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R E S E A E C H A R T I C L E

Synthesis of Some Novel Benz imidazole Derivatives & Evaluation of Their Antibacterial Activity

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A B S T R A C T

Benzimidazoles are heterocyclic compounds in which benzene is fused with five membered ring containing two hetero atoms. Both hetero atoms are nitrogen (N), which are present at non-adjacent position. It has broad spectrum of activity which are anti-ulcer, antitumor, antiviral and antibacterial agent and many more due to these biological effects it has drawn more interest in synthesis and derivatization of benzimidazole derivatives by modifying the antimicrobial activity. The benzimidazole moiety is a core structure we have focussed on the antibacterial and antimicrobial activity of the newly synthesized derivatives by suitable methods.

Key words: benzimidazole, hetero atom, anti-bacterial, anti-microbial.

A R T I C L E I N F O

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C O N T E N T S

1. Introduction

Benzimidazoles are heterocyclic compounds in which benzene is fused with five membered ring containing two hetero atoms[1]. Both hetero atoms are nitrogen (N), which are present at non-adjacent position. These are very important compounds due to their wide spectrum of biological activity such as anti-hypertensive, anti-viral, anti-fungal, antitumour, anti-helminthic, anti-microbial, anti-tumour , antiviral, antioxidant, antiulcer , ant amoebic and antihistaminic activity[2,5].

2. Materials and Methods

The novel benzimidazole derivatives were synthesized by using O-phenyl diamine and Formic acid. 2 parenteral novel benzimidazoles were prepared by using the chemicals:O-phenyl diamine + Formic acid and O-phenyl diamine + Thioglycolic acid. These parenteral benzimidazoles were named as NB-1a,NB-1b.The other 2 novel benzimidazoles were prepared by using the chemicals:Benzene sulfonyl chloride and Benzoyl chloride. These are often named as NB-2a and NB-2b.

Synthesis

Extensive survey of literature very few methods have been reported for the synthesise the benz imidazole derivatives by modifying anti-microbial activity[9-16]. Then need to synthesise and characterise the benz imidazole derivatives by various suitable methods.

Synthesis of Novel Benzimidazole (Nb -1)

O-Phenyl diamine (0.25mol) and Thioglycolic acid (0.34mol) was heated on a water bath at 100c for 7-8hrs. This completion of reaction was monitored by TLC. After completion of reaction, the reaction mixture was cooled and basified to a PH of 7-8 by using 10% NaOH solution. The crude benzimidazole was filtered at the pump, washed with cold water. The crude product was dissolved in 200 ml of boiling water and 2g of decolourizing carbon was added and digested for 15 min. The solution was filtered while hot, cooled the filtrate about 10C . The pure product was filtered, washed with 25 ml of cold water and dried at 100C.

Synthesis of 2-mercapto methyl 1H-benzimidazole -1-yl methanone (NB-1a):

To a solution of NB-1 (0.05mol) and anhydrous potassium carbonate (0.04mol) in acetone (25ml), benzoylchloride (0.05mol) was added slowly. The mixture was refluxed for about 14hrs.the mixture was then poured on to water and extracted with ethylacetate, dried over sodium sulphateanhydrous and concentrated under vacuum to give the pure product.

Synthesis of 2-mercapto methyl-1-benzene-sulfonyl-2-benzimidazole(NB -1b):

To a solution of NB1 (0.05mol) and anhydrous potassium carbonate (0.04mol) in acetone (25ml), benzenesulphonylchloride (0.05mol) was added slowly. The mixture was then stirred for about 12hrs.The mixture was then poured on to water and extracted with ethyl acetate, dried over sodium sulphate anhydrous and concentrated under vacuum to give the pure product.

Synthesis of Novel Benzimidazole (Nb-2)

O-Phenyl diamine (0.25mol) and formic acid (0.34mol) was heated on a water bath at100C for 7-8hrs.This completion of reaction was monitored by TLC. After completion of reaction, the reaction mixture was cooled and basified to a PH of 7-8 by using 10% NaOH solution. The crude benzimidazole was filtered at the pump, washed with cold water. The crude product was dissolved in 200 ml of boiling water and 2g of decolourizing carbon was added and digested for 15 min. The solution was filtered while hot, cooled the filtrate about 10C. The pure product was filtered, washed with 25 ml of cold water and dried at 100C.

