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ONE-POT SYNTHESIS OF SUBSTITUTED BENZIMIDAZOLE DERIVATIVES UNDER ULTRASONIC IRRADIATION USING $ZnFe_2O_4$ REUSABLE CATALYST

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Abstract. An efficient one-pot synthesis of benzimidazole derivatives by the condensation between various *o*-phenylenediamine and substituted aromatic aldehyde using $ZnFe_2O_4$ as a nano-catalyst under ultrasonic irradiation conditions was described. Remarkable advantages of the present synthetic strategy over the previously reported methods are shorter reaction times, higher isolated yields and simple work-up procedure. The presence of electron withdrawing and electron donating groups on the aromatic rings did not affect the yield of the product. The $ZnFe_2O_4$ catalyst was recycled after completion of reaction and was reused.

Keywords: one pot reaction, substituted benzimidazole, ultrasound irradiation, $ZnFe_2O_4$ catalyst, biological activity.

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Introduction

Nitrogen containing heterocycles are of great importance due to the synthetic utility and extensive attention in organic chemistry and benzimidazole is one amongst them [1-3]. The NH group in benzimidazole is very weakly basic and relatively strongly acidic and benzimidazoles are able to form salts [4]. Outstanding uses of benzimidazoles in medicinal as well pharmaceutical fields include treating fungus pathogens, to treat nematode and trematode infection in animals and humans, stopping hyphal growth. Other benzimidazoles play an important role as preservative agents in fruits, paints, textiles, leather industry, papermaking process. Various pharmaceutical drugs have been manufactured from benzimidazole ring such as astemizole, esomeprazole, nitazene, etonitazene, clonitazene, anti-tuberculosis *etc*. [5-7]. Several authors have reviewed the spectrum of benzimidazole's pharmacological activity [8-11]. Numerous of its derivatives exhibit pharmacological effects and thus have been promoted in commercialization of medications as shown in Figure 1, therefore there is a continuous inetrest in developing new methods of synthesis and improving the existing ones.

In recent years, various methods have described syntheses of substituted benzimidazoles using several catalysts, such as rose Bengal [12], *p*-tolunesulfonic acid/graphine and *N*,*N*-dimethyl aniline/graphine [13], NH_4Cl [14], $[Yb(OPf)_3]$ [15], $In(OTf)_3$ [16], $FeCl_3$ [17], $VO(acac)_2$ [18], I_2 [19], NH_4OAc [20], nano-catalyst such as $COFe_2O_4$ [21], Co/SBA-15 [22], ZnO [23], MNPs@Cu-PMT [24], MNP-IL [25], ZnS [26], $Co(OH)_2$/CoO(II) [27], CuMVs [28] and MIL-53(Fe) [29]. Many of these processes endure limitations, such as extreme reaction conditions, low yields, dreary work-up procedures and co-occurrence of several side reactions.

