IJPSR (2022), Volume 13, Issue 9 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 11 January 2022; received in revised form, 31 March 2022; accepted, 26 April 2022; published 01 September 2022

MORINGA OLEIFERA (MO) SEED CATALYZED THE SYNTHESIS OF BENZIMIDAZOLE DERIVATIVES

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Keywords:

Green synthesis, O-phenylenediamine, substituted benzaldehydes, MO seed extract, Microwave irradiation

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ABSTRACT: A simple, one-pot, and efficient method for the synthesis of benzimidazole derivatives *via* the condensation of o-phenylenediamine and substituted aromatic aldehydes in the presence of *Moringa oleifera* (MO) seed extract acts as a biocatalyst under microwave irradiation. The method provides several advantages such as simple operation, clean reaction ways, and high to the excellent yield of product. The aqueous extract of *Moringa oleifera* (MO) seed as a green catalyst corresponds to an excellent yield for the synthesis of 2, 4, 5-trisubstituted imidazole derivatives under microwave irradiation method as a greener heating technique and one-pot multicomponent reaction acts as a green routine. All synthesized compounds were characterized by spectroscopic techniques such as FT-IR, ^{1}H-NMR, ^{13}C-NMR and LC-MS analysis.

INTRODUCTION: Heterocyclic compounds are a great attraction within biological, pharmaceutical, and medicinal compounds. Benzimidazole nuclei are the important and famous heterocyclic nuclei, showing common and essential features of various interesting biological activities [1]. They showed a wide range of applications in medicinal chemistry such as antidepressant [2], anticonvulsant [3], anti-inflammatory [4-5], antimicrobial [6-8], anti-tumor [9], anti-viral [10], anti-hypertensive [11], anti-ulcer [12-13], anti-histamine [14], anti-arrhythmic [15], anti-cancer [16-19], anti-proliferative [20], anti-parasites [21] anti-diabetics [22-23], anti-oxidant [24-25], anti-bacterial [26-27], anti-fungal [28-29], anthelmintic activity [30-31] *etc*.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.13(9).3550-60

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.13(9).3550-60

Two general methods are reported for the synthesis of 2-substitute benzimidazoles. In the first method, coupling of o-phenylenediamine and carboxylic acids [32] or their derivatives (nitriles, imidates or orthoesters) [33] is done. Whereas in the second method, a two-step procedure that consist of oxidative cyclodehydrogenation of anilines Schiff's bases, which are often generated in situ from the condensation of phenylenediamine with aldehyde [34] is carried.

The 2-substituted benzimidazoles were also synthesized by different catalysts [35-38] or different Lewis acids catalysts such as $TiCl_3OTf$ [39], $SnCl_2$ [40], $HFCl_4$ [41], Graphene oxide [42] *etc*. In the past few years, the use of heterogeneous catalysts has received considerable interest in the synthesis of various substituted benzimidazole derivatives. Different supported or unsupported catalysts, including MoO_3 [43], ZnO [44], CuO [45], cobalt oxide [46], iron oxide [47], aluminum silicates [48] and various nanoparticles [49-52 are] being used for this purpose.

Supported hetero poly acid catalysts have been proved very good and efficient catalysts in such processes [53-55]. Green synthetic chemistry fellow a set of principles that remove the use or generation of hazardous substances in the design, manufacture, and applications of chemicals, pharmaceuticals, and medicinal products.

Bio-catalyzed synthetic reaction is the oldest chemical transformation known to humans with great significance for green chemistry. MO seed is an important part of the plant.

The chemical constituents of MO seed extract contain many anti-oxidant contents such as phenolic (Gallic acid), flavonoids (Quercetin), tannin (Gallic acid) *etc*. [56-58]. Gallic acid is also called phenolic acid having trihydroxy monocarboxylic acid as a functional group.

In literature survey, the seed have been extracted with various solvents, which has led to the presence of different phytochemicals and commonly used solvents such as water, ethanol, methanol *etc* water being a universal solvent is commonly used in the extraction of phytochemicals from the seed because of its ease of handling of extract and non-toxicity.

The present report synthesizes 2-substituted benzimidazole derivatives with o-phenyl-enediamine, various substituted benzaldehyde using MO seed as a catalyst. The synthesized product were characterized by FT-IR, ^{1}H-NMR, ^{13}C-NMR and Mass spectroscopy.

MATERIALS AND METHODS: All the chemicals used are of analytical reagent (AR) grades and used without further purification.

All chemicals required are obtained from Sigma-Aldrich. All synthesized compounds or derivatives were characterized by FT-IR spectra, ^{1}H-NMR, ^{13}C-NMR, and Mass spectroscopy. FT-IR spectra were recorded on SHIMADZU FT-IR-8400 using KBr pallets. The ^{1}H-NMR spectra were recorded in $CDCl_3$/DMSO-d^6 on BRUKER-400 MHz, Mass spectra were recorded on SHIMADZU-MODEL-8045 at ESI-APCI interface.

The microwave oven Cata R system utilized for this work (700 W, 120 ^{o}C). The reaction was performed in glass tube (10 mL).