Synthesis of 1H-benzimidazol-1-yl methenone(NB-2a):

To a solution of NB-2(0.05mol) and anhydrous potassium carbonate(0.04mol)in acetone(25ml),benzoylchloride(0.05mol)was added slowly.The mixture was refluxed for about14hrs.the mixture was then poured on to waterandextracted with ethyl acetate,dried over sodium sulphateanhydrous and concentrated under vacuum to give the pure product.

Synthesis of1- benzene sulfonyl-2-benzimidazole (NB -2b): To a solution of NB-2(0.05mol) and anhydrous potassium carbonate (0.04mol) in acetone (25ml), benzenesulphonylchloride (0.05mol) was added slowly. The mixture was then stirred for about 12hrs.The mixture was then poured on to water and extracted with ethyl acetate, dried over sodium sulphate anhydrous and concentrated under vacuum to give the pure product.

Evaluation of Antibacterial Activity

The antibacterial activity of synthesized compounds were screened in the concentration of 50, 100, and 150 µg in diethyl formamide against gram positive *S.aureus* and gram negative *E.coli*in Muller Hinton agar medium by cup - plate method. The antimicrobial activity was evaluated by measuring zone of inhibition in mm. the details of the procedure are given below.

Preparation of Muller Hinton Agar:

Composition

Beef extract	10.grams
Casein acid hydrolysis	17.5 grams
Starch	1.5 grams
Agar	20.0 grams
Distilled water	1000 ml

All the ingredients are taken in 1000 ml of distilled water in a conical flask and heated in a steam bath to dissolve. The pH was adjusted to 7 ± 0.2 and sterilized in autoclave at 15 lb at 120^0C for 15 minutes. The sterile medium was poured into Petri dish and allowed to solidify.

Preparation of the Disks:

Paper disks of 6 mm diameter and 2 mm thickness were sterilized by autoclaving at 121^0C for 15 minutes. Ciprofloxacin (10 µg/ disk) was used as standard antibiotic for the comparation of antibacterial activity of the synthesized compounds.

Preparation of Standard and Test Solution:

10 mg of ciprofloxacin is dissolved in water and made up to 100 ml. The above solution was used as stock solution. This contains 10 µg per ml of the standard drug. 5 mg of synthesized compounds was dissolved in 15 ml of DMF. From the above solution 2.5 ml was taken and made up to 5 ml. which gives a concentration of 500 µg/ml. 0.1 ml of the solution contains 50 µg of the sample transferred into cup in the Petri plate.

Evaluation of Antifungal Activity

Preparation of Sabouraud's Agar Media:

Composition

Dextrose	- 20 gms
Peptone	- 10 gms
Purified water	-1000 ml
pH	-5.4± 0.2
Agar	15 gm

The media was prepared by dissolving the specified quantities of the dehydrated ingredients (Hi-media) in purified water and was distributed in Petri dish to a thickness of 3-4 mm. The plates sterilized by autoclaving at 121^0C for 15 minutes. Each Petri plate contains Sabouraud's medium was inoculated with one microorganism culture by spreading the suspension of the organism with a sterile cotton.

Each plate was divided into five equal portions and in each portion a cup of 6 mm diameter was cut with a cork bores. Two cups were filled with 0.1 ml of the sample while other two were filled with 0.1 ml of standard drug. All the plates were kept in the refrigerator for 30 minutes to allow the diffusion of sample in to the surrounding agar medium. Petri dishes were incubated at 37^0C for 24 hrs. Diameters of zone of inhibition of each sample produced were measured. This was compared with zone of inhibition of standard drug, ciprofloxacin. The diameter of zone of inhibition was propositional to antibacterial activity of the sample.

3. Results and Discussions

According to scheme we have prepared novel benzimidazoles by using suitable reagents.Satisfactory yield were obtained from the reagents.The completion of the work was checked by thin layer chromatography, silica gel was used as stationary phase and chloroform: methanol was used as mobile phase. The iodine vapor was used as detecting agent. The compounds were purified by recrystallization with chloroform: petroleum ether mixture. The structures of the synthesized compounds were consistent with IR, spectra and mass spectroscopy.

Spectral Analysis

The synthesized compounds were characterized by various methods such as IR, and Mass spectroscopy.

