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SYNTHESIS AND EVALUATION OF ANTI MICROBIAL ACTIVITY OF 2-METHYLAMINO BENZIMIDAZOLE DERIVATIVES

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ABSTRACT

Substituted 2-methylamino benzimidazoles were synthesized by refluxing 2-methylamino benzimidazole with urea and thiourea in presence of methanol. Synthesis of 2-methylamino benzimidazole from o-phenylene diamine by refluxing with glycine in presence of HCl. The structures of final synthesized compounds were assigned on the basis of IR spectral data. All the newly synthesized compounds were screened for their *in-vitro* antimicrobial activity against various species of bacteria by cup plate method. The zone of inhibition exhibited by all the derivatives at a concentration of 250µg and 500µg was compared to that of standard ciprofloxacin at a concentration of 5µg. The compounds were good antibacterial agents against the tested organisms when compared to the standard ciprofloxacin.

Key Words: Benzimadazole, o-phenylene diamine, glycine, antimicrobial.

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INTRODUCTION

Medicinal chemistry is the application of chemical research techniques to the synthesis of pharmaceuticals Benzimidazole is an aromatic heterocyclic compound with the chemical formula $C_7H_6N_2$ The basic structure of benzimidazole (Fig-1) consist of benzene ring fused with 4, 5 position of imidazole. It is a ring structure compound of 2 nitrogen atoms chemical formula $C_7H_6N_2$. Benzimidazole is a privileged bicyclic ring system. Due to its potent and significant biological activities it has great pharmaceutical importance; hence, synthesis of this compound is of considerable interest. The small and simple benzimidazole nucleus if present in compounds involved in research aimed at evaluating new products that possess interesting biological activities. Combination of 2- methyl aminobenzimidazole with other heterocyclic is a well known approach to design new drug like molecules, which allows achieving new pharmacological profile, action, toxicity lowering (1-4).

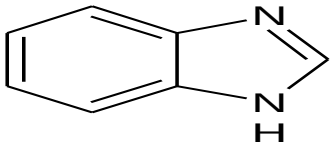

Fig-1 Structure of Benzimidazole

MATERIAL AND METHODS (5-11)

Scheme of synthesis of pyrimidine derivatives Fig-2)

Step 1

O-Phenylenediamine (11.0 mmol) was dissolved in 20 ml water under heating with constant stirring. Conc. HCl (20mL)was added with glycine (, 8.0 mmol)to the reaction mixture. Resulted mixture was refluxed for 50-55 minutes at 70-73°C and reaction was monitored by TLC. After completion of reaction, reaction mixture was cooled by water and then neutralized with ammonia solution to precipitate the product, separated by vacuum filtration and recrystallized from 95%ethanol.

Step 2

In a 100 ml round bottom flask fitted with water condenser, were placed, 2-aminobenzothiazole (0.02 mole) and 4 ml of dry benzene. To this, chloroacetyl chloride (0.02 mole) was added drop wise. Then reaction mixture was refluxed on water bath at 80°C for 3 hr. after completion of reaction, excess of chloroacetylchloride was removed under reduced pressure. The resulting solid residue was washed with aqueous solution of 5% sodium bicarbonate (50 ml) followed by ice cold water. The resulting crude product of 2-chloroacetamido benzothiazole thus obtained was recrystallized from ethanol.

Step 3 (a)

In a 100ml round bottom flask fitted with reflux condenser, placed 2 – methyl chloro acetamide benzimidazole(0.02mol) dissolved in methanol(50ml) and refluxed with urea(0.025mol) for 3hrs. Cooled and poured in to crushed ice. The separated product was filtered and washed with sodium bicarbonate (2%)solution and recrystallized from ethanol.

Step 4 (b)

In a 100ml round bottom flask fitted with reflux condenser, placed 2-methylchloroacetamido benzimidazole (0.02mol) dissolved in methanol(50ml) and refluxed with thiourea(1.9g, 0.025mol) for 3hrs. It was cooled and poured onto crushed ice. The separated solid was filtered and recrystallized from ethanol.

