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Research Article

SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL BENZIMIDAZOLE DERIVATIVES

A. Viswanath*, B. Keerthana, G. HimaBindu, B. Sudha Rani and P. Srinivasa Babu

Vignan pharmacy college, Vadlamudi, Guntur, Andhra Pradesh-522 213, India.

ABSTRACT

Benzimidazoles are replaced with a variety of pharmacological activities like anti-hypertensive, anti-tumor, anti-helmintic along with anti-microbial activity. In this we synthesize various benzimidazole derivatives with the substitution of second position. Ortho phenylenediamine is treated with different substituted aromatic aldehydes in the presence of p-toluene sulphonic acid catalyst. P-TsOHwas used to be a catalyst for the synthesis of 2-arylsubstituted benzimidazoles efficiently. Simple and convenient procedure, easy purification and shorter reaction time are the advantageous features of this method. These synthesized compounds showed significant activity against Gram +ve& Gram-ve Bacteria.

Keywords: Benzimidazole derivatives,o-phenylenediamine-toluene sulphonic acid.

INTRODUCTION

In present days anti bacterial and antifungal diseases are very common in the world. Currently used antimicrobial agents are not effective due to the resistance developed by the microbes and therefore it is an ongoing effort to synthesize new antimicrobial agents.

From the literature that the benzimidazole functions are quite stable, and have inspired chemists to utilize these stable fragments in bioactive moieties to synthesize new compounds possessing biological activities like antimicrobial, anti inflammatory, anthelmintic, anti diabetic, anti tumor, antiprotozoal, anti amoebic, anti leukemic.

While many strategies are available for benzimidazole synthesis, there are twogeneral methods for the synthesis of 2-substituted benzimidazoles. One is the coupling of phenylenediamine and carboxylic acidsor their derivatives (nitriles, imidates, or orthoesters), which often requires strong acidic conditions, and sometimes combines with very high temperatures or microwave irradiation. The other way involves a two-step procedure that includes the oxidative cyclo-dehydrogenation of Schiff bases, which are often generated from the condensation of phenylenediamines and aldehydes. Various oxidative and catalytic reagentssuch as $FeCl_3 \cdot 6H_2O$, In $(OTf)_3$, Yb $(OTf)_3$, Sc $(OTf)_3$, $KHSO_4$, etc have been employed.Because of the availability of a vast number of aldehydes, the condensation of phenylenediamines and aldehydes has been extensively used. While many published methods are effective, some of these methods suffer from one or more disadvantages such as high reaction temperature, prolonged reaction time, and toxic solvents etc. Therefore, the discovery of mild and practicable routes for synthesis of 2-substituted benzimidazoles continues to attract the attention of researchers.So we tried to synthesize benzimidazoles using an organic catalyst p-toluene sulphonic acid. In this paper, *p*-TsOH was used for the synthesis of 2-arylsubstituted benzimidazoles by the condensation of aryl aldehydes with *o*-phenylenediamine and screen them for spectral studies and anti bacterial activity.

MATERIALS AND METHODS

S.No	Aldehydes used	Molecular formula
1	4-Chlorobenzaldehyde	$C_6H_5CHOCl_2$
2	3,4-Dihydroxy benzaldehyde	$C_6H_5CHO(OH)_2$
3	3,4,5-Tri methoxybenzaldehyde	$C_6H_5CHO(OCH_3)_3$

By using these aldehydes the compounds are synthesized. The purity of the compounds was checked by TLC using silica gel coated plates and spots were visualized by exposing the dry plates in iodine vapours or in UV cabinet.IR spectra (in

cm^{-1}) were recorded by using KBr technique. The1H NMR spectra of the compounds were carried out in Bruker AMX 400 MHz NMR instrument using DMSO-d6 as solvent.

Experimental section

Synthesis of compound-A

4-Chloro benzaldehyde (0.70g,1M) and *o*-phenylenediamine (0.54g,1M) were thoroughly mixed in ethanol(20ml), then *p*-TsOH (0.38g,1M) was added, and the solution was made to reflux for about 6-8hrs (monitored by TLC using 7:3v/v ethyl acetate and pet ether as eluents). When the reaction was finished the solvent was completely evaporated. Later by using ethyl acetate the compound was recrystallised.

