© 2016 IJSRST | Volume 2 | Issue 4 | Print ISSN: 2395-6011 | Online ISSN: 2395-602X
Themed Section: Science and Technology

Microwave Assisted Synthesis, Characterization and Antibacterial Activity of 2- Chloromethyl Benz Imidazole Derivatives

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ABSTRACT

Objective-the objective of present research work to synthesize and screen novel 2-chloromethyl-1-h-benzimidazole derivative for antibacterial activity. Method-2-chloromethyl-1-H-benzimidazole was prepared by condensing 2-chloromethyl-1-h-benzimidazole with different aromatic amines and heterocyclic. The synthesized compounds were screened for their antibacterial activity against stap. Aurious by well plate method. 2-chioromethyl benzimidazole can be synthesized by the reaction of o-phenylenediamine with chloroaceticacid. This on reaction with substituted anilines in presence of ethanolic KOH gives corresponding benzimidazolederivatives. The synthesized compounds were characterized by TLC & IR data.

Keywords : 2-Chloromethyl Benzimidazole, O-Phenylenediamine, Chloroacetic Acid Aniline.

I. INTRODUCTION

In the field of science of technology, medicinal chemistry has been a fascinating subject. The rapid development in the last 7 decades has been truly a challenging and very exciting. Medical chemistry according to Burger, tries to be based on the ever inceasing hope that biochemical rationals for drug discovery may be found.

Medicinal chemistry is the branch of science, which has remarkable value for synthesis of novel drugs with intense therapeutic activity. It concern with discovery, development, identification and interpretation of mode of action of biologically active compounds at molecular level.

These developments have provided new challenges and opportunities for drug research in general and drug desings in particular. Pure organic compounds, natural or synthetic products are the chief source of agents for the cure, the mitigation or the prevention of disease today. The major objectives of the medicinal chemists are transformation of path biochemical and physiological data into a ‘chemical language’ with the aim of designing molecules interacting specifically with the derailed or degenerating processes in the diseased organisms.

The development of chemotherapy during past 60 years constitute one of most important therapeutic advances in history of medicine and antibacterial drugs are the greatest contribution of present century to therapeutics. Potential therapeutic targets are being disclosed with increasing frequency and the exponential growth will continue during the next decates.

A. Benzimidazole

The benzimidazole contain a phenyl ring fused to an imidazole ring,was shown in structure (1).

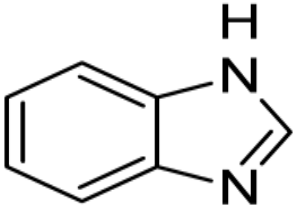

Figure 1. Benzimidazole

Compounds bearing Benz imidazole nucleus have been of great interest to synthetic and medicinal chemists for a long time due to their unique chemical and biological properties. Historically the first Benz imidazole was prepared in 1872 by Hoebrecker who obtained 2,5 or 2,6-dimethyl Benz imidazole by the reduction of 2-nitro-4-methylacetanilide. Several years later Ladenburg obtained the same compound by refluxing 3,4-diaminotoluene with acetic acid. The Benz imidazole are known also as Benz imidazole or benzoglyoxalines.Thus,Benz imidazole according to this nomenclature would be called methyl-o-phenylenediamine and 2-methyl Benz imidazole.

This tautomerism is analogous to that found in the imidazole and amidines. In fact,the Benz imidazole may be considered as cyclic analogs of the amidines.

Benz imidazole is a aromatic heterocyclic compound having imidazole ring fused to benzene. The most prominentBenz imidazole compound in nature is N-ribosyl –dimethyl Benz imidazole,which serves as an axial ligand for cobalt in vitamin B12. The nucleus is present in some drugs such as proton pump inhibitors and anthelmintic agents.

