_3@HAp@PBABMD@Cu MNPs is shown in Fig. 3. The absorption peaks at 478 and 567 cm^{-1} were referred to the Fe-O bonds. The signals at 567 and 603 are due to the bending vibration O-P-O which were overlapping with the Fe-O stretching bands. The signal at 1045 and 1100 cm^{-1} showed the presence of phosphate group (PO_4^{3-}, P-O). The signals at 1633 cm^{-1} and 3445 cm^{-1} were assigned to C=N and O-H groups respectively. The ICP-OES analysis showed that 4.65% of Cu was anchored on catalyst γ-Fe_2O_3@HAp@PBABMD@Cu. ICP-OES data show that there is about 0.72 mmol g^{-1} of Cu in γ-Fe_2O_3@HAp@PBABMD@Cu. The Fe-SEM image of the catalyst nanocrystallites (16-22 nm) is presented in Fig. 4. The spherical morphology was proved in the Fe-SEM image of the catalyst.

In the present research, we have developed the one-pot three-component approach for the synthesis of indole-pyrido[2,3-*d*]pyrimidine hybrids (4a-p) by the reaction of thiouracil or 6-amino-*N*,*N*-dimethyluraciles (1), aldehyde (2), and 3-cyanoacetylindole (3) in the presence of γ-Fe_2O_3@HAp@PBABMD@Cu as nanocatalyst in EtOH

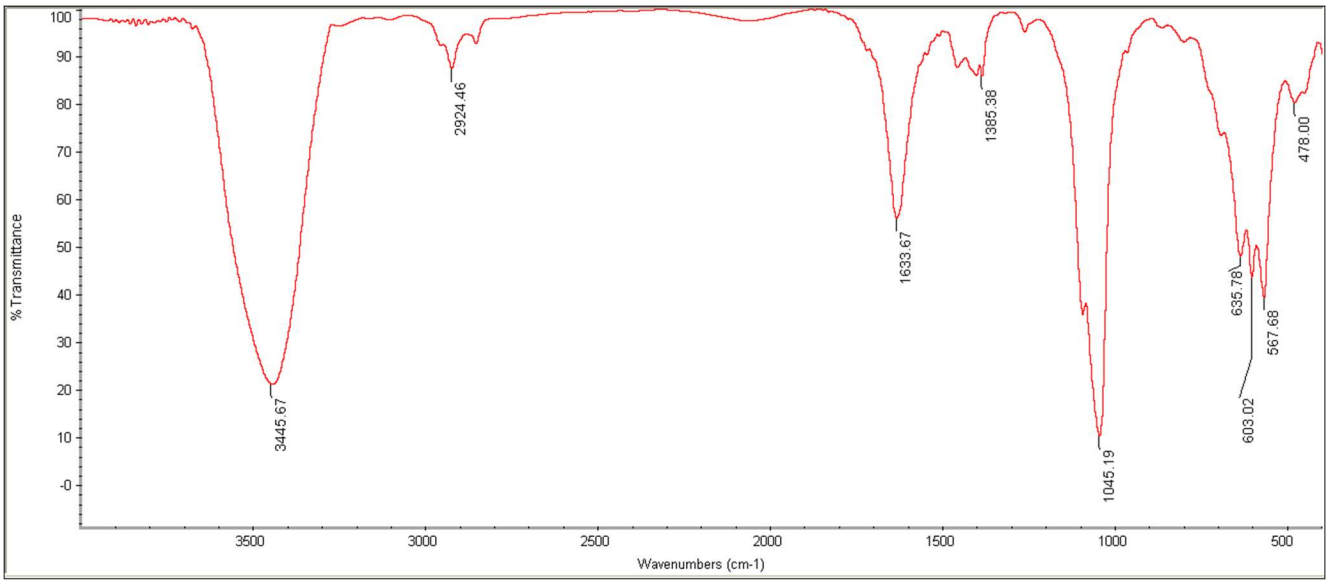


Fig. 3. FT-IR spectra of γ-Fe_2O_3@HAp@PBABMD@Cu MNPs.