Synthesis of compound-B

3,4-Dihydroxybenzaldehyde (0.69g,1.1M) and *o*-phenylenediamine (0.54g,1M) were thoroughly mixed in ethanol(20ml), then *p*-TsOH (0.38g,1M) was added, and the solution was made to refluxfor about 6-8hrs (monitored by TLC using 7:3v/v ethyl acetate and pet ether as eluents). When the reaction was finished the solvent was evaporated. Later by using isopropyl alcohol the compound was recrystallised.

Synthesis of compound-C

3,4,5-Trimethoxy benzaldehyde (0.68g,1.1M) and *o*-phenylenediamine (0.54g,1M) were thoroughly mixed in ethanol(20ml), then *p*-TsOH (0.38g,1mole) was added, and the solution was made to reflux for about 6-8 hrs (monitored by TLC using 1:1v/v ethyl acetate and pet ether as eluents). When the reaction was finished the solvent was completely evaporated. Later by using isopropyl alcohol the compound was recrystallised.

Spectral data of the synthesized derivative compounds

Compound-A

IR:3273 (N-H str); 1631 (C=N str); 1515-1381 (C-C str)

NMR:7.1-7.8(9H, Ar-CH); 8.3(1H, NH)

Compound-B

IR:1579(O-H str); 3384(N-H str); 2825(C=N str); 1384(C-O str)

NMR: 8.85-8.89(2H, OH); 6.3-7.6(7H, Ar-CH); 9.2(1H, NH)

Compound-C

IR:1537(OH-str); 3416 (NH-str); 1579(C=N str); 1417(C-O str)

NMR: 7.1-7.6(6H, Ar-CH); 12.84(1H, NH); 3.3-3.9(9H, OCH_3)

Antibacterial activity

Antibacterial screening was done by using disc diffusion method. Nutrient agar plates were prepared aseptically to get a thickness of 4-5 mm and plates were allowed solidify and inverted to prevent the condensate from falling on the agar surface. The inoculums were inoculated into agar plates and then discs were placed. The drug solutions were prepared using DMSO as a vehicle having conc. 500µg and 1000µg/disc was applied. DMSO solution was used as a control and Ciprofloxacin of 5µl/disc was used as standard. The Petri dishes were incubated at 37^0C for about 18-24hrs after placing them in the air flow chamber for uniform diffusion. The observation was made for the zone of inhibition around the discs. Four compounds synthesized were tested for antimicrobial activity.

RESULTS AND DISCUSSION

All the compounds were synthesized and undergone spectral analysis like IR and NMR and also screened for antibacterial activity. In the antibacterial activity the first two compounds show significant activity than that of third compound when compared to the standard.

Table 2: Characterisation of synthesized compounds

Name of the compound	Aldehydes used	Chemical name of the product	Mol. weight of the compound (gm/mole)	Amount of compound obtained (gm)	% yield of compound (m/m)	Melting point Range(ºC)	R_f values
Compound A	4-Chlorobenzaldehyde	2-(4-chlorophenyl)-1H-benzimidazole	228	0.90	78%	243-245	0.76
Compound B	3,4-Dihydroxy benzaldehyde	4-(1H-benzimidazole-2yl)benzene1,2-diol	225	0.59	52%	210-215	0.375
Compound C	3,4,5-Trimethoxy benzaldehyde	2-(3,4,5-trimethoxy)1H-benzimidazole	284	0.32	22%	223-226	0.72