Mebendazolethiabendazolewhich have anthelmintic and antifungal properties are Benz imidazole class of compounds.Benz imidazole and its derivatives are widely used as intermediate in synthesisof organic target compound includingpharmaceuticals,agrochemicals,dyes,photographic chemicals, corrosion inhibitors ,epoxy curing agents ,adhesives and plastic modifiers Benz imidazole is a white to slightly being solid; melting at 145-150 c, boils at 360°c,slightly soluble in water, soluble in ethanol. Benz imidazole and its derivatives are used in organic synthesis and vermicides and fungicides.

Melting points of the synthesized compounds were determined by open capillary method and were uncorrected.IR spectral analysis was carried out using FTIR-410 ,Jasco at Rajarambapu college of pharmacy,Kasegaon.

Physical properties of Benzimidazole:

1) Benzimidazoleshaving high melting points.The introduction of substituents at 1-position lowers the melting point.
2) Benzimidazoles are usually soluble in polar solvents and sparingly soluble in non-polar solvents.
3) Benzimidazoles are weakly basic,being somewhat less basic than imidazole.
4) Benzimidazoles are also sufficiently acedic to be generally soluble in aq. alkali and form N-metaliccompounds.The acidic properties of benzimidazole,like those of imidazole,seem to be due to stabillisation of the ion by resonance.
5) The pKa value of BenzimidazolespKa=5.30 for 2-methyl Benzimidazoles and pKa=12.33 for 2-amino Benzimidazoles.

B. Role of Pharmaceutical Chemistry in Drug Discover

Pharmaceutical chemistry plays important role in identification of lead compound it is also known as Hit. So 1) Identification of lead, 2) Optimization of lead,3) Lead Development these are most important steps in discovery.

Further chemistry and analysis is necessary, first to identify and “triage” compounds that do not provide series displaying suitable SAR and chemical characteristics associated with long-term potential for development, then to improve remaining hit series with regard to the desired primary activity,as well as secondary activities and physicochemical properties such that agents will be useful when administered in real patients.

The next through final synthetic chemical stages involve production of lead compound in suitable quantity and quality to allow large scale animal and eventual, extensive human clinical trials. This involves the optimization of the synthetic route for bulk industrial production, and discovery of the most suitable drug formulation.

Review of Literature:

1) Z. Kazimirerczuk, M. Anderzejewska ET; al. Are evaluated the synthesized compound for their activity agaist 4 mycobacterium strains.
2) A. Idhaya Dhullaet. Al.(2011) reported synthesis of Benz imidazole derivative and their antimicrobial activity.
3) R. K. Bansal (2005) Heterocyclic chemistry reported I.R and NMR interpretation.

C. Need of Investigation

Many important biochemical compounds and drugs of natural origin contain heterocyclic ring structure .Among thisee. Gcarbohydrate, essential amino acid, vitamins, alkaloids, glycosides, etc the presence of heterocyclic structures in diverse type of compounds is strongly indicative type of the pharmacological activity and recognition of this is reflected in efforts to find useful synthetic drugs.

The development of resistant to current antibacterial therapy continuous to stimulate search for more agents, the increasing clinical importance of drug resistant and bacterial pathogens has lent additional urgency to microbiological research and development of novel biologically active compounds. Hence the aim of this work is to synthesize some novel 2-chloromethyl 1-H-Benzimidazole derivative and carry out antibacterial potentials with good activity and less toxic effects .the biological activity of the compounds containing basic moiety have been well documented.

(1) The present work describes the 2-chloromethyl 1-H-Benzimidazole and their derivatives in search of bioactive molecules.
(2) Work also emphasized on the structural elucidation and pharmacological screening for antibacterial activity of synthesized compounds.

D. Objectives

The discovery and development of pharmacologically active molecules has been guided not only by classical medicinal chemistry but also by the use of sophisticated mechanistic approaches and biochemical assay.