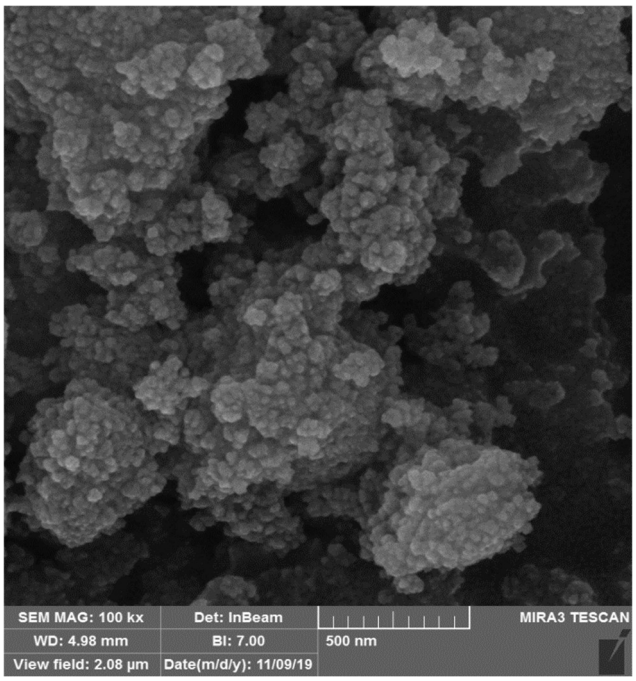


Fig. 4. Fe-SEM image of magnetic γ-Fe_2O_3@HAp@PBABMD@Cu MNPs.

Table 1. Synthesis of 4a in Various Solvents and Temperatures in the Presence of γ-Fe_2O_3@HAp@PBABMD@Cu[a]

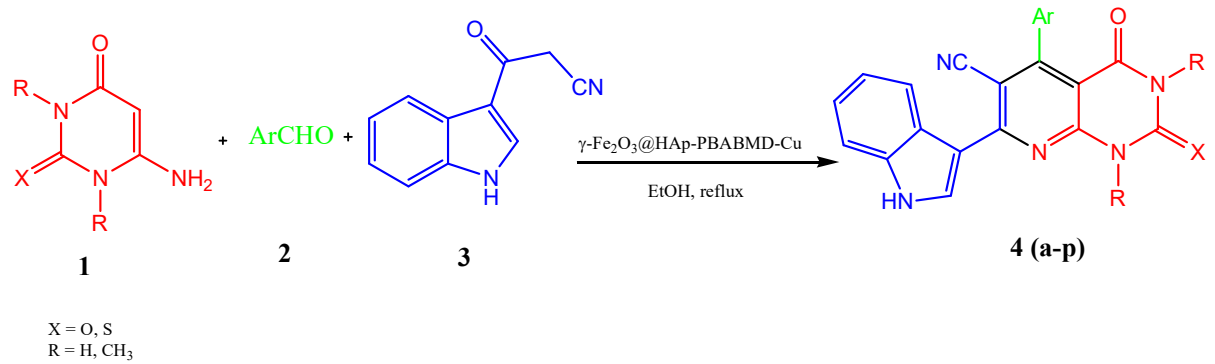
Entry	Solvent	Temperature (°C)	Time (min)	Yield (%)[b]
1	EtOH	Reflux	20	92
2	MeOH	65	60	70
3	DMF	110	52	81
4	CH_3CN	80	87	58
5	H_2O	80	100	-
6	CH_2Cl_2	42	90	54

[a]Reaction conditions: In the presence of γ-Fe_2O_3@HAp@PBABMD@Cu (20 mg)/mmol substrate. [b]Isolated yields.

under reflux condition (Scheme 1). This procedure afforded the corresponding indole-pyrido[2,3-*d*]pyrimidines (4a-p) in lower reaction times (18-40 min) and high yields (82-95%) .

