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Synthesis, characterization and potent antimicrobial and antifungal activity of 2-substituted benzimidazole derivatives

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Benzimidazole is the heterocyclic compound formed by the fusion of benzene and imidazole ring. Benzimidazole analogs are of great significance because of their clinical application and biological activity. Benzimidazoles are considered as an optimistic class of bioactive heterocyclic compound that possesses a range of biological activities. We have synthesized five substituted Benzimidazole derivative using on both microwave irradiation and conventional heating method. The newly synthesized compounds are characterized by IR, NMR and Mass spectra analysis. In the present study, we have reported the synthesis, spectral studies and biological evaluation of some benzimidazole derivatives. Benzimidazole play important role in medical field with so many pharmacological activities such as antimicrobial, anti bacterial, *etc*. The potency of this clinically useful drug in treatment in microbial action and other activities has encouraged the development of some more potent and significant compounds.

Keywords: Benzimidazole synthesis, benzimidazole derivatives, antimicrobial activity, antifungal activity

Extensive survey of literature revealed that Benzimidazoles are very important intermediate/ subunits for the development of molecules of pharmaceutical or biological interest. Due to their wide range of pharmaceutical activity and synthetic application. Various methods were reported for the synthesis of benzimidazole derivatives by using different variety of starting materials[1–3]. Among these methods one is the coupling of O-Phenylenediamine and Carboxylic acid[4,5] or their derivative (Nitriles or orthoesters)[2] which often requires acidic condition and sometimes combines with high temperature or condensation of O-Phenylenediamine and Aldehydes, various oxidative and catalytic reagent such as microwave irradiations[6]. The other involve a two step procedure that includes the oxidative cyclohydrogenation of Schiff base which are often generated from the Sulfamic acid[7], I_2[8], Air [9], Oxane[10] has been employed.

Experimental Section

Materials and Methods

Chemical and Solvent used for this work were obtained from Merk and Sigma, used without further purification. Melting Points were determined in open capilaries in an electrically heated block are uncorrected.The purity of compound was checked by TLC and spots were visualized by exposure to an atmosphere of the Iodine vapours. Silica gel plates were used for all compounds. The elemental analysis of the samples were done at CDRI Lucknow. IR Spectra were recorded on Perkin –Elmer 1430 spectrophotometer using KBr pellets and ^{1}H NMR and ^{13}C NMR spectra obtained on Bruker F 200 MHz NMR Spectrometer in $CHCl_3$, CD_3OD and DMSO-d_6 using TMS as an internal standard. Mass Spectra were recorded on a Va 70-70H Spectrometer at 70 eV. IR, Mass and ^{1}H NMR Studies were performed at IIT Kanpur Microbial studies on the synthesized compounds were done at the Department of Microbiology, Bundelkhand University, Jhansi (U.P).

General procedure for the synthesis of 2-substituted benzimidazole

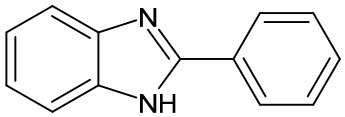
o-Phenylenediamine (1 mole) and aldehyde derivative (1 mole) was well stirred with $BF_3.OEt_2$ (7 mL) at RT for 30 minute. To this reaction mixture

CH_2Cl_2 (25mL) was added and washed with water and then with brine. The organic phase was separated dried (Na_2SO_4) and concentrated in vaccum to get the crude compound. On completion the reaction, the reaction mixture was cooled and poured on to crush ice. The crude compound was purified by silica gel chromatography using CH_2Cl_2: MeOH (99: 1) as eluent.

Results and Discussion

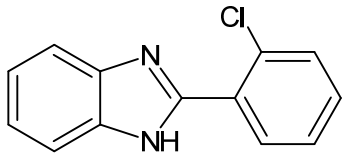
Physical Properties: The analytical data and the physical properties of the different types of synthesized compounds of Benzimidazole derivatives. The purity of synthesized compound was checked by TLC and Melting Points. The physicochemical data of all synthesized compound was represented in Table I.

Spectroscopic Data



2-Phenyl-1*H*-benzimidazole

Molecular weight 194.23588 (calculated) 194.2319 (Found), Melting Point 289-291°C. Yield 90 %, C 80.3883(calc) 80.3899 (found), H 5.1892 (calc) 5.1893 (found), N 14.4224 (calc) 14.4226 (found), IR Spectra 3382 (N-H Stretching), 3062.57 (Ar-CH Streching), 1697.78 (Ar-C-N Streching), 1458.61 (C=C Streching), 1392.89 (C-H Streching) 745.38 (Aromatic), 697.01 (Alkene) cm^{-1}; ^1H NMR (200 MHz, $CHCl_3$) δ ppm (J,Hz): 7.95(s,1H), 7.25-7.35 (m, 2H), 7.05(m,5H) in Table I, Table II and Table III.