The reviews clearly emohasizes the importance of heterocyclic in naturally occurring as well as synthetic agents and does an important class itself posses diversified pharmacological actions such as antimicrobial, antiprotozoal, antimalarial and antiallergic etc. This point encouragement further investigation in the field. The logic supporting the work presented in this dissertation was formulated, bearing in mind that the biological activities of known moieties and attempting certain structural modification or adaptation in light of the recent trends in drug research incorporating newly emerged pharmacophores on existing moiety.

The development of resistance to current anti-bacterial therapy continues to stimulate the search for more effective agents. The increasing clinical importance of drug resistant and bacterial pathogens has lent additional urgency to microbiologicl research and development of novel biologically active compounds. Hence in the present study we plan synthesized some novel benzimidazoles with good activity and less toxic effect.

E. Microwave Technique

Some derivatives were synthesized by using Microwave technique. This technique also refers as Green chemistry.By this technique required time was less and yield was higher as compare to conventional technique.
Melting points were taken by using Thiele's tube apparatus and were uncorrected. Thin layer chromatography was used to assess the course of reaction and the purity of intermediate and final compounds, giving single spot on TLC plate (silica gel) , using various solvent systems. Visualization of spot on plate was done by exposure to iodine vapours.

Infrared(IR) spectra were recorded in KBR disc on aJasco FT-IR-410 spectrometer.

F. Chemicals

All chemicals and solvents werw produced from commercial sources and purified and dried using standard procedures from literature whenever required. Chemicals used for the synthesis were enlisted below with their manufacturer mentioned in parentheses.

O-phenylenediamine - Research laboratory, Islampur
Hydrochloric acid - Research laboratory, Islampur
Chloroacetic acid - Research laboratory, Islampur
Ethanol - Research laboratory, Islampur
Potassium hydroxide - Research laboratory, Islampur.
Ammonium hydroxide - Research laboratory, Islampur
Dimethyl sulfoxide (DMSO).- Research laboratory, Islampur

G. Preparation of TLC Reagent

For the identification of benzimidazoles using thin layer chromatographic technique the reagent used is a mixture of Chloroform and methanol was taken in a ratio of 9:1as shown in fig no. 2

Figure 2. TLC plate of intermediate

Mobile phase: Chloroform:Methanol-9:1
Rf value= Distance travelled by solute/ Distance travelled by solvent
= 6/9
=0.66

H. Methodology- Scheme of The Experiment

O-Phenylenediamine was condensed in microwave by using chloroacetic acid in the presence of 5N NaCl to give 2-chloromethyl-1-h-benzimidazoles using different aniline derivatives.

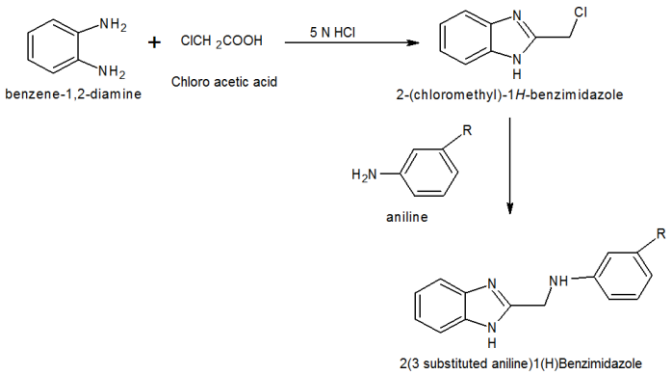

Figure 3. Scheme of the Experiment

1st step-Procedure-

In a 250ml three necked flask a solution containing 3gm of chloroacetic acid and 3gm of O-phenylenediamine dissolved in a 30ml of 5N HCL. The mixture was heated for 35 min. on 7th power with constant stirring in microwave. The reaction mixture is cooled to about 5˚c. It was neutralized with aq. Ammonium hydroxide or dil. NaOH. The product was filtered and washed with water to remove traces of chloromethyl-1 H-benzimidazole derivatives by using different aromatic amines and heterocyclic and to evaluate them for antibacterial activity.