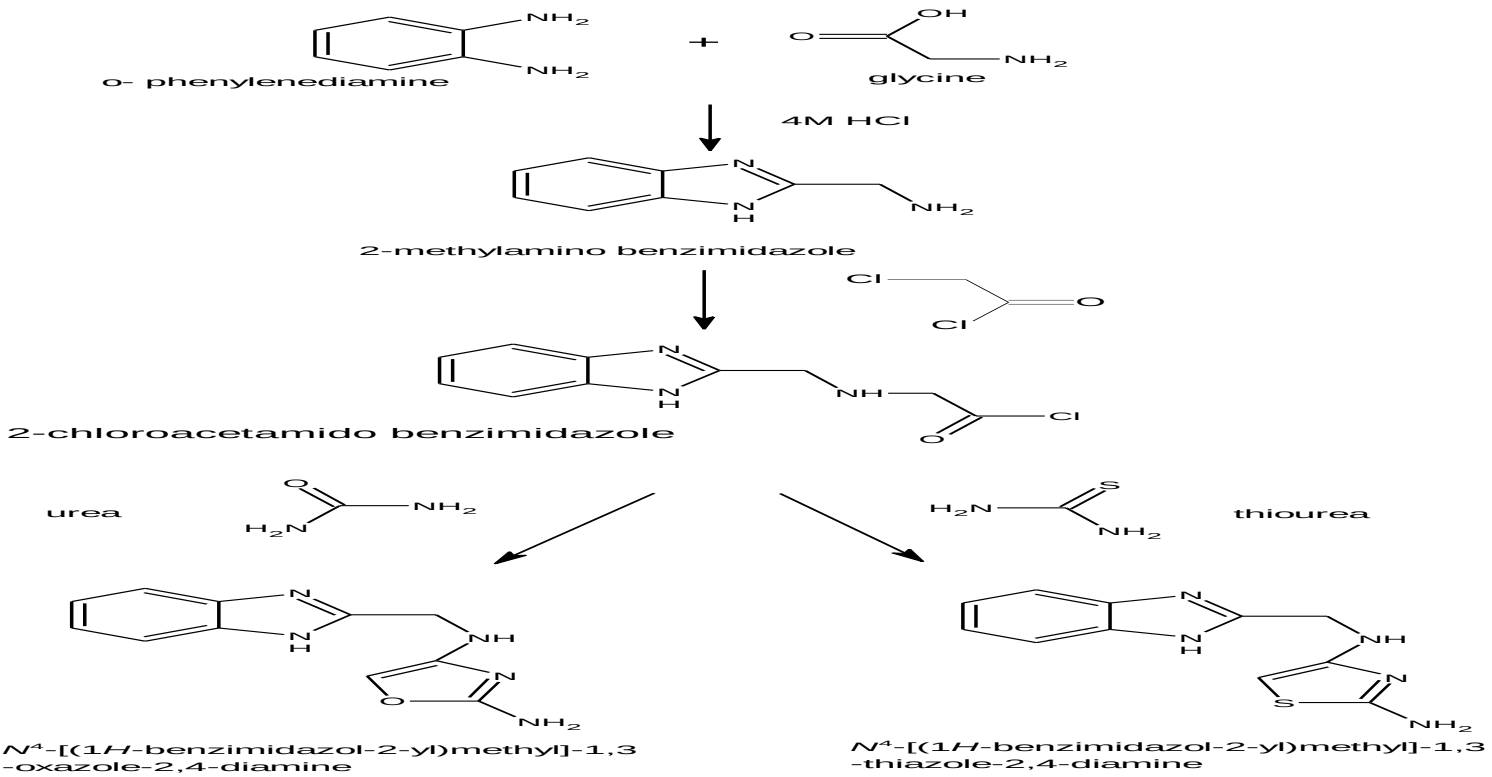

Fig-2 Scheme of synthesis of benzimidazole derivatives

Derivatives were prepared through above procedures with reasonably good yields. The melting point of the new compounds was determined. The functional groups in the structure of product derivatives were confirmed by IR spectra studies.

Antimicrobial Screening

Each petridish containing nutrient agar medium was inoculated with one bacteria culture. Dip the swab in broth culture of the organism. Gently squeeze the swab against the inside the tube to remove excess fluid**.** Use the swab to streak a nutrient agar plate for a lawn of growth**.**This is best accomplished by streaking the plate in one direction, then streaking at right angle to the first streaking and finally streaking diagonally. End by using the swab into to streak the outside diameter of the agar**.** Allow the plate to dry for 5 minutes**.** In each plate cups of 6mm diameter were made at equal distances using a sterile cork borer. One cup was filled with standard drug i.e. ciprofloxacin, one was filled with 10µl of sterile methanol; others were filled with 10µl synthesized compound's solution in sterile methanol by using micropipette. All the plates were kept in the refrigerator for 30minutes to allow the diffusion of sample to the surrounding agar medium and incubated at 37ºC for 24 hrs. Diameter of the zone of inhibition was measured by using a metric ruler measure. The diameter obtained for the test sample were compared With that produced by standard drug to determine if the bacterial species tested is resistant or sensitive to drug.

