

## SYNTHESIS AND ANTIBACTERIAL EVALUATION OF BENZOTHIAZOLE DERIVATIVES

Dr. Rashmi Kumari<sup>1\*</sup>, Dr. Brij Bihri Sharma<sup>1</sup> and K. Bhanukiran<sup>2</sup>

<sup>1</sup>Department of Chemistry, Magadh University, Bodh Gaya, Gaya, Bihar, India.

<sup>2</sup>Department of Pharmaceutical Engineering and Technology, IIT (BHU), Varanasi.

Article Received on  
16 August 2017,

Revised on 06 Sept. 2017,  
Accepted on 26 Sept. 2017

DOI: 10.20959/wjpr201712-9708

**\*Corresponding Author**

**Dr. Rashmi Kumari**

Department of Chemistry,  
Magadh University, Bodh  
Gaya, Gaya, Bihar, India.

### ABSTRACT

Benzothiazole nucleus was synthesized by para amino acetanilide, then it is subjected to treatment with various substituted aromatic aldehydes to get the corresponding Schiff's bases followed by treatment with phthalic anhydride to form 2-(6-acetamidobenzo[d]thiazol-2-ylcarbonyl)benzoic acid. The structures of synthesized compounds were confirmed by various spectroscopic methods such as IR, <sup>1</sup>H NMR and mass spectroscopy. The products were evaluated for their antibacterial activity. Some of the compounds exhibited potent activity when compared with the standards.

**KEYWORDS:** Benzothiazole, Schiff's base, Antimicrobial activity, NMR.

### INTRODUCTION

Benzothiazole nucleus is one of the most important heterocyclic that has received much attention due to its diversified molecular design and remarkable optical and electronic properties. Among all the benzoheterocycles, benzothiazole has a considerable place in the area of research especially in synthetic as well as in pharmaceutical chemistry due to its potent and diversified pharmacological activities such as antimicrobial<sup>[1-2]</sup>, antitubercular<sup>[3]</sup>, anthelmintic<sup>[4]</sup>, anti-inflammatory<sup>[5-6]</sup>, analgesic<sup>[7]</sup>, antidiabetic<sup>[8]</sup>, anticancer<sup>[9-10]</sup>, antioxidant.<sup>[11]</sup> etc. Research in this area is still unexplored, therefore the present study is directed towards the synthesis of newer derivatives of benzothiazole with good yield and enhance antibacterial activity.

### MATERIALS AND METHODS

All the chemicals procured from CHEMCO Labs, NICE chemicals. The melting points were determined in open glass capillaries and were uncorrected. Thin Layer Chromatography using

silica gel G (E. Merck) plates were used to access the reaction and purity of synthesized compounds. The IR spectra were recorded on Shimadzu FTIR system in KBr pellets and noted the absorption levels ( $\text{cm}^{-1}$ ) were listed.  $^1\text{H}$  NMR spectra were run on Bruker DPX 400 FTNMR in  $\text{DMSO-d}_6$  as solvent and TMS as an internal standard. The Mass spectra were recorded on JEOL JMS600H mass spectrometer.