2-[2-Chlorophenyl]benzimidazole

Molecular weight 229.0471 (calculated) 228.68 (Found), Melting Point 291-293℃, Yield 88.9 %, C 68.0893 (calc) 68.2801 (found), H 4.2362 (calc) 4.2481 (found), N 12.2158 (calc) 12.2500

Table I — Analytical data and physical properties of synthesized compounds

Compd	Elemental Analysis Calculated (Found)					Molecular Weight	Yield (%)	M.P. (°C)	Time (min)	Rf Value
	C	H	N	O	Cl					
$C_{13}H_{10}N_2$	80.3883 (80.3899)	5.1892 (5.1893)	14.4224 (14.4226)	-	-	194.23588 (194.2319)	90 %	289-291	30	0.68
$C_{13}H_9ClN_2$	68.0893 (68.2801)	4.2362 (4.2481)	12.2158 (12.2500)	-	15.4617 (15.5050)	229.0471 (228.68)	88.9 %	291-293	45	0.40
$C_{13}H_9ClN_2$	68.0893 (68.1068)	4.2362 (3.9292)	12.2158 (12.2243)	-	15.4617 (15.4986)	229.3208 (229.0517)	89 %	289-291	90	0.40
$C_{14}H_{12}ON_2$	74.9809 (74.9850)	5.3933 (5.3936)	12.4913 (12.4920)	7.1342 (7.1346)	-	224.26216 (224.0938)	90 %	199-201	45	0.35
$C_{15}H_{12}N_2$	81.7918 (81.4100)	5.4905 (5.8796)	12.7176 (12.6637)	-	-	220.27248 (221.1030)	96%	280-282	30	0.52

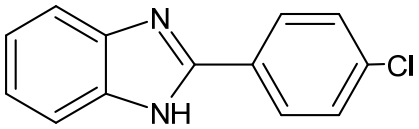
Table II — IR Spectral Data of Compounds

Synthesized Compd	N-H Streching cm^{-1}	Ar-CH Streching cm^{-1}	Ar-C-N Streching cm^{-1}	C=C Streching cm^{-1}	C-H Streching cm^{-1}	O-C stretching cm^{-1}	Aromatic cm^{-1}	Alkene cm^{-1}
2-Phenyl 1-H Benzimidazole	3382.00	3062.57	1697.78	1458.61	1392.89	-	745.38	697.01
2-[2-Chloro Phenyl] Benzimidazole	-	3063.15	1593.67	1443.96	1396.98	-	747.30	681.78
2-[4-Chloro Phenyl] Benzimidazole	3343.16	3054.67	1598.50	1456.29	1383.39	-	743.51	688.87
2-[4-Methox Phenyl] Benzimidazole	3359.65	3057.67	1608.89	1458.61	1391.32	1027.59	748.64	691.96
2-[1-Ethyene - 2- Phenyl] Benzimidazole	3346.18	3059.22	1697.09	1451.33	1393.21	-	744.02	698.99

Table III — ^{1}HMR data of compounds

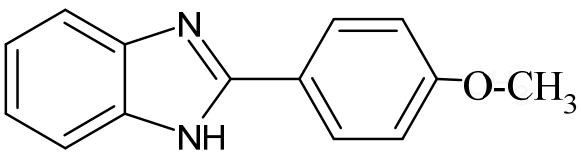
S.No.	Compd	δ Value of 200 MHz $CHCl_3$ δ ppm	Nature of Ligand
1	2-Phenyl 1-H Benzimidazole	7.95	s, 1H NH
		7.25-7.35	m, 2H C2-H, C6-H
		7.05	m, 5H C4-H, C7-H, C3-H, C4-H, C5-H
2	2-[2-Chloro Phenyl] Benzimidazole	12.5	s, 1H NH,
		8.20	d, 2H
		7.30	m, 2H C4-H, C7-H
		7.10	m, 2H C5-H, C6-H
3	2-[4-Chloro Phenyl] Benzimidazole	3.9104	s, 1H NH,
		0.8386	d, 2H
		2.8754	m, 2H C4-H, C7-H
		2.6303	m, 2H C5-H, C6-H
4	2-[4-Methox Phenyl] Benzimidazole	7.2012	s, 1H NH,
		4.9442-4.5994	d, 2H
		6.2787	m, 2H C4-H, C7-H
5	2-[1-Ethylene -2- Phenyl] Benzimidazole	0.1252	s, 1H NH,
		1.0405	d, 2H
		0.2338	m, 2H C4-H, C7-H