RESULTS AND DISCUSSION

Spectral studies

The characterization requires the identification of molecular framework, the nature of functional groups that are present and their location within the skeletal structure and finally the establishment of any stereo chemical relationships, which might exist. In the resent work, IR spectroscopic analysis was carried out to confirm the structures of newly synthesized compounds, and all the compounds were in agreement with their molecular structures.

i. SPECTRAL FEATURES OF SAMPLE 'U'

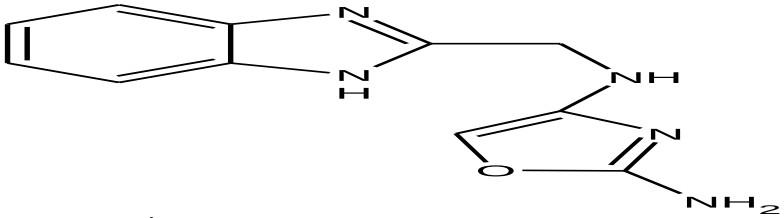

Fig-3 Proposed structure of N^4-[(1*H*-benzimidazol-2-yl) methyl]-1,3-oxazole-2,4-diamine

Molecular formula: $C_{11}H_{11}N_5O$, Molecular weight: 229g and Physical state: white colored solid**.** The suggested groups of the derivative 6d were confirmed by IR Spectra shown in the fig-4. Absorption between 3498cm^{-1} and 3486cm^{-1} indicate the presence of $-NH_2$ group. Absorption between 1306cm^{-1} and 1258cm^{-1} indicate the presence of aromatic C-N group. Absorption between 1074 cm^{-1} and 1026cm^{-1} indicate the presence of aliphatic C-N group. Absorption between 1074 cm^{-1} and 1026 cm^{-1} indicate the presence C-O group (5,6).

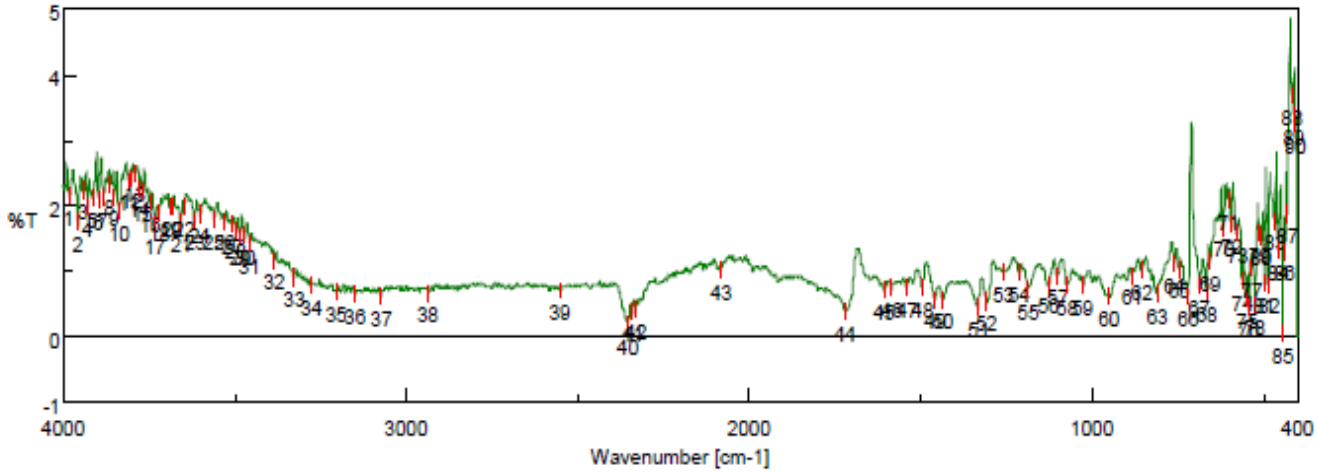

Fig- 4 IR spectra of compound 1

ii. **STRUCTURAL FEATURES OF SAMPLE 'T'**

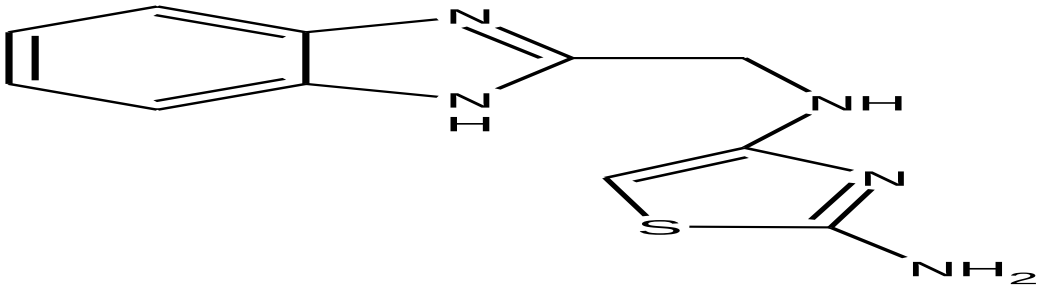

Fig-5 Proposed structure of N^4-[(1*H*-benzimidazol-2-yl)methyl]-1,3-thiazole-2,4-diamine