Melting point of synthesized compounds were determined by melting point apparatus with an open capillary tubes and were uncorrected.

Collection of Plant Material: Fresh or matured MO seeds were collected from a rural area. There plant seed were heat-dried at 50°C for 4 days.

The dry seed were pulverized using an electric blender to crush the kernels of the seeds through into fine powder.

The fine powder was stored at 4°C temperature in the refrigerator in an air-tight container for further analysis.

Preparation of Plant Extract: In a clean 250 mL beaker, 10 g of MO seed powder was added to 100 mL water as a solvent and boiled for 15 min. The solution was filtered through Whatman filter paper no. 1 to remove unwanted content.

The resultant aqueous extract was used as a catalyst for the preparation of benzimidazole derivatives.

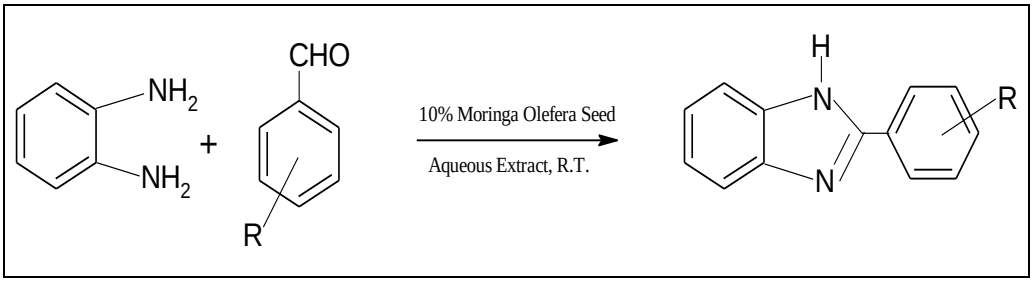
Synthesis of 2-substituted Benzimidazole Derivatives (Convenient Method): In a clean 25 mL round bottom flask, o-phenylenediamine (1mmol), substituted benzaldehyde (1mmol) and a catalytic amount of MO seed extract (10% w/v), all the reaction mixture stirred at room temperature for the appropriate time in scheme 1. The progress of the reaction was checked by TLC.

After completion of the reaction, thin layer chromatography (TLC) was monitored on silica gel coated Al-sheets in a solvent (n-hexane: Ethyl acetate-1:4). The solid benzimidazole product was filtered, washed with water & recrystallized from ethanol.

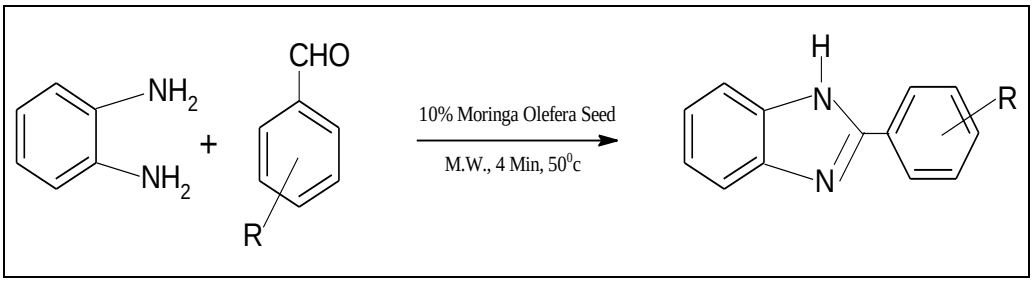
Synthesis of 2-substituted Benzimidazole Derivatives (Microwave Irradiation Method): In a clean 25 mL RBF, o-phenylenediamine (1 mmol), substituted benzaldehyde (1mmol) were thoroughly mixed, then the catalytic amount of MO seed extract (10% w/v) was added and the reaction mixture was kept in the microwave irradiation at optimized power of 40% level with intermittent cooling after each 10 sec of irradiation in scheme 2. After next process is similar to convenient method.

Reaction Scheme:

SCHEME 1:



SCHEME 2:



Spectral Data: 2-Phenyl-1H-Benzimidazole (1a) M.P. 288-289 °C FT-IR (KBr, cm^{-1}) – 3564.85, 3034.27, 1694.50, 1552.60, 1484.33, 1446.85, 1369.42,1217.23, 1134.66, 1069.50, 758.34, 690.03, 622.09, ^{1}H-NMR ($CDCl_3$/DMSO-d^6) – δH 7.18-7.29 (m, 2H), δH 7.32-7.48 (m, 5H), δH 7.68 (d, 2H), δH 10.1 (s, 1H), ^{13}C-NMR- δC 117.03, 119.99, 123.04, 127.85, 128.27 128.60, 128.76, 137.34, 171.59. Mass Spectrum (m/z) - Calculated ($C_{13}H_{10}N_2$)-194.23, Observed-195.0 2-(4-ChloroPhenyl)-1H-Benzimidazole (1b) M.P. 281-282 °C FT-IR (KBr, cm^{-1}) – 3626.73, 3508.24, 1587.14, 1427.09, 1312.01, 1079.44, 869.72, 731.99, ^{1}H-NMR ($CDCl_3$/DMSO-d^6) – δH 7.138-7.146 (m, 2H), δH 7.446-7.595 (m, 4H), δH 8.114 (d, 2H), δH 12.775 (s, 1H), ^{13}C-NMR- δC 128.36, 129.16, 129.21, 135.18, 150.65. Mass Spectrum (m/z) - Calculated ($C_{13}H_9N_2Cl$) -228.68, Observed-229.0 2-(4-hydroxyPhenyl)-1H-Benzimidazole (1c) M.P. 229-230 °C FT-IR (KBr, cm^{-1}) – 3509.94, 3358.49, 1648.03, 1435.67, 1382.81, 1234.42, 821.79, 739.40, ^{1}H-NMR ($CDCl_3$/DMSO-d^6) – δH 5.293(s, 1H, OH), δH 6.497-7.184 (m, 2H), δH 7.431-7.599 (m, 4H), δH 7.824 (d, 2H), δH 9.638 (s, 1H), ^{13}C-NMR- δC 110.82, 115.86, 118.69, 119.11, 126.92, 127.40, 130.67, 142.87, 156.98, 159.23. Mass Spectrum (m/z) - Calculated ($C_{13}H_{10}N_2O$)-210.23, Observed-211.0

RESULTS AND DISCUSSION: To optimize the reaction conditions, the one pot reaction of o-phenylenediamine and substituted benzaldehyde using MO seed as a catalyst at room temperature. The result is obtained in **Table 1** shows that amongst the different solvents investigated at room temperature. We have carried out reactions in different amounts of catalysts to synthesize benzimidazole. The yield of product is increased with an increase in the concentration of catalyst, and found that 10% mole of catalyst is sufficient, further increasing the amount of catalyst does not affect the percentage yield of product. Also, the microwave irradiation method provides an excellent yield of 10 % (W/V) of catalyst amount in **Table 2**. The optimization clearly suggested that the microwave oven's power was 40 % and conventional heating at room temperature in water solvent and the catalytic amount of 10 % (W/V) MO seed extract. In **Table 3**, MO seed extract is compared to other catalysts under the MW irradiation method.

MO seed extract acts as a biocatalyst for the synthesis of 2-substituted benzimidazole derivatives. The reaction of o-phenylenediamine and substituted benzaldehyde was investigated as the model technique under both conventional and microwave irradiation methods under the power of a microwave oven. This procedure generated a collection of functionalized imidazole with a high functional group level for electron-withdrawing and electron-donating groups. It was observed that electron-donating substituents of benzaldehyde increase the reaction time and decrease the reaction

rate while electron-withdrawing substituents of benzaldehyde decrease the reaction time and increase the reaction rate, as shown in **Table 4.** The reaction process is eco-friendly since no solvent is used in this procedure. It is observed that the use of the microwave irradiation method was a powerful technique and had a greater effect on the rise of the reaction rate, providing an excellent yield of product in a shorter reaction time. Compared with the microwave irradiation method, the conventional method shows a longer reaction time with a lower yield of the expected product.

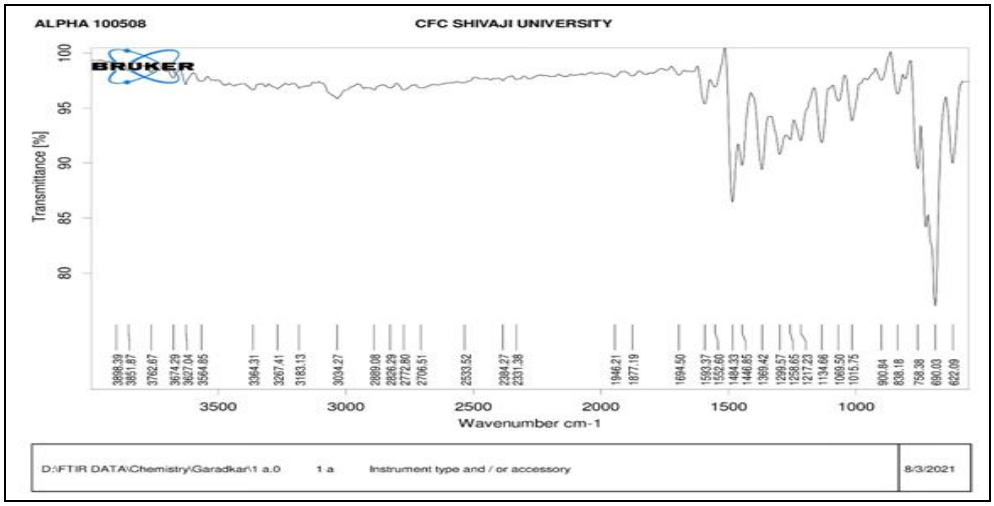


FIG. 1: FT-IR ANALYSIS OF 2-PHENYL-1H-BENZIMIDAZOLE (1A)