Scheme-1

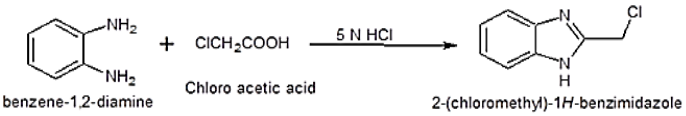

Figure 4. 1st step

Scheme-2

2nd step- procedure

General procedure for synthesis of 1-H-benzimidazole 2-yl-methyl-amine derivatives.

In the ethanolic KOH solution 2-chloromethyl benzimidazole and substituted anilines were added and it was heated for 35 min. on 7th power in microwave.Hot mixture was poured in crushed ice with constant stirring. Seperated solid was filtered, dried and recrystallized from ethanol .The yields ranged from 30-45%.

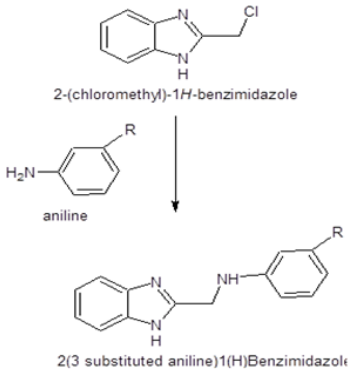

Figure 5. 2nd step- procedure

Physiochemical data of intermediate and derivatives (1A, 1B, 1C):

Sr. no.	Comp. code/name	R	Theroti cal yield	Practi cal yield	% yield	Melting point	RF value	Mol. wt
1	Intermed iate	R	3.54gm	2.2gm	62.14%	153-155°c	0.66	166
2	1A)	-N=N-C_6H_5	3.93gm	2.80g m	71.24%	148-150°c	0.54	327
3	1B)	-Br	1.81gm	1.42g m	77.34%	152-154°c	0.76	302
4	1C)	-O-CH_3	1.46gm	1.10g m	75.34%	150-154°c	0.61	122

Table 1. Physiochemical data of intermediate and derivatives

I.R of compound 1A N(1-H-benzimidazole-2ylmethyl)3-phenyldiazonyl aniline:

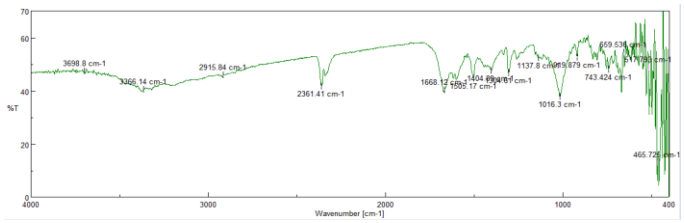

Figure 6. I. R. spectrum of comp. 1A

Sr.no.	Functional Group	Peak
1	N=N	1505
2	C=C	1668
3	NH	3366
4	C=N	1668
5	Phenol	1404

Table 2. I.R spectral data of comp. 1 A

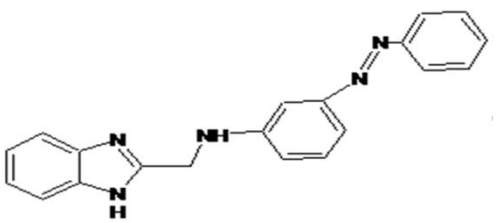

Figure 7. Structure of comp. 1A

I.R of comp. N(1-H-benzimidazole 2ylmethyl) 3-bromo aniline.