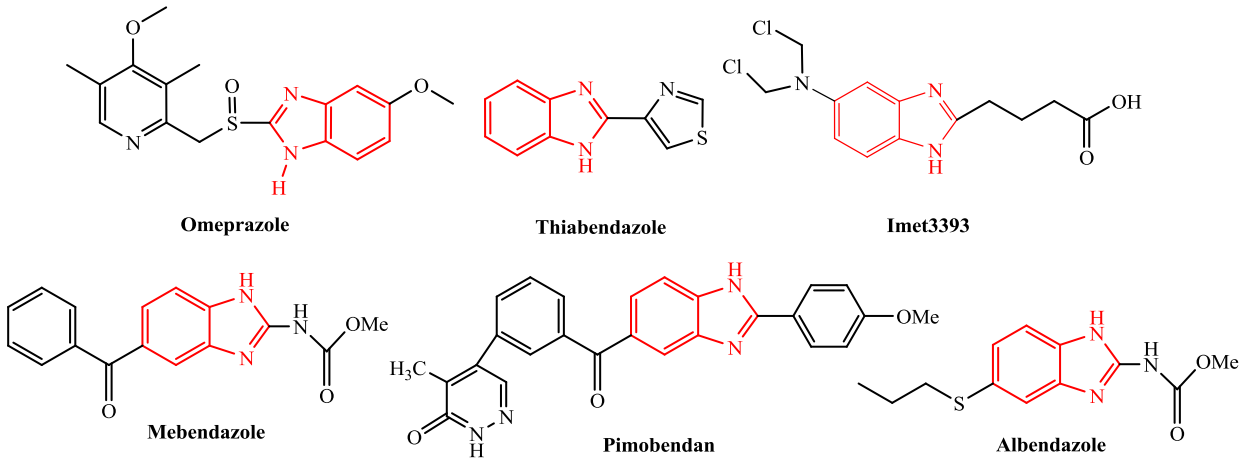


Figure 1. Benzimidazole incorporated drug molecules.

The introduction of green methods to overcome these limitations is still an important experimental challenge. Recently, $ZnFe_2O_4$ mixed metaloxide nanoparticles have been broadly used in modern heterocyclic organic synthesis. $ZnFe_2O_4$ is one of the economically efficient, insoluble in organic solvents, easily recoverable, having low surface area, heterogeneous, and inexpensive nanocatalyst [30-33]. Use of $ZnFe_2O_4$ nanocatalyst in organic synthesis resulted in several advantages such as commercially efficient, yield improvement, time reduction, suitable experimental procedure to work up and easily recovery of catalyst etc. Some examples of synthesized heterocyclic compounds by using $ZnFe_2O_4$ nanocatalyst are 2,3-dihydroquinazolin 4(*1H*)ones [34] and pyrano[2,3-d]pyrimidines [35] derivatives. Also, nanocatalyzed reactions in ultrasonic technique have given excellent yield of product within time [36] in comparison to other.

Thus, above mentioned heterocycles having tremendous significance in various areas, organic chemists have challenge to overwhelm them by searching a surrogate for the conventional bases, which can work in water, and to develop efficient methods for this nucleus using milder, non-hazardous and inexpensive reagents. In continuation to the earlier work, herein it is explored the straightforward synthesis of benzimidazoles by condensation of *o*-phenylenediamine and benzaldehyde under ultrasonication, in hydrated ethanol as a solvent, using $ZnFe_2O_4$ nanoparticles as catalyst. According to the literature survey, there are no available reports in the literature for the above mentioned procedure.

Herein the aim of this study is the synthesis of benzimidazole derivatives using $ZnFe_2O_4$ nanoparticles as a catalyst under ultrasonic irradiation.

Experimental

Generalities

All chemicals were purchased from Aura Chemical Laboratory and purified before starting the reactions. The $ZnFe_2O_4$ nano-catalyst was also purchased from Aura Chemical Laboratory. Ultrasonic bath sonicator conditions were established at: 230 V AC, 50 Hz, liquid holding capacity 5.5 L and temperature 70°C. Melting point values were registered on a *SRS* Opti-melt instrument and all synthesized compounds were analyzed by means of ^1H and ^{13}C NMR spectroscopy (Bruker), using DMSO-d_6 solvent and TMS as internal standard, at 400 and 100 MHz respectively. Electrospray ionization coupled to mass spectrometry method was carried out on ESI QTOF instrument. IR spectra were recorded on a Perkin Elmer FTIR spectrometer using KBr pallets. Elemental analysis was performed on an Elementer-Vario MICRO cube Analyzer Instrument.

General procedure for synthesis of substituted benzimidazole derivatives (3a-j)

The reaction mixture (*o*-phenylenediamine **1a-c** (0.1 mol), aromatic aldehydes **2a-j** (0.1 mol) and a nano-catalyst in 3 mL of solvent) was ultrasonically irradiated for 30 minutes. The progress of the reaction was monitored by TLC plate using (7:3) ethyl acetate and *n*-hexane. After completion of reaction, 10 mL of ethanol was added to reaction mass and the resulting mixture was stirred for 5 minutes. The obtained solution was filtered to remove the catalyst. The solvent was distilled out under reduced pressure. The product was purified by column chromatography using (1:1) *n*-hexane and ethyl acetate. NMR data of synthesized compounds are presented in supplementary material.