Molecular formula: $C_{11}H_{11}N_5S$, Molecular weight: 245g and Physical state: white colored solid. IR in cm^{-1}: Absorption between 3498cm^{-1} and 3486cm^{-1} indicate the presence of $-NH_2$ group. Absorption between 1306cm^{-1} and 1258cm^{-1} indicate the presence of aromatic C-N group. Absorption between 1074 cm^{-1} and 1026cm^{-1} indicate the presence of aliphatic C-N group. Absorption between 808cm^{-1} and 753 cm^{-1} indicate the presence of C-S group (Fig-6).

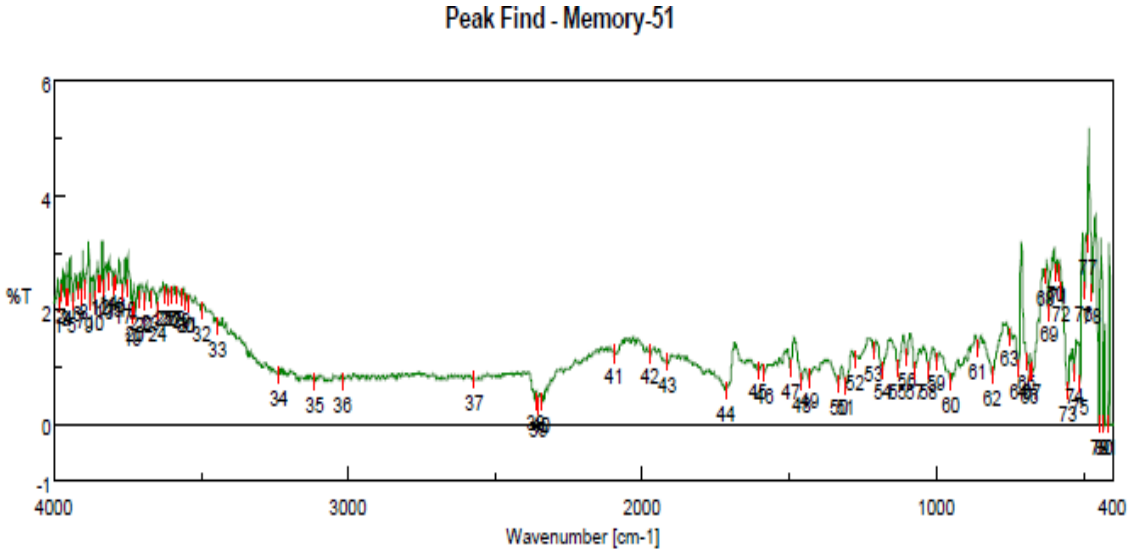

Fig- 6 IR spectra of compound 1

Antimicrobial Screening

The synthesized derivatives were screened for anti microbial activity. The results were shown in the table-1.

Table-1 Zone of inhibition in bacterial strains

Compound Code	Diameter of zone of inhibition in mm			
	Staphylococcus aureus		*Escherichia coli*	
	250µg/well	500µg/well	250µg/well	500µg/well
01	2	20	3	33
02	5	36	5	8
Standard Ciprofloxacin (5µg/disc)	40		36	

Note- Solvent used: DMSO, (-) indicates no zone of inhibition, (Diameter of zone of inhibition:17 mm & above: Sensitive, 13-16mm: Moderately sensitive, <12 mm: resistant).

CONCLUSION

Synthesis of 2-methylamino benzimidazole derivatives resulted in compounds with good yields**.** IR spectroscopic analysis was carried out to confirm the structures of newly synthesized compounds, and all the compounds were in agreement with their molecular structures. All the newly synthesized compounds were screened for their *in-vitro* antimicrobial activity against various species of bacteria by cup plate method. The zone of inhibition exhibited by all the derivatives at a concentration of 250µg and 500µg was compared to that of standard ciprofloxacin at a concentration of 5µg. The compounds were good antibacterial agents against the tested organisms whwn compared to the standard ciprofloxacin.

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