In the initial experiments, the starting compounds 1 and 3 were prepared [30,31] and to obtain optimized reaction conditions, synthesis of 1,2,3,4-tetrahydro-7-(1*H*-indol-3-yl)-5-(3-nitrophenyl)-4-oxo-2-thioxopyrido[2,3-*d*] pyrimidine-6-carbonitrile (4a) was performed by the reaction between 6-amino-2,3-dihydro-2-thioxopyrimidin-4(1*H*)-one (1 mmol) (1), 3-nitrobenzaldehyde (1 mmol) (2) and 3-cyanoacetylindole (1 mmol) (3) as model reaction in the presence of γ-Fe_2O_3@HAp@PBABMD@Cu (20 mg). Different solvents and temperatures were screened to provide the desired product (Table 1). The results revealed that the reaction in refluxing EtOH is the most effective conditions (Entry 1). This reaction was also carried out in the presence of different catalysts and without catalyst (Table 2).

The Amount of catalyst was also studied and the result demonstrated the shortest reaction times (20 min) and highest yields (92%), was obtained using 20 mg of



Scheme 1. Synthesis of indole-pyrido[2,3-*d*]pyrimidines in the presence of γ-Fe_2O_3@HAp@PBABMD@Cu

γ-Fe_2O_3@HAp@PBABMD@Cu per mmol substrate (Table 3). To demonstrate the efficiency of this catalyst, in Table 4, this method was compared with the reported procedure, and the results showed the superiority of this catalyst.

A number of indole-pyrido[2,3-*d*]pyrimidine derivatives were synthesized under optimal conditions, which are listed in Table 5. The results revealed that arylaldehydes with both

Table 2. The Effect of Different Catalysts on the Synthesis of 4a[a]

Entry	Catalyst	Amount of catalyst (mol%)	Time (min)	Yield (%)[b]
1	-	-	20 h	-
2	DABCO	20	120	52
3	DBU	20	240	40
4	*P*-TSA	20	90	60
5	AcOH	10	80	81
6	$CuCl_2$	10	60	70
6	γ-Fe_2O_3@HAp@PBABMD@Cu [18][c]	1.5 (20 mg)	20	92

[a]Reaction conditions: reflux in EtOH. [b]Isolated yields. [c]According to ICP analysis, the amount of Cu in 1 g of catalyst is ~0.72 mmol.

Table 3. Optimization of the Amount of γ-Fe_2O_3@HAp@PBABMD@Cu in the Synthesis of 4a[a]

Entry	Amount of γ-Fe_2O_3@HAp@PBABMD@Cu mgmmol^{-1} substrate	Time (min)	Yields (%)[b]
1	10	35	84
2	20	20	92
3	25	20	92

[a]Reaction conditions: reflux in EtOH. [b]Isolated yields.

Table 4. Comparison of the Efficiency of Present Catalyst with some Reported Ones in the Synthesis of 4a

Entry	Catalyst	Temperature (°C)	Solvent	Time	Yield (%)[a]
1	γ-Fe_2O_3@HAp@PBABMD@Cu	Reflux	EtOH	20 min	92 [This work]
2	$lnCl_3$	Reflux	EtOH	6 h	77 [32]
3	Fe_3O_4@FAp@Ni	60 °C	EtOH	1 h	90 [18]
4	$CuCl_2$	reflux	EtOH	2 h	60

[a]Isolated yields.

Table 5. Synthesis of Indole-pyrido[2,3-*d*]pyrimidine Derivatives (4a-p) Under Optimized Conditions