Anti-tuberculosis activity testing

The investigation of *in vitro* anti-tuberculosis activity of synthesized substituted benzimidazole derivatives **3a-j** was carried out by the CLAIRO COMBI method [37]. The synthesized compounds **3a-j** were tested against *M. Tuberculosis* bacterial stain with reference to standard Streptomycin by using Liquefied sterile Lowenstein-Jensen agar media [37].

Results and discussion

An efficient and green protocol for the synthesis of benzimidazoles **3a-j** using $ZnFe_2O_4$ catalyst is established. To synthesize the target molecule, ultrasound assisted (70°C) condensation of substituted *o*-phenylenediamine **1a-c** with aromatic aldehydes **2a-j** one-pot synthesis was carried out, according to Scheme 1. To establish the efficiency and advantages of the catalytic activity of $ZnFe_2O_4$, the synthesis was also carried out in the same reaction conditions (ethanol as solvent, and temperature of 70°C), by using other catalysts (see Table 1). Results demonstrate that the $ZnFe_2O_4$ nano-catalyst is more efficient than the other catalyst (Table 1, Entry 6).

To determine the optimum quantity of $ZnFe_2O_4$ nano-catalyst, the condensation of *o*-phenylenediamine (**1a**) and benzaldehyde (**2a**) was carried out in hydrated ethanol as solvent under ultrasonic irradiation at 70°C (water as an liquid used in the ultrasonic bath) using variable quantities of $ZnFe_2O_4$ nano-catalyst as presented in Table 2. In Table 2, Entry 3, the results show that 10 mol% nano-catalyst produced an excellent product of yield. Further increase in the concentration of catalyst did not improve the yields. It was therefore concluded that the optimum concentration of catalyst was 10 mol%.

Table 1

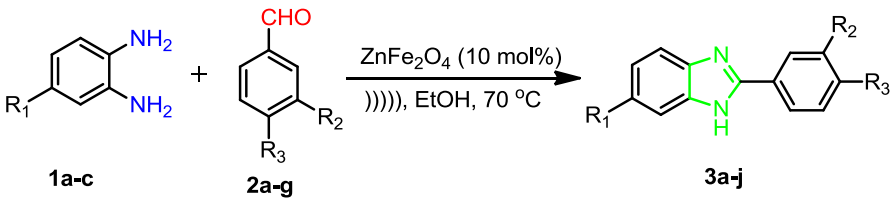
Evaluation of the different catalysts under ultrasonic irradiation conditions for synthesis of 2-phenyl-1*H*-benzimidazole 3a.

Entry	*Catalyst (10 mol%)*	*Time (min)*	*Yield (%)*
1.	-	30	25
2.	NH_4Cl	30	47
3.	$Yb(OTf)_3$	30	60
4.	$FeCl_3$	30	40
5.	$CdCl_3$	30	20
6.	$ZnFe_2O_4$	30	92

Table 2

Screening of amount of $ZnFe_2O_4$ nano-catalyst under ultrasonic irradiation for the synthesis of 2-phenyl-1*H*-benzimidazole 3a.

Entry	*Catalyst (mol%)*	*Time (min)*	*Yield (%)*
1.	-	30	0
2.	5	30	76
3.	10	30	92
4.	15	30	93
5.	20	30	93



1a-c **2a-g** **3a-j**

1a; R_1= H
1b; R_1= Me
1c; R_1= NO_2

2a; R_2 & R_3= H,
2b; R_2= Me, R_3= H,
2c; R_2= H, R_3= Me,
2d; R_2= H, R_3= OMe,
2e; R_2= H, R_3= Cl,
2f; R_2= H, R_3= NO_2,
2g; R_2= H, R_3= Cl