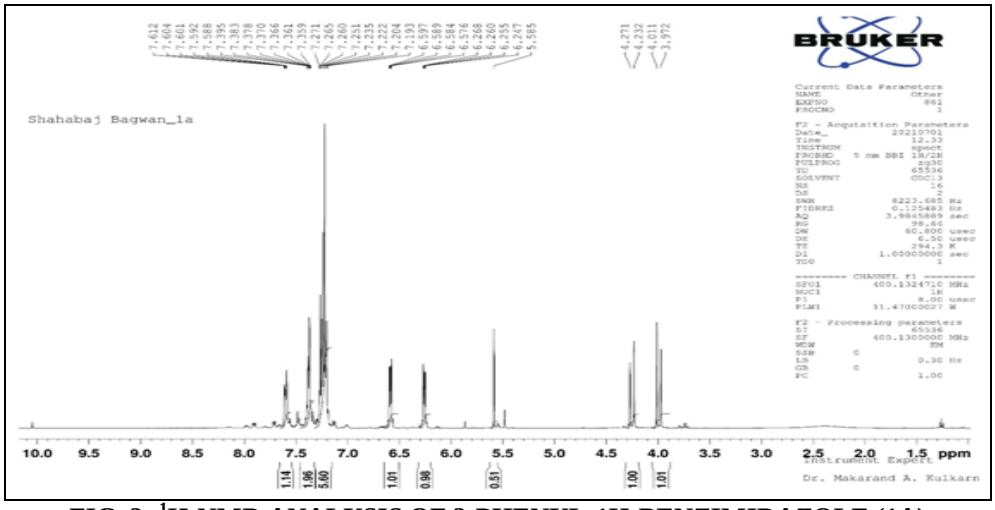


FIG. 2: ^{1}H-NMR ANALYSIS OF 2-PHENYL-1H-BENZIMIDAZOLE (1A)

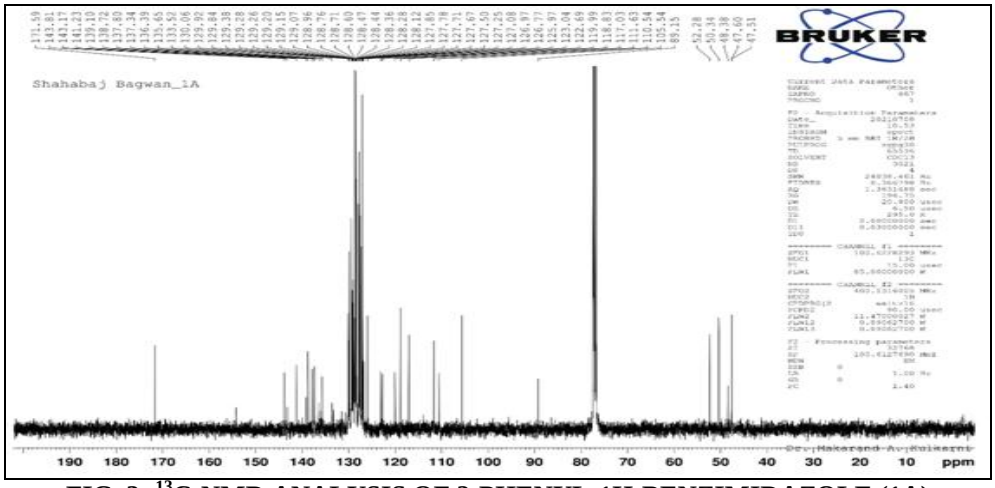


FIG. 3: ^{13}C-NMR ANALYSIS OF 2-PHENYL-1H-BENZIMIDAZOLE (1A)