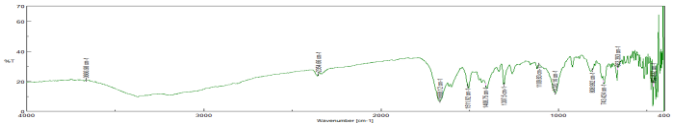

Figure 8. I.R. spectrum data of compound 1B

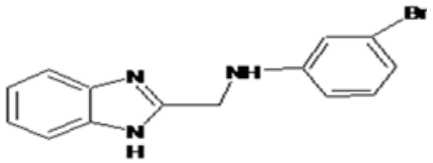

Figure 9. Structure of compound 1B

Sr.no.	Functional Group	Peak
1	C-Br	600-500
2	CH2	1408
3	C=C	1511
4	C=N	1408
5	C-N	1109

Table 3. I. R. spectral data of compound 1B

I. R. of comp. N(1-H-benzimidazole-2ylmethyl) 3-methoxy aniline:

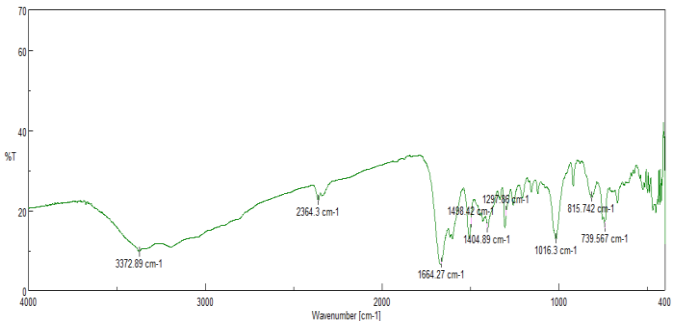

Figure 10. I. R. spectrum data of comp. 1C

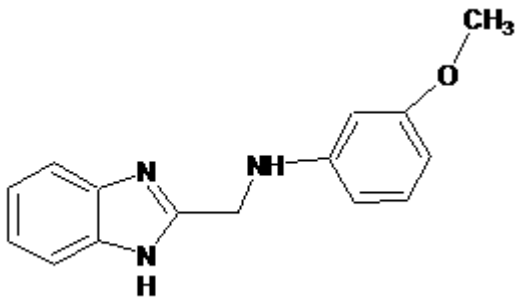

Figure 11. Structure of compound 1C

Sr.no.	Functional Group	Ranges
1	C=C	1498
2	N-H	3372
3	CH2 str.	1498
4	C=N	1664

II. METHODS AND MATERIAL

A. Chemicals

All chemicals and solvents were procured from commercial sources, purified andsterilized using standard procedures from literature whenever required. Nutrient agar medium (Research lab, Mumbai)

B. Dilution of the compounds

All the synthesized compounds were dissolved in dimethyl sulfoxide (DMSO) so as to get concentration of 200µg/ml and standard drugs Ciprofloxacin in DMSO as aconcentration of 10mg/ml.

C. Preparation of nutrient agar medium slant:

Nutrient agar medium 112 mg and agar powder 100 mg was dissolved in 4 ml distilled water, boiled and then poured in the test tube then plugged with cotton and sterilized in autoclave at 15lbs pressure (121^0C) for 15 min. after sterilization thetubes containing the nutrient agar medium were kept in inclined position for 30min.then on the surface of slants pure culture of bacillus Substiles, Escherichia coliwere streaked in aseptic condition and incubated at 37^0C for 24 hrs.

Antimicrobial Drug sensitivity Tests : Antimicrobial sensitivity test have been carried out by using disc-diffusion method, performed in nutrient agar for bacterial and saboraud's agar for fungi. Inoculation of suspension of bacteria and fungi on culture media: Sterile, non-toxic cotton swab were dipped in to the standardized inoculums (turbidity as adjusted as to obtained confluent growth on the Petri plate) and then the entire agar surface of the plate was streaked with the swab three times, turning the plate at 60°angle between streaking. Then the streaked inoculums were allowed to dry for 5-15mins with lid in place.