(found), IR Spectra 3063.15 (Ar-CH Streching), 1593.67 (Ar-C-N Streching), 1443.96 (C=C Streching), 1396.98 (C-H Streching), 747.30 (Aromatic), 681.78 (Alkene) cm^{-1} ; ^{1}H NMR (200 MHz,$CHCl_3$) δ ppm (J, Hz): 12.5 (s, 1H), 8.20 (d, 2H), 7.3 (m,2H), 7.10 (m,2H) in Table I, Table II and Table III.



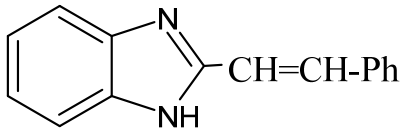
2-[4-Chlorophenyl]benzimidazole

Molecular weight 229.3208 (calculated) 229.0517 (Found), Melting Point 289-291°C, Yield 89 %, C 68.0893 (calc) 68.1068 (found), H 4.2362 (calc) 3.9292 (found), N 12.2158 (calc) 12.2243 (found), IR Spectra 3343.16 (N-H stretching) 3054.67 (Ar-CH Streching), 1598.50 (Ar-C-N Streching), 1456.29 (C=C Streching), 1383.39 (C-H Streching), 743.51 (Aromatic), 688.87 (Alkene) cm^{-1}; ^{1}H NMR (200 MHz, $CHCl_3$) δ ppm (J,Hz): 3.9104 (s,1H), 0.8386 (d, 2H), 2.8754 (m,2H), 2.6303 (m,2H) in Table I, Table II and Table III.



2-[4-Methoxyphenyl]benzimidazole

Molecular weight 224.26216 (calculated) 224.0938 (Found), Melting Point 199-201°C, Yield 90 %, C 74.9809 (calc) 74.9850 (found), H 5.3933 (calc) 5.3936 (found), N 12.4913 (calc) 12.4920 (found) O 7.1342 (calc) 7.1346 (found), IR Spectra 3359.65 (N-Stretching) 3057.67 (Ar-CH Streching), 1608.89(Ar-C-N Streching), 1458.61(C=C Streching), 1391.32 (C-H Streching), 1027.59(O-C Streching), 748.64 (Aromatic), 691.96 (Alkene) cm^{-1} ; ^{1}H NMR (200 MHz,$CHCl_3$) δ ppm (J,Hz): 7.2012 (s,1H), 4.9442-4.5994 (d, 2H), 6.2787 (m,2H) in Table I, Table II and Table III.



2-[1-Ethyne-2-Phenyl]benzimidazole

Molecular weight 220.27248 (calculated) 221.1030 (Found), Melting Point 280-282°C. Yield 96%, C 81.79187 (calc) 81.4100 (found), H 5.4905 (calc) 5.8796 (found), N 12.7176 (calc) 12.6637 (found),

IR Spectra 3346.18 (N-H Stretching), 3059.22 (Ar-CH Streching), 1697.09 (Ar-C-N Streching), 1451.33 (C=C Streching), 1393.21 (C-H Streching), 744.02 (Aromatic), 698.99 (Alkene) cm^{-1} ; ^{1}H NMR (200 MHz, $CHCl_3$) δ ppm (J,Hz): 0.1252 (s,1H), 1.0405 (d, 2H), 0.2338 (m,2H) in Table I, Table II and Table III.

Table IV — Standard pathogenic micro organism with ATTC NO. (Americal Type Culture Collection)

S.No.	Microorganism	ATTC No.
1.	*Escherichia coli*	2109
2.	*Staphylococcus aureus*	2079

From the above data, it is confirmed that the synthesise compound is given below and the structure of the compound is 1-5.

Antimicrobial Activity

The antifungal activity of benzimidazole is due to its close relationship with structure of purines. The purines is one of the essential component of biological system. 5,6-dimethyl-1-(a-D-ribofuranosyl) benzimidazoleis integral part of structure of Vitamin B12. A fungal selective 14 a-demethylase inhibitor is expected to act as an antifungal agents.