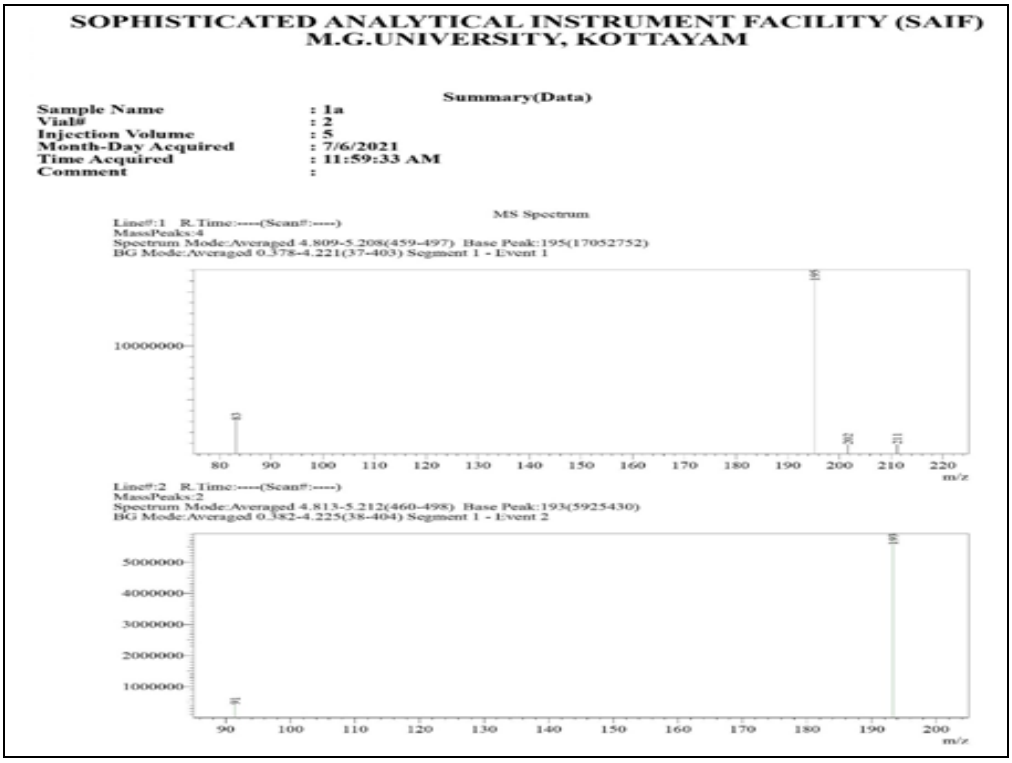


FIG. 4: MASS ANALYSIS OF 2-PHENYL-1H-BENZIMIDAZOLE

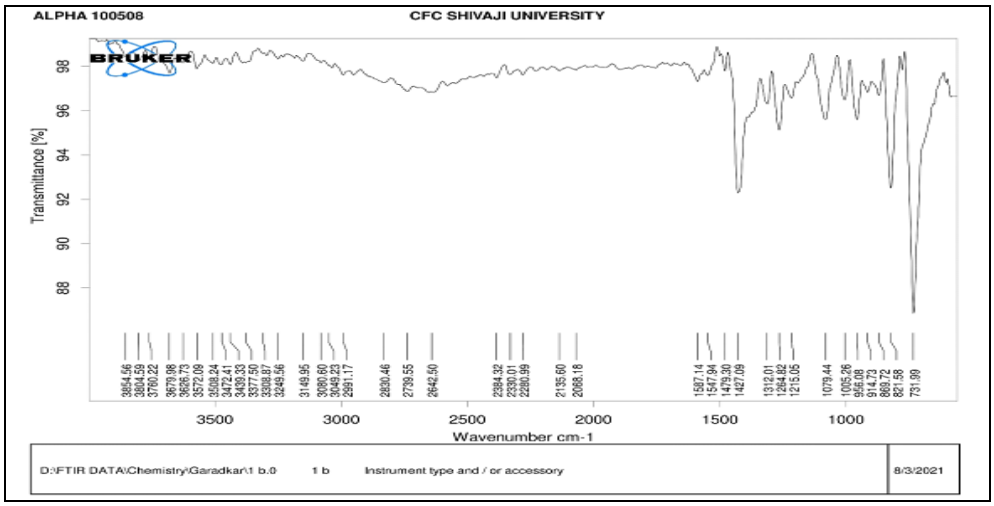


FIG. 5: FT-IR ANALYSIS OF 2-(4-CHLOROPHENYL)-1H-BENZIMIDAZOLE (1B)

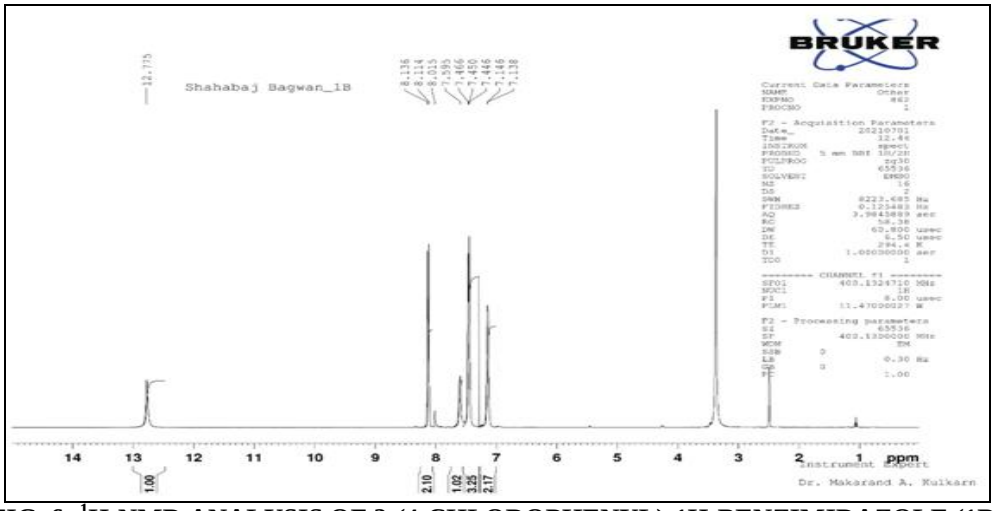


FIG. 6: ^{1}H-NMR ANALYSIS OF 2-(4-CHLOROPHENYL)-1H-BENZIMIDAZOLE (1B)