IR spectral analysis of compounds

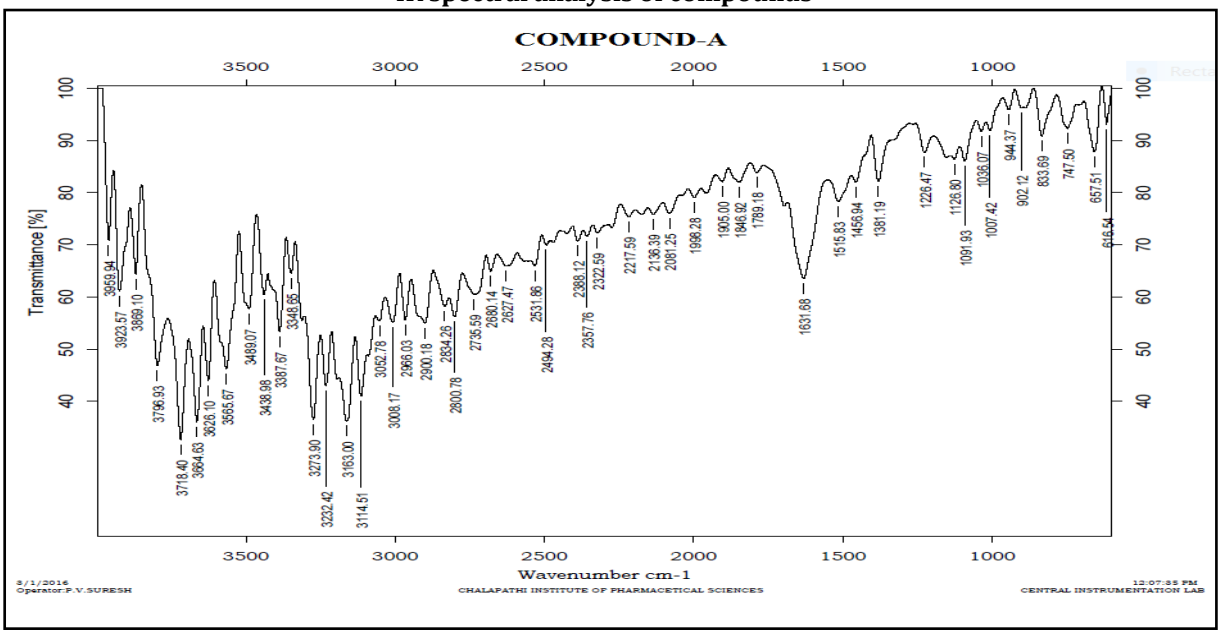

Fig. 1: IR spectrum of Compound-A

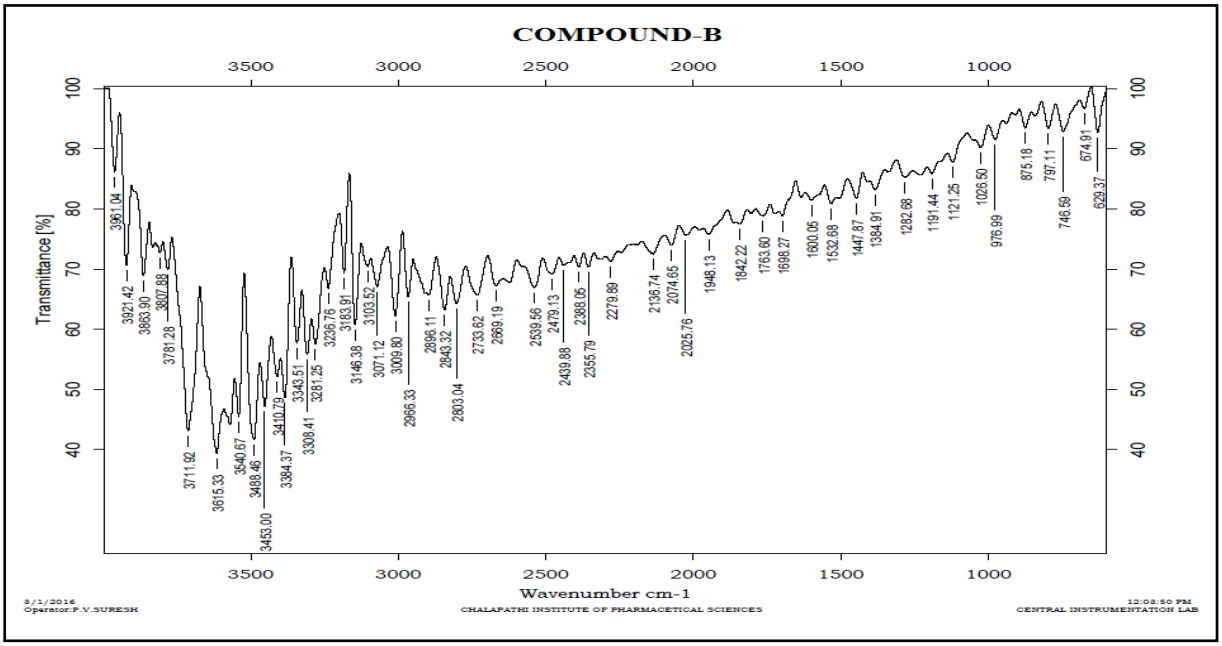

Fig. 2: IR spectrum of Compound-B

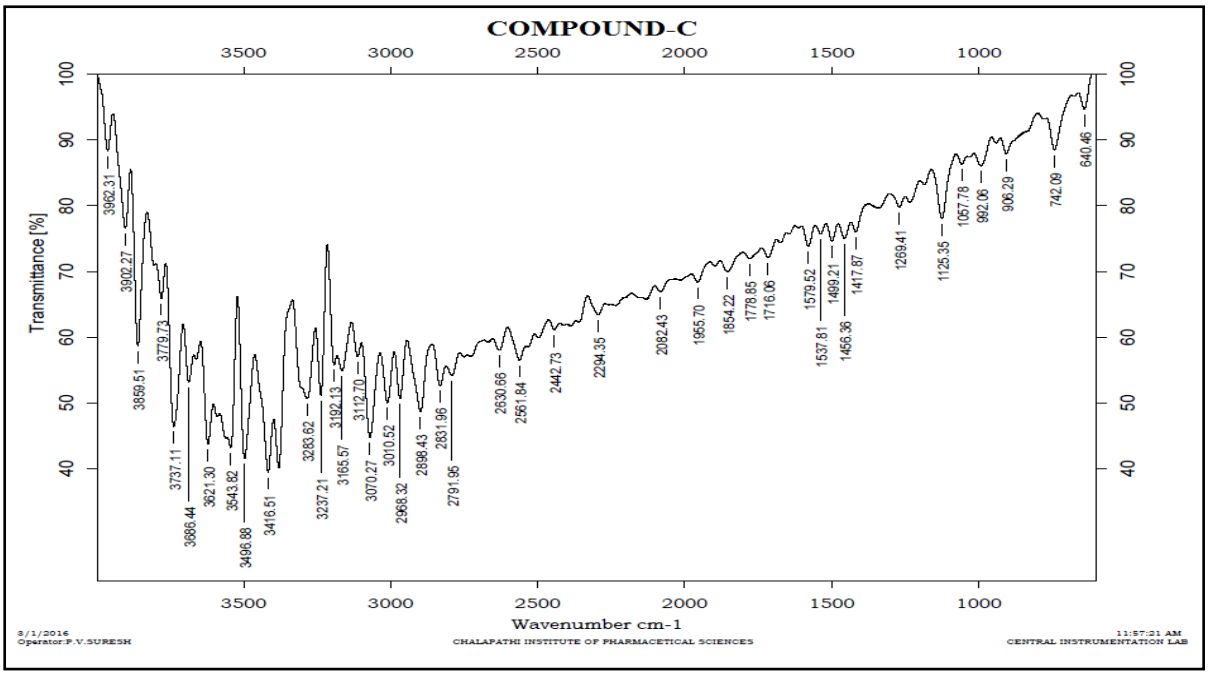

Fig. 3: IR spectrum of Compound-C

IR interpretation of synthesized compounds

Table 3: IR interpretation values of compound-A

S.No.	Type of stretching	Observed wave number values
1.	C=N stretch	1631cm^{-1}
2.	N-H stretch	3273 cm^{-1}
3.	C-C stretch	1381cm cm^{-1}

Table 4: IR interpretation values of compound-B

S.No.	Type of stretching	Observed wavenumber values
1.	O-H stretch	1579 cm^{-1}
2.	N-H stretch	3384 cm^{-1}
3.	C=N stretch	2825 cm^{-1}
4.	C-O stretch	1384 cm^{-1}
5.	C-C stretch	1532-1384 cm^{-1}

Table 5: IR interpretation values of compound-C

S.No.	Type of stretching	Observed wavenumber values
1.	C-O stretch	1417 cm^{-1}
2.	N-H stretch	3416 cm^{-1}
3.	C=N stretch	1579 cm^{-1}
4.	C-C stretch	1456-1537 cm^{-1}
5.	O-H stretch	1282-1447 cm^{-1}