3a; R_1= H, R_2= H, R_3= H; **3b**; R_1= H, R_2= Me, R_3= H,
3c; R_1= H, R_2= H, R_3= Me; **3d**; R_1= H, R_2= H, R_3= OMe,
3e; R_1= H, R_2= H, R_3= Cl; **3f**; R_1= H, R_2= H, R_3= NO_2,
3g; R_1= Me, R_2= H, R_3= H; **3h**; R_1= Me, R_2= H, R_3= NO_2,
3i; R_1= NO_2, R_2= H, R_3= H; **3j**; R_1= NO_2, R_2= H, R_3= Me

Scheme 1. Synthesis of substituted benzimidazole derivatives 3a-j using $ZnFe_2O_4$ nano-particles.

Screening of various solvents for model reaction with reflux condenser such as acetonitrile (ACN), ethanol (EtOH), dichloromethane (DCM), dichloroethane (DCE) and water (H_2O), different amounts of product yield observed due to chemical properties of solvent under ultrasonic conditions. In EtOH solvent, the percentage of product yield was excellent (Table 3, Entry 2); maximum yield of product was observed after 28 minutes (**3a**) [38].

In the next step, the reaction with regard to the temperature parameter was examined. Initially, the reaction was carried out at room temperature and then elevated to 50, 65 and 70°C, respectively. It is observed that the yield of the product was considerably enhanced by increasing the temperature (Table 4, Entries 1-4). Hence, the cyclo-condensation accomplishes smoothly at 70°C and is more efficient with respect to reaction time and excellent yield of the desired product **3a**. After screening the reaction conditions, the synthesis of substituted benzimidazole derivatives (**3a-j**) was carried out by the reaction of different diamines (**1a-j**) with various aromatic aldehydes (**2a-j**).

Thus, substituted benzimidazole derivatives **3a-j** were synthesized using the ultrasonic irradiation method and the yield of reactions were found between 88-92% due to the ultrasonic effect. From that, electron withdrawing substituent of reactants showed slightly higher percentage of product yield. All prepared benzimidazole derivatives **3a-j** showed significant amount of product yield (Table 5).

Table 3

Screening of various solvents under ultrasonic irradiation at 70°C for synthesis of 2-phenyl-1*H*-benzimidazole 3a.

Entry	*Solvent*	*Time (min)*	*Yield (%)*
1.	ACN	30	79
2.	EtOH	30	92
3.	DCM	30	64
4.	DCE	30	71
5.	H_2O	30	0

Table 4

Screening of ultrasonic temperature for synthesis of 2-phenyl-1*H*-benzimidazole 3a.

Entry	*Temperature (°C)*	*Time (min)*	*Yield (%)*
1.	r.t.	30	20
2.	50	30	65
3.	65	30	85
4.	70	30	92

Table 5

Synthesis of substituted benzimidazole derivatives 3a-j using recyclable $ZnFe_2O_4$ nano-catalyst.

Sr. No.	*Compound*	*Time (min)*	*Yield [a](%)*		*Melting point values (°C)*	
			Found	*Reported [Ref.]*	*Found*	*Reported [Ref.]*
1.	**3a**	25	92	90 [38]	285-287	288-290 [38]
2.	**3b**	27	90	-	287-289	-
3.	**3c**	28	88	-	276-278	-
4.	**3d**	24	89	87 [38]	234-236	230-232 [38]
5.	**3e**	25	91	-	294-296	-
6.	**3f**	22	92	95 [38]	306-308	303-304 [38]
7.	**3g**	26	89	90 [38]	245-247	232-233 [38]
8.	**3h**	23	90	95 [38]	240-242	235-238 [38]
9.	**3i**	24	91	87 [38]	203-205	198-200 [38]
10.	**3j**	25	89	-	286-288	-

Reaction conditions- o-phenylenediamine (0.1 mole), Aromatic aldehydes (0.1 mole), $ZnFe_2O_4$ nanoparticles catalyst (10 mol%), 3 mL ethanol solvent and ultrasonic irradiation for 70°C, ultrasonic bath liquid - water.
[a] yield refers to the isolated product, characterized by NMR, IR, MS spectral analysis.