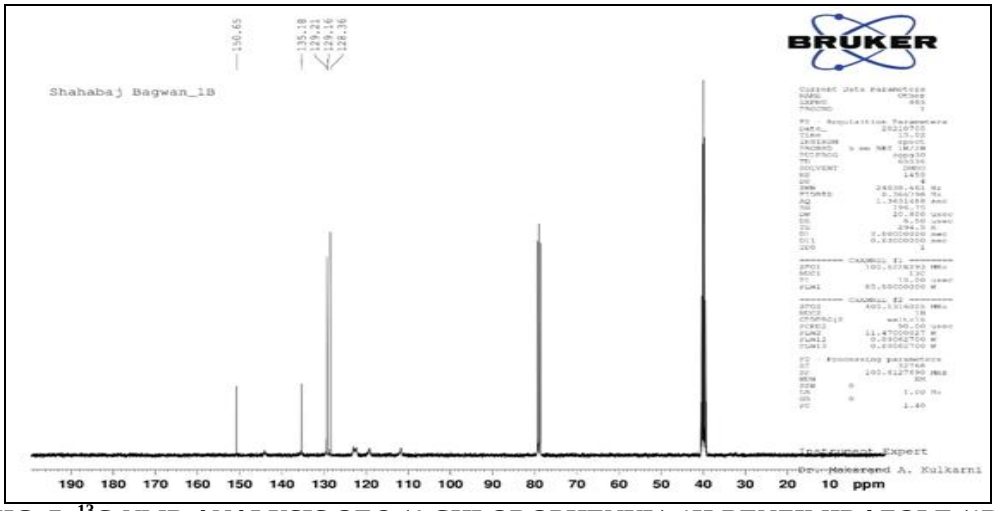


FIG. 7: ^{13}C-NMR ANALYSIS OF 2-(4-CHLOROPHENYL)-1H-BENZIMIDAZOLE (1B)

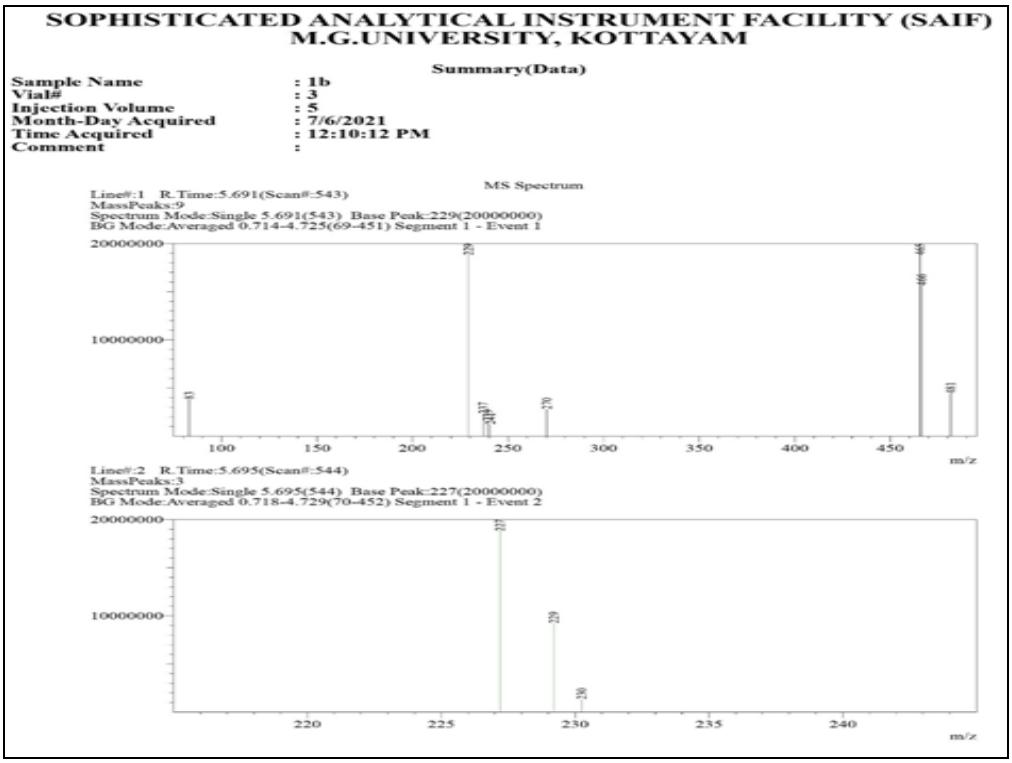


FIG. 8: MASS ANALYSIS OF 2-(4-CHLOROPHENYL)-1H-BENZIMIDAZOLE (1B)