Product	X	R	Ar	Time (min)	Yield (%)[a]	M.p. (°C)	
						Found	Reported [Ref.]
4a	S	H	3-$O_2NC_6H_4$	20	92	298-301	-
4b	S	H	2-$O_2NC_6H_4$	23	87	303-304	-
4c	S	H	4-ClC_6H_4	25	90	304-305	>300 [32]
4d	S	H	3-ClC_6H_4	18	95	305-306	-
4e	S	H	2-ClC_6H_4	19	93	307-310	-
4f	S	H	4-$OHCC_6H_4$	18	87	300-301	>300 [32]
4g	S	H	4-MeC_6H_4	32	89	301-303	>300 [32]
4h	S	H	4-$MeOC_6H_4$	27	84	303-304	>300 [32]
4i	S	H	4-BrC_6H_4	22	89	297-300	>300 [32]
4j	S	H	4-$NO_2C_6H_4$	18	82	302-303	>300 [32]
4k	O	CH_3	4-$NO_2C_6H_4$	28	91	309-310	>300 [18]
4l	O	CH_3	4-MeC_6H_4	35	95	311-314	>300 [18]
4m	O	CH_3	4-$MeOC_6H_4$	40	87	306-308	>300 [18]
4n	O	CH_3	4-ClC_6H_4	27	91	305-308	>300 [18]
4o	O	CH_3	3-BrC_6H_4	29	93	299-301	>300 [18]
4p	O	CH_3	C_6H_5	32	83	309-312	-

[a]Isolated yields.

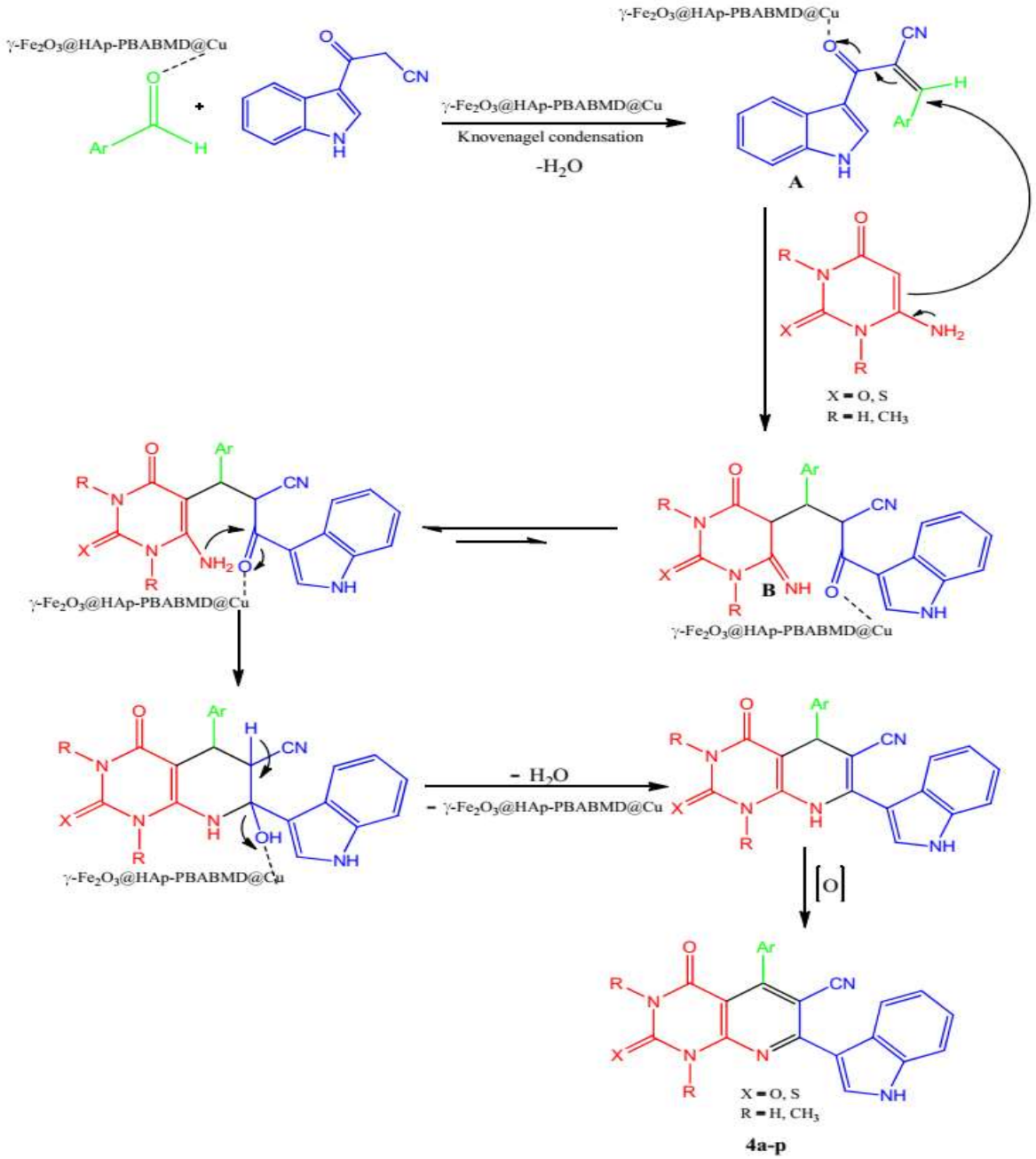
electron-deficient and electron-rich substituents afford desired products in high yields (82-95%) and lower reaction times (18-40 min). The structures of all the new products were established on the basis of their analytical and spectroscopic data (FT-IR, ^{1}H NMR and ^{13}C NMR).