Infra-Red Spectral Analysis:

The IR spectrum was recorded in JASCO FT-IR spectrophotometer. The significant IR values are measured in cm^{-1} and the results given in the table 2 & 3.

Mass Spectral Analysis:

Mass spectrum of the sample was recorded in JEOL GCmate by Electron impact method as ionization mode. The m/z values of the samples are given in the table 4&5.

Screening of Antimicrobial Activity:

The antibacterial activities of synthesized compounds were screened against both gram positive *S .aureus* and gram negative *E. coli* by agar cup-plate method using ciprofloxacin as standard drug. The results are given below.

Screening of Antifungal Activity:

The antifungal activities of synthesized compounds were screened against *Candida albicans* by agar cup-plate method using ketaconazole as standard drug.

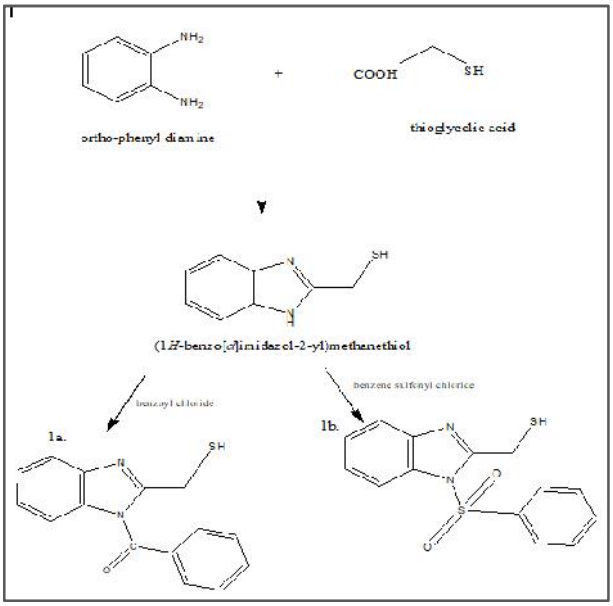


Fig 1: Scheme-1

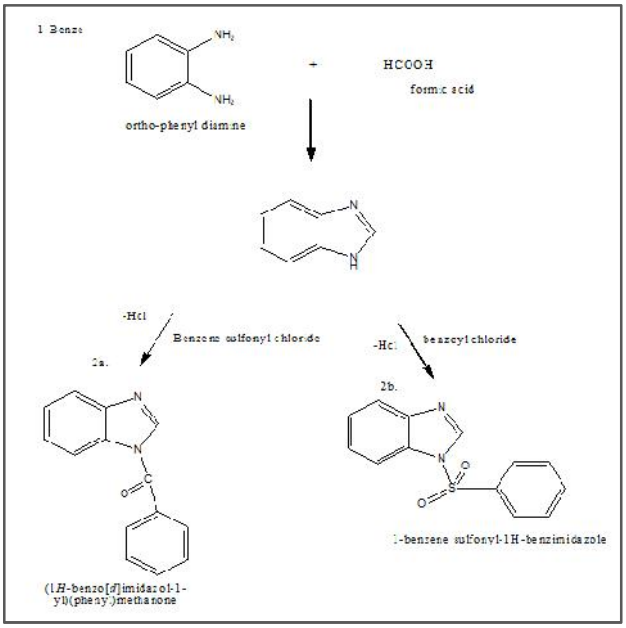


Fig 2: Scheme-II

Table 1: Physical Data of the synthesized Compounds

S. No	Product name	Molecular Formula	Molecular Weight	Physical State	M.P(^{0}C)	Yield(%)
1	NB 1a	$C_{15}H_{12}N_2OS$	268.33	Solid brown colour	80.2	74.2%
2	NB 1b	$C_{14}H_{12}N_2O_2S_2$	304.39	Solid light brown colour	82.2	76.4%
3	NB 2a	$C_{13}H_{10}N_2O_2S$	258.3	Solid dark brown colour	81.2	78.5%
4	NB 2b	$C_{14}H_{10}N_2O$	222.4	Solid Broun colour	82.3	79.4%