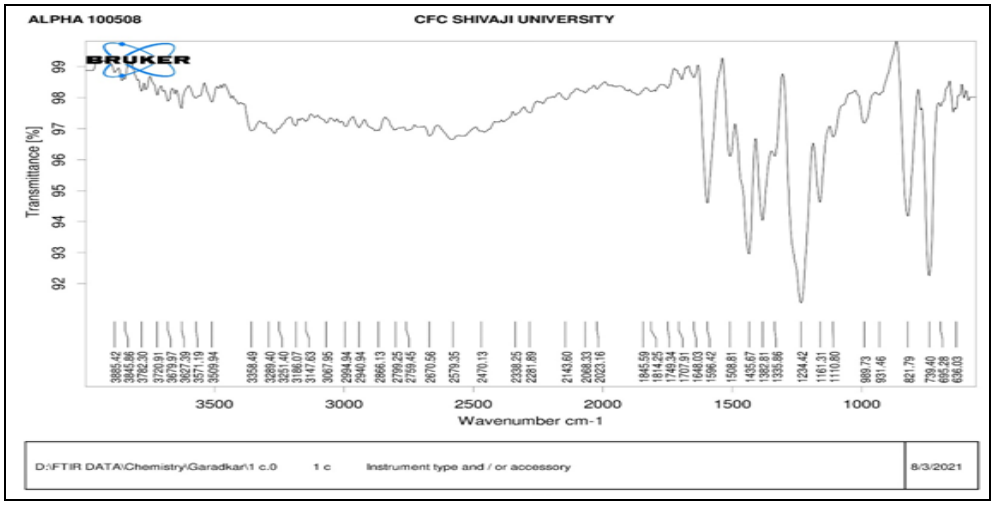


FIG. 9: FT-IR ANALYSIS OF 2-(4-HYDROXYPHENYL)-1H-BENZIMIDAZOLE (1C)

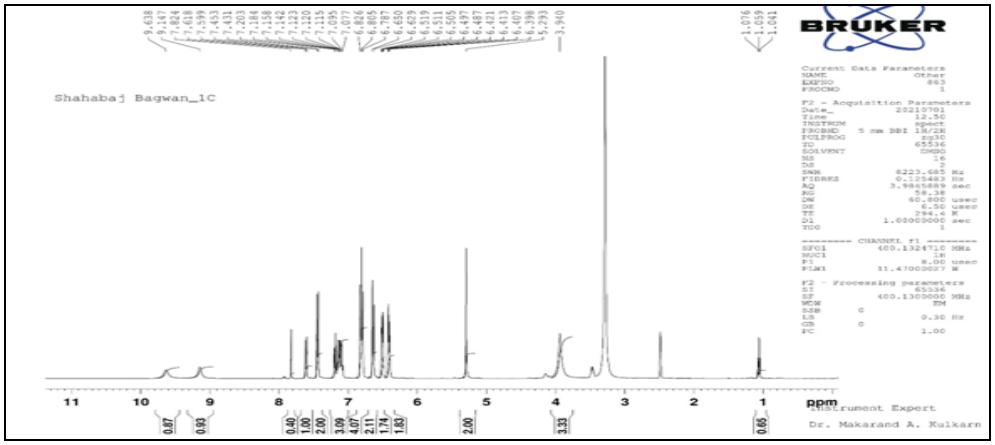


FIG. 10: 1H-NMR ANALYSIS OF 2-(4-HYDROXYPHENYL)-1H-BENZIMIDAZOLE (1C)

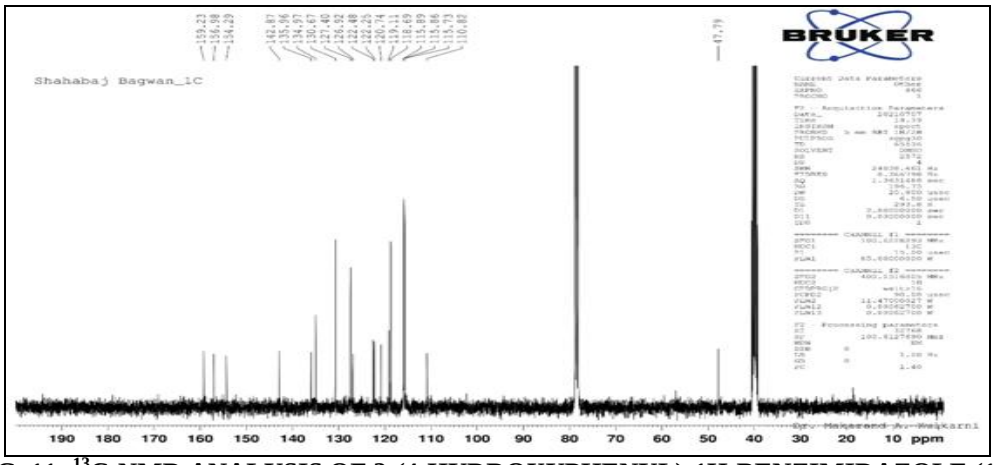


FIG. 11: ^{13}C-NMR ANALYSIS OF 2-(4-HYDROXYPHENYL)-1H-BENZIMIDAZOLE (1C)