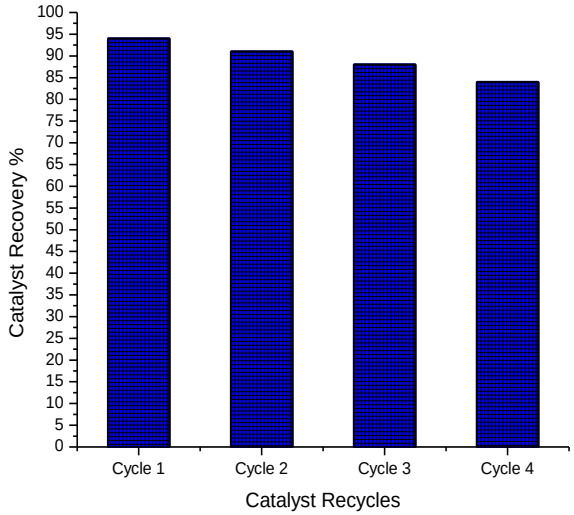


Figure 2. Recyclability of $ZnFe_2O_4$ nanoparticles catalyst.

Further, the catalyst was recovered by a simple filtration method as shown in Figure 2. The recovered catalyst was implemented again in the optimized reactions 4 times by using 94, 91, 88 and 84% of recovered catalyst. The recycled catalyst gave very good yield of product.

Antituberculosis analysis

Benzamidazoles were showed to detain efficient antituberculosis activity [39]. Hence, the newly synthesized substituted benzimidazole derivatives **3a-j** were evaluated for the antitubercular activity by the zone of inhibition method. Streptomicin was used as a reference standard drug. The obtained results show that the newly synthesized substituted benzimidazole derivatives **3a-j** possessed moderate antitubercular activity (Table 6) and thus have scope in treating tuberculosis (moderate to good). Among all the synthesized compounds **3a-j**, compound **3i** exhibited excellent antitubercular activity compared to the standard drug.

Table 6

Anti-tuberculous activity for prepared substituted benzimidazoles derivatives 3a-j.

Entry	*Product*	*M. Tuberculosis (inhibition zone in diameter mm)*
1.	**3a**	8
2.	**3b**	10
3.	**3c**	7
4.	**3d**	9
5.	**3e**	8
6.	**3f**	12
7.	**3g**	8
8.	**3h**	12
9.	**3i**	13
10.	**3j**	11
11.	Standard	14

Antituberculosis results (Table 6) clearly indicated that the electron withdrawing groups containing benzimidazoles products displayed anti-tuberculous activity as **3i** (13 mm), **3f**, **3h** (12 mm), but not greater than standard (14 mm).

Conclusions

In conclusion, herein is reported the synthesis of substituted benzimidazole derivatives from various *o*-phenylenediamine, different aromatic aldehydes using $ZnFe_2O_4$ as a recyclable nano-catalyst in ethanol solvent under ultrasonic irradiation conditions. This methodology provides an easier, facile, safe and environmentally benign green protocol synthesis.

The optimized methodology offers reduced reaction time 22 to 28 minutes, recyclability of catalyst up to four cycles with better yields up to 88 to 92%. The main aim of the investigation claims application of ultrasonic irradiation and recyclability of catalyst to synthesize various substituted benzimidazole derivatives by reducing the cost of products, waste and pollution.

All synthesized substituted benzimidazole derivatives exhibited moderate **3c** (7 mm) to good **3h** (12 mm), **3i** (13 mm) anti-tuberculosis activity. Compound 6-nitro-2-phenyl-1*H*-benzo[d]imidazole exhibited excellent anti-tubercular activity comparable to that of the standard drug (14 mm).

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Supplementary information

Supplementary data are available free of charge at http://cjm.asm.md as PDF file.

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