The newly synthesized compounds were screened for their antibacterial and anti fungal screening using filter paper disc method[11,12].

The antibacterial activity of test compound were evaluated against Gram –Positive bacteria *Staphylococcus aureus* and Gram- Negative bacteria, *Escherichia coli.*

Antifungal activity was screened against fungal strain, *Candida albicans*.

The antimicrobial activity was performed by filter paper disc method at concentration 100µg/mL. Mueller Hinton Agar (MHA) and Potato Dextrose Agar (PDA) were employed as culture medium and DMSO was used as solvent control for antimicrobial activity, investigated by Kirby-Bauer method reported by Prescott *et al*.[13] Ampicillin and Amphotericin B were used as standard for antibacterial and anti fungal activities respectively.

The Potato Dextrose Agar (PDA) media was taken in 1000 mL beaker and made up the volume to 1000 mL with water then the media was sterilized by autoclaving at 121°C for 15 min at 15-16 psi pressure. The media removed and cooled at 40-45°C. Whatmann filter paper -1 disc (6mm) was sterilized by dry heat were saturated with test solution and placed on (PDA) media in petri dish in triplicate. The petri dish were covered and aside for an hour and then incubated at 37°C for 48 hours. The zones of inhibition were measured and the average of the three readings was calculated (Table IV and Table V).

Table V — Antibacterial and anti fungal activities of compound

S.No.	Compd	Gram – Positive bacteria *S. aureus*	Gram- Negative bacteria *E. coli*	Fungi Tested
1	2-Phenyl 1-H Benzimidazole	12.4 +0.4	11.9+0.4	NA
2	2-[2-Chloro Phenyl] Benzimidazole	12.9+0.5	11.8+0.3	NA
3	2-[4-Chloro Phenyl] Benzimidazole	13.8+0.3	13.4+0.6	NA
4	2-[4-Methox Phenyl] Benzimidazole	13.2+0.2	12.8+0.3	NA
5	2-[1-Ethyene -2-Phenyl] Benzimidazole	13.3+0.6	12.9+0.1	NA
6	Ampicillin	16.0+0.2	15.9+0.3	_
7	Amphotericin	_	_	14.0+0.1

Conclusion

All the newly synthesized benzimidazole derivatives were analysed with different spectral techniques and screened *in vitro* for their antibacterial acivity against both Gram –Positive bacteria *Staphylococcus aureus* and Gram- Negative bacteria, *Escherichia coli* and also subjected for the antifungal activity. The result of antimicrobial screening reveals all compounds exhibited good activity against all strain and no activity against *Canadida albicans.*

References

1 Grimmet M R, in *Heterocyclic Chemistry*, edited by Katritzy A R and Rees C W, 457 (1984).

2 Fairley T A, Tidwell R R, Donker I, Naiman N A, Ohemeng K A, Lombardy R J, Bentley J A & Cory M, *J Med Chem*, 36 (1993) 1746.

3 Czarrny A, Wilson W D & Boykin D W, *J Heterocycl Chem*, 33 (1996) 1393.

4 Raut C N, Mane R B, Bangul S M, Janroa R A & Mahulikar P P, *Arkivoc* xi, 10.5 (2009).

5 Javed K A & Chazi K A, *Oriental J Chem*, 34(4) (2018) 2131.

6 Hisano T, Ichikawa M, Tsumoto K & Tasaki M, *Chem Pharm Bull*, 30 (1982) 2996.

7 Reddy G V, Rao V R, Narsaiah B & Rao P S, *Synth Commun*, 32 (2002) 2467.

8 Chakrabarty M, Karmakar S, Mukherji A, Arima S & Harigaya Y, *Heterocycles*, 68 (2006) 967.

9 Zaineb M N, Elsyed A, Soliman, Somaia S, Abdel K, Megdy A, Elzahar Aladdin M, Srour, Madhava S S & Maher T J, *Acta Poloniac Pharmaceuticals Drug Research*, X638(4) (2011) 519.

10 Paneer Selvan T P P, Radhika S, Janagarag A & Kumar S, *Res Biotechnol*, 2(3) (2011) 56.

11 Ansari K F & Lal C, *Eur J Med Chem*, 44 (2009) 4028.

12 Sarker M, Nurnabi M & Islam M R, *World J Pharm Res*, 6(12) (2017) 1473.

13 Prescott L M, Harley J P & Klein D A, *Microbiology*, 6th edn (McGraw-Hill, Boston), 992 (2005)