TABLE 1: OPTIMIZED CONDITIONS FOR SYNTHESIS OF 2-SUBSTITUTED BENZIMIDAZOLE BY THE CONVENTIONAL METHOD

S. no.	Amount of catalyst	Solvents	Temp (°C)	Time (Min)	Yield
1	10	Chloroform	R.T.	60	46 %
2	10	Methanol	R.T.	60	47%
3	10	Acetonitrile	R.T.	60	39 %
4	10	Ethanol	R.T.	60	60%
5	10	Ethyl acetate	R.T.	60	61 %
6	10	Toluene	R.T.	60	56%
7	**10**	**Water**	**R.T.**	**30**	**80 %**
8	2.5	Water	R.T.	60	21%
9	5	Water	R.T.	60	39%
10	15	Water	R.T.	30	80%
11	20	Water	R.T.	30	80%
12	10	Water	60	60	80%
13	10	Water	80	60	80%
14	10	Water	100	60	82%

TABLE 2: OPTIMIZATION OF CATALYST FOR SYNTHESIS OF 2-SUBSTITUTED BENZIMIDAZOLE DERIVATIVES BY MICROWAVE IRRADIATION

S. no.	% mole of catalyst	Power of Microwave Irradiation (%)	% Yield
1	----	40	26 %
2	2.5 %	40	53 %
3	5 %	40	72 %
4	**10 %**	**40**	**96 %**
5	10 %	20	55 %
6	15 %	40	96 %
7	20 %	40	96 %

8	10 %	60	96 %
9	10 %	80	96 %
10	10 %	100	96 %

TABLE 3: COMPARISON OF *MORINGA OLEIFERA* WITH OTHER CATALYSTS FOR THE SYNTHESIS OF 2-SUBSTITUTED BENZIMIDAZOLE DERIVATIVES

S. no.	Catalyst [Ref]	% mole of catalyst	Temp. (°C)	Time (Min)	Yield (%)
1	PPA [59]	25 % mole	100-150	10	88
2	Alumina, Silica gel or Zeolite [60]	20 % mole	160-560	9	80
3	Aluminium-pillared interlayered clay [61]	15 % mole	200	2	85
4	$ZnCl_2$-SiO_2 [62]	20 % mole	100	5	90
5	HPF_6 [63]	10 % mole	115	5	90
6	$Cu(OH)_2$ [64]	10 % mole	100	480	98
7	**MO Extract [Present Work]**	**10 % mole**	**50**	**4**	**96**

TABLE 4: SYNTHESIS OF 2-SUBSTITUTED BENZIMIDAZOLE BY MORINGA OLEIFERA SEED CATALYZED REACTION OF O-PHENYLENEDIAMINE WITH SUBSTITUTED BENZALDEHYDE UNDER MICROWAVE IRRADIATION AND CONVENTIONAL CONDITIONS METHOD

Entry	R	Product	Conventional Method		Microwave Method		M.P
			Time (Min)	Yield (%)	Time (Min)	Yield (%)	
1a	H	2-Phenyl-1H-Benzimidazole	30	80	4	96	288-289°C
1b	4-Cl	2-(4-Chlorophenyl)-1H-Benzimidazole	35	73	4	95	281-282°C
1c	4-OH	2-(4-Hydroxyphenyl)-1H-Benzimidazole	38	71	5	93	229-230°C
1d	4-NO_2	2-(4-Nitrophenyl)-1H-Benzimidazole	30	77	3	96	309-310°C
1e	2-Cl	2-(2-Chlorophenyl)-1H-Benzimidazole	35	73	4	95	227-228°C
1f	3-NO_2	2-(3-Nitrophenyl)-1H-Benzimidazole	34	78	3	95	185-186°C
1g	2-OH	2-(2-Hydroxyphenyl)-1H-Benzimidazole	39	72	5	92	241-242°C
1h	P-OCH_3	2-(4-Methoxyphenyl)-1H-Benzimidazole	40	70	5	90	230-231°C
1i	Furfural	2-(Furfural-2-yl)-1H-Benzimidazole	38	71	4	92	296-297°C
1j	Cinnamal-dehyde	2-(3-Phenylprop-2-ene)-1H-Benzimidazole	37	72	4	93	200-201°C

CONCLUSION: We have developed a facile, one-pot and efficient protocol for synthesizing 2-substituted benzimidazole derivatives from the condensation of o-phenylenediamine and substituted benzaldehyde using inexpensive and non-toxic MO seed as a catalyst in both conventional and microwave irradiation conditions. It was found that the microwave irradiation method is an excellent method as compared to the conventional method. The noticeable aspects of the present report are the fast rate of reaction, mild reaction condition, high to the excellent yield of product and environmentally ecofriendly.

ACKNOWLEDGEMENT: We are thankful to Dr. Mazahar Farooqui, Principal, Maulana Azad College, Aurangabad. We are also thankful to Dr. Arif Pathan, in Incharge of Maulana Azad Research Center, Aurangabad, for his constant support, encouragement, and guidance in providing laboratory facilities for conducting the research work.

CONFLICTS OF INTEREST: The authors declare no conflict of interest.

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How to cite this article:
Bagwan SM and Asif M: *Moringa oleifera* (MO) seed catalyzed synthesis of benzimidazole derivatives. Int J Pharm Sci & Res 2022; 13(9): 3550-60. doi: 10.13040/IJPSR.0975-8232.13(9).3550-60.