The plausible mechanism of the present multi-component reaction is outlined in Scheme 2. Intermediate A is initially formed from the condensation of 3-cyanoacetylindole and aryl aldehyde using the magnetic nano-catalyst γ-Fe_2O_3@HAp@PBABMD@Cu. The Michael addition of 6-amino-*N,N*-dimethyluracyl to arylidine A, produces intermediate B. Cyclisation, dehydration, remove of the catalyst and oxidation of intermediate B, furnishes the final product (4a-p). At all stages, γ-Fe_2O_3@HAp@PBABMD@Cu accelerates various stages of the reaction as Lewis acid catalyst.

The reusability of the nanocatalyst and its effect on the efficiency of the synthesis of 4a was also investigated (Fig. 5). The catalytic activity of this magnetic nanocatalyst was almost retained without a significant loss of activity after 6 cycles. To recover the catalyst, the nanocatalyst was removed from the reaction mixture with an external magnet and then washed with hot ethanol to remove impurities, and then was dried and reused.

CONCLUSIONS

In this research, a new and green procedure for the preparation of some pyridopyrimidine derivatives with indole substitution in ethanol, under reflux conditions



Scheme 2. The plausible mechanism for the synthesis of indole-pyrido[2,3-*d*]pyrimidine in the presence of γ-Fe_2O_3@HAp@PBABMD@Cu

and in the presence of γ-Fe_2O_3@HAp@PBABMD@Cu nanocatalyst was presented. Studies have shown that the reaction with the γ-Fe_2O_3@HAp@PBABMD@Cu nanocatalyst gives a high yields of the desired products in short reaction times. The catalyst is recyclable and after 6 runs in the synthesis of the model product, showed no significant changes in its activity. The varieties of products, high efficiency and catalyst recyclability are the advantages

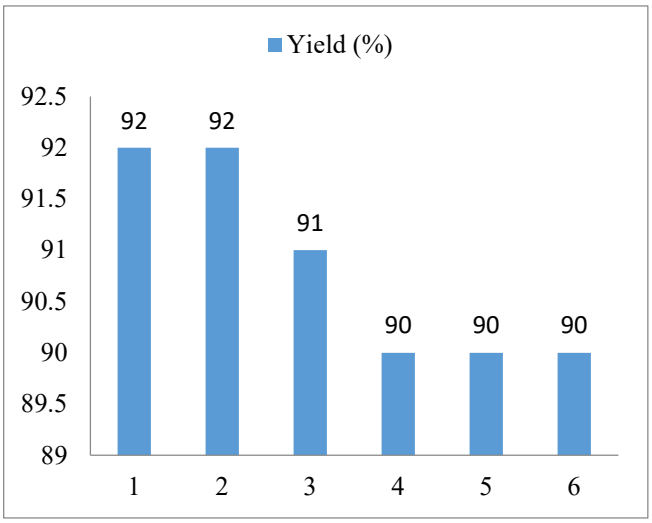


Fig. 5. The reusability of the catalyst in the synthesis of 4a under optimized conditions.

of this green procedure for the synthesis of indole-pyrido[2,3-*d*]pyrimidines hybrids.

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