NMR analysis of compounds

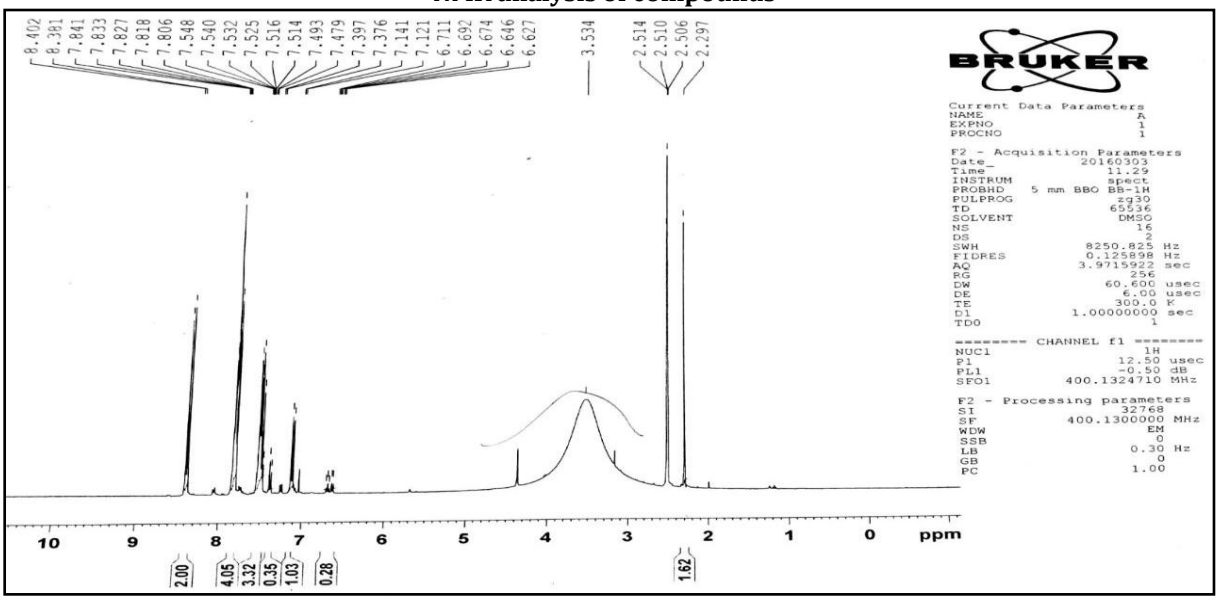

Fig. 4: NMR spectrum of compound-A

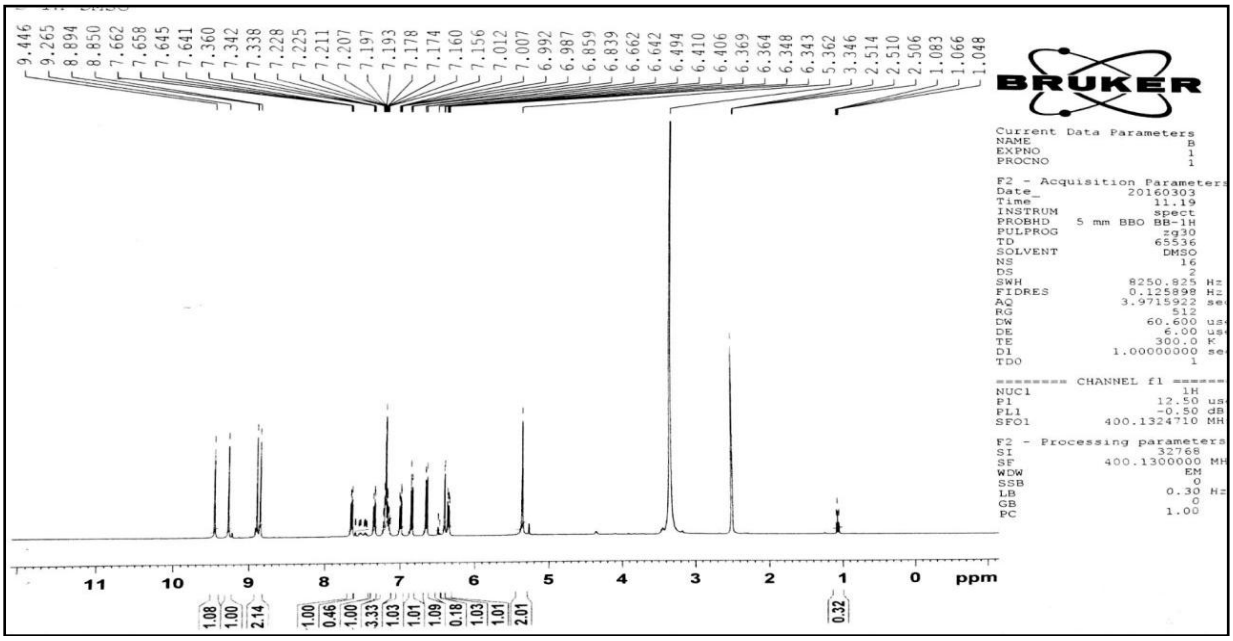

Fig. 5: NMR spectrum of compound-B

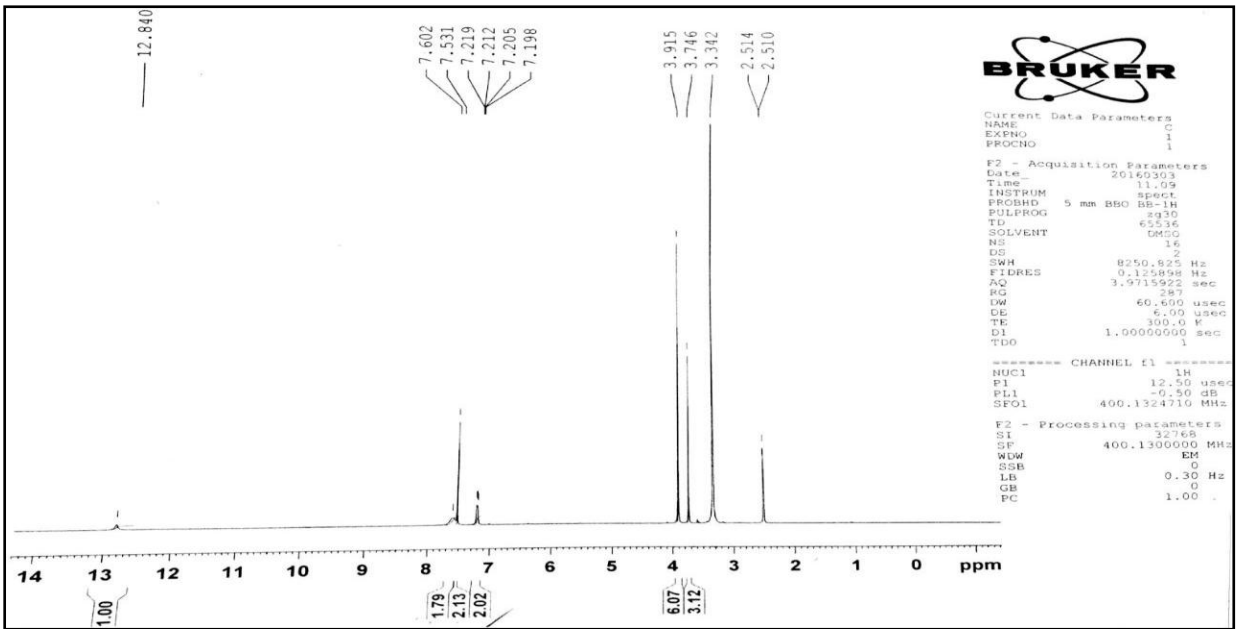

Fig. 6: NMR spectrum of Compound-C

NMR interpretation of synthesized compounds

Table. 6: NMR interpretation values of 2-(4-chlorophenyl) 1H-benzimidazole [compound-A]

S.No	Type of proton	No. of protons	Chemical Shift range
1.	Aromatic-C-H	8	7.40-7.80
2.	N-H	1	8.30-8.40

Table 7: NMR interpretation values of 4(1H-benzimidazol-2yl) benzene-1, 2-diol [compound-B]

S.No	Type of proton	No. of protons	Chemical Shift range
1.	Aromatic – CH	7	7.00-7.70
2	Phenolic-OH	2	8.85-8.89
3.	N-H	1	9.2

Table 8: NMR interpretation values of 4(1H-benzimidazol-2yl) benzene-1, 2-diol[compound-C]

Results of Antibacterial activity

S.No	Type of proton	No. of protons	Chemical Shift range
1.	Aromatic -CH	6	7.10-7.70
2.	N-H	1	12.840
3.	CH_3	9	3.40-3.95

Table 9: Zone of inhibition (in mm) obtained on bacteria

Compounds	Organisms							
	B.Subtilis		E.coli		K.pneumoniae		S.Aureus	
	500µg	1000 µg	500µg	1000µg	500µg	1000 µg	500µg	1000 µg
Compound-A	19	23	13	16	14	20	12	19
Compound-B	12	14	11	14	12	17	13	18
Compound-C	05	09	04	10	07	10	05	10
Control(DMSO solution)	-		-		-		-	
Standard(Ciprofloxacin)	33		32		37		32	

CONCLUSION

In our present work we synthesized substituent benzimidazoles by using new class of substituents i.e. aromatic aldehydes with PTSA catalyst. The synthesized compounds were characterized by spectral analysis i.e., IR and NMR and also these are tested for anti-bacterial activity and the compounds show significant activity.

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