Table 2: Interpretation of IR spectrum of NB 1

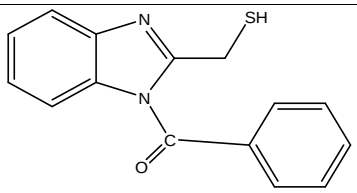
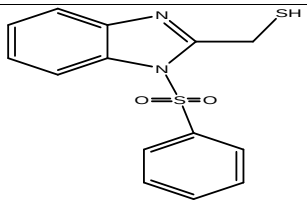
NB 1a		**NB 1b**	
			
Wave number(cm^{-1})	**Functional groups**	**Wave number**	**Functional groups**
1447	(C=C) str	3268	(S=O) str
3061	(Ar-C-H) str	1553	(C=N) str
2858	(Aromatic C=O) str	1488	(C=C) str
1770	(C=O) str	1271	(C-N) str
1589	(C=N) str	3062	(Ar-C-H) str

Table 3: Interpretation of IR spectrum of NB 2

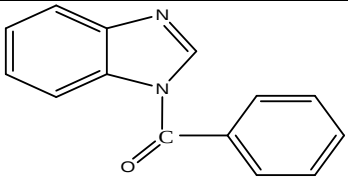
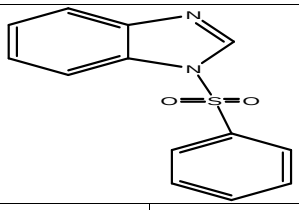
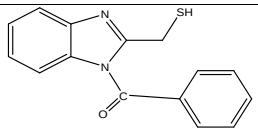
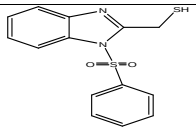
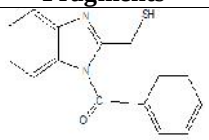
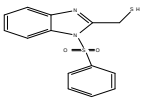
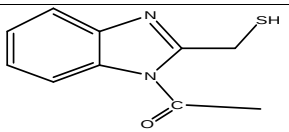
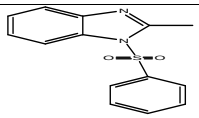
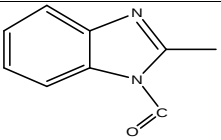
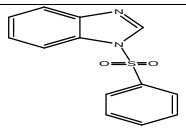
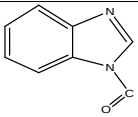
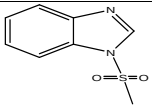
NB 2a		**NB 2b**	
			
Wave number (cm^{-1})	**Functional groups**	**Wave number**	**Functional groups**
3420	(S=O) str	1770	(C=O) str
1254	(C-N) str	1477	(C=C) str
1477	(C=C) str	1245	(C-N) str
1586	(C=N) str	1589	(C=N) str
3064	(Ar C-H) str	3061	(Ar C-H) str

Table 4: Interpretation of Mass Spectral analysis of NB 1

NB 1a		**NB 1b**	
			
m/z	**Fragments**	**m/z**	**Fragments**
268.35		304.39	
203.6614		270.2	
160.755		257.4	
145.77		193.45	

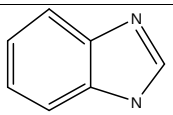
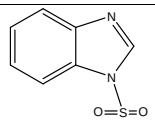
105.78		180.18	

Table 5: Interpretation of Mass Spectral analysis of NB 2

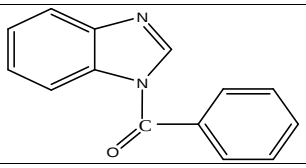
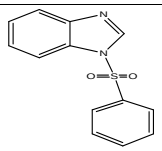
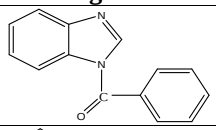
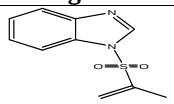
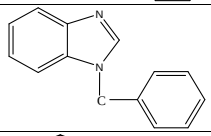
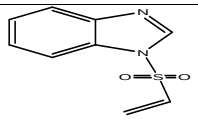
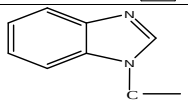
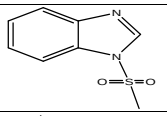
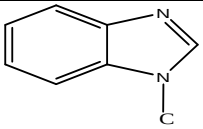
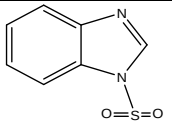
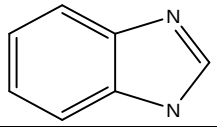
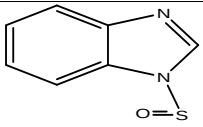
NB 2a		**NB 2b**	
			
m/z	**Fragments**	**m/z**	**Fragments**
250.30		218.8	
230.37		207.2	
171.49		194.2	
141.41		185.2	
109.51		164.2	