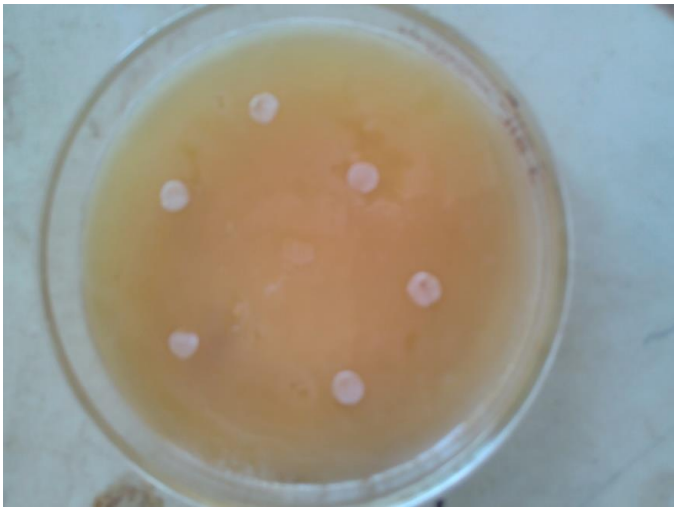

Figure 12. Inoculation of suspension of bacteria and fungi on culture media

Sterile paper disc made by punching whatman (No.41) paper were dipped separately in to the solutions containing synthesized drug (300µg/ml of DMSO) and standard drug ciprofloxacin (10 mg/ml of DMSO.) & Flucanazole (10 mg/ml of DMSO) in aseptic condition with help of sterile forceps and were then placed on the surface of inoculated culture media after which the plates were kept in refrigeration for 30 mins. For the diffusion of the drug from the paper disc in to the culture media. After 30 mins the plates were incubated at 37^0C.

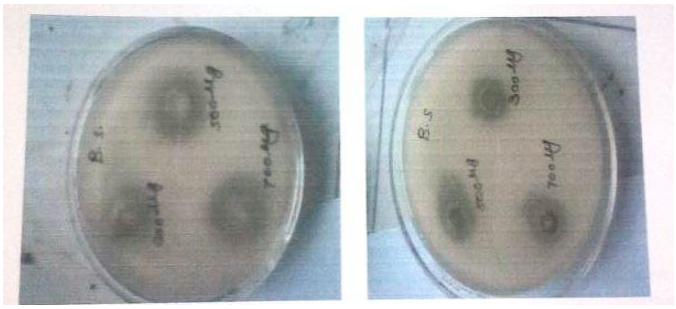

Figure 13. Standard (ciprofloxacin) derivative (1A)

SR. NO.	COMP. NO	NAME OF ORGANISM	
		E. Coli	B.Subtilis
1	1A	++	++
2	Ciprofloxacin	+++	+++

Table 5. Zone of inhibition

Below 6 mm it shows negative activity (-)
Between 6 mm -9 mm (and) sign. (Slight activity)
In between 9 mm – 12 mm (++) sign. (Moderate activity)
In between 12 mm-16mm (+++) sign. (Higher activity)

III. RESULT AND DISCUSSION

The antibacterial activities of synthesized (1A) was carried out by using disc diffusion method and screened against Bacillus subtilis, E. Coli microorganism using standard ciprofloxacin (300µg/ml) and derivative compound 300,500,700 per ml.

Discussion

Novel compounds 1A, 1B and 1C were found to show antibacterial activity when checked with Ciprofloxacin as standard .Compound 1A showed moderate antibacterial activity against Gram positive, Bacillus subtilis, while higher activity against Gram negative (Escherichia-coli).

IV. CONCLUSION

Evaluation of the novel compounds established that some of the synthesized comp. N (1-H-benzimidazole-2ylmethyl) 3-phenyldiazonyl aniline, N (1-H-benzimidazole-2ylmethyl)3-bromoaniline, N (1-H-benzimidazol-2ylmethyl) 3-methoxy aniline. Showed antibacterial activity which was not found to be less than that of ciprofloxacin in case of Gram positive (Bacillus subtilis) while moderate activity against Gram negative (E.coli).

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