Table 6: Results of Antibacterial Activity

S. No	**Compounds**	**Zone of Inhibition (in mm)**					
		S.aureus			***E.coli***		
		50 µg	**100 µg**	**150 µg**	**50 µg**	**100 µg**	**150 µg**
1	**NB-1a**	20	25	32	19	23	27
2	**NB-1b**	21	23	30	20	21	27
3	**NB-2a**	21	23	31	21	20	29
4	**NB-2b**	23	26	33	20	24	31
	Ciprofloxacin (50 µg)		42			40	

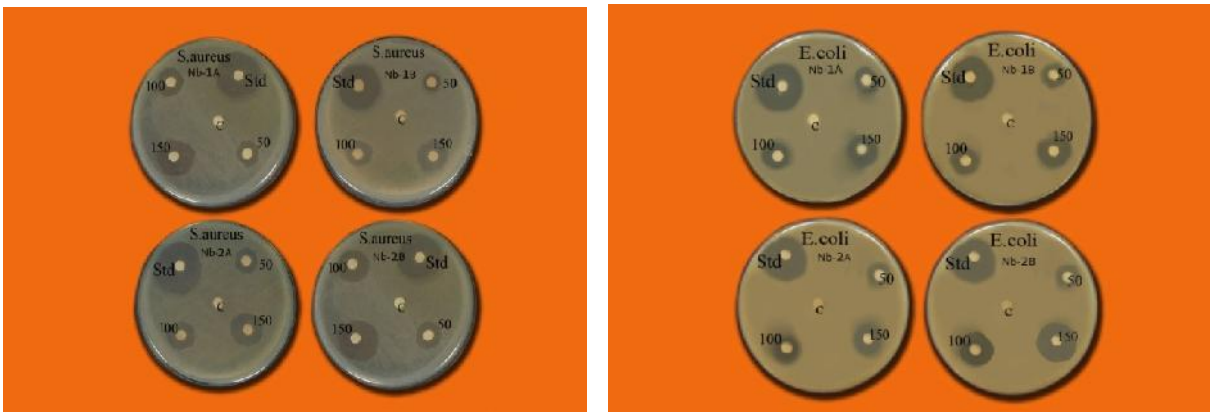


Fig 3: Results for anti-microbial activity

Table 6: Results of Antifungal Activity

S.No	Compounds	Zone of Inhibition (in mm)		
		C.albicans		
		50µg	**100 µg**	**150 µg**
1	**NB-1a**	22	27	33
2	**NB-1b**	23	26	31
3	**NB-2a**	22	25	29
4	**NB-2b**	25	28	34
5	**ketoconazole 50 µg**		44	

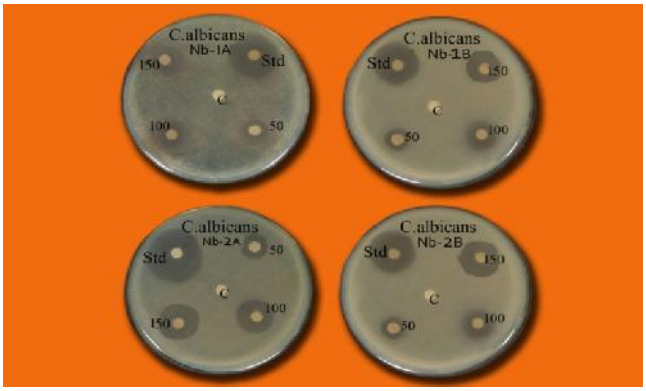


Fig 4: Results for antifungal activity

4. Conclusion

The synthesized compounds shown significant activity against bacteria and fungal organisms. Few compounds (i.e.) NB-1a, NB2-b shown better activity than the other compounds. Further research is needed on these novel benzimidazoles and the substituted novel benzimidazoles to justify the antimicrobial activity of the modified benzimidazoles.

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