### **Step1: Synthesis of N-(2-aminobenzo[*d*]thiazol-6-yl)acetamide**

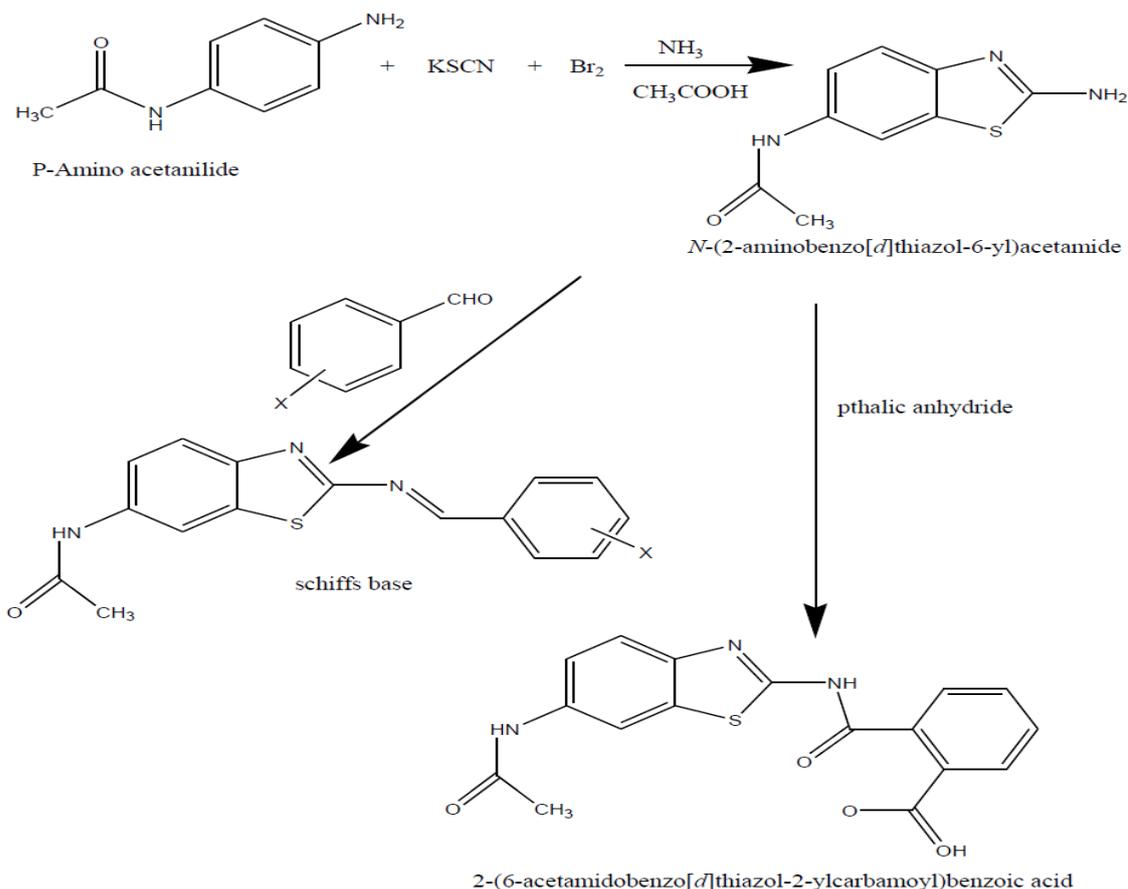
Glacial acetic acid (150ml) pre-cooled to  $50\text{ }^\circ\text{C}$  was added to potassium thiocyanate (5.82g, 0.06mole) and P-amino acetanilide (8.73g, 0.06mole) solution. The mixture was placed in freezing mixture of ice and salt and mechanically stirred while bromine (1.6ml, 0.02mol) in 10ml glacial acetic acid was added from the dropping funnel at such a rate that the temperature does not rise beyond  $0\text{--}50\text{ }^\circ\text{C}$ . After all the bromine was added (102 min.), the solution was stirred for an additional 2h at  $0\text{--}100\text{ }^\circ\text{C}$ . The residue was filtered off and then it was dissolved in hot water (150ml). The solution was filtered and the filtrate was neutralized with ammonia solution to pH 6. The precipitate was collected and recrystallized with ethanol.

### **Step 2: Synthesis of Schiff's bases**

N-(2-aminobenzo[*d*]thiazol-6-yl)acetamide (0.02mol) in toluene, substituted aromatic aldehydes (0.01mole) and 10 ml glacial acetic acid were added and the reaction mixture was refluxed on the steam bath for 10 hrs. The solvent was distilled off and the residue was filtered to get desired Schiff's bases ( $\text{BT}_2\text{--}\text{BT}_5$ ).

### **Step3: Synthesis of 2-(6-acetamidobenzo[*d*]thiazol-2-ylcarbamoyl) benzoic acid**

A solution of pure phthalic anhydride (0.05mol) in ether (20ml), N-(2-aminobenzo[*d*] thiazol-6-yl)acetamide (0.05mol) in ether (20ml) was added with swirling at room temperature. The warm reaction mixture was cooled. When a colorless product separated out, filtered off the product, Washed with ether and recrystallised from ethanol ( $\text{BT}_1$ ).



Where X=P-Chloro, P-Methoxy, 3-Nitro, P-methyl

### Antibacterial activity<sup>[12]</sup>

Antibacterial activity of the synthesized compounds was screened using the disc diffusion method against selected pathogens such as *Staphylococcus aureus*, *Escherichia coli*. The compounds were dissolved in DMSO and sterilized by filtering through 0.45  $\mu\text{m}$  millipore filter. Nutrient agar (anti bacterial activity) was prepared and sterilized by an autoclave (121° C and 15 lbs for 20 min) and transferred to previously sterilized petridishes (9 cm in diameter). After solidification, petriplates were inoculated with bacterial organisms in sterile nutrient agar medium at 45°C Sterile whatmann filter paper discs (previously sterilized in U.V. lamp) were impregnated with synthesized compounds at a concentration of 500 $\mu\text{g/ml}$ , 300 $\mu\text{g/ml}$  and 150  $\mu\text{g/ml}$  (*E.coli*) and 150  $\mu\text{g/ml}$ , 100  $\mu\text{g/ml}$  and 50  $\mu\text{g/ml}$  (*S. aureus.*) were placed in the organism impregnated petri plates under sterile condition. The plates were left for 30 min to allow the diffusion of compounds at room temperature. Antibiotic discs of Ertapenam-10 mcg/disc, Netilmycin-30 mcg/disc and Streptomycin-100  $\mu\text{g/ml}$  was used as positive control, while DMSO used as negative control. Then the plates were incubated for 24

H at  $37 \pm 1$ . The zone of inhibition was calculated by measuring the minimum dimension of the zone of no microbial growth around the each disc.

## RESULTS AND DISCUSSION

The melting points of all synthesized compounds were found in open capillary tubes and readings were uncorrected. The structures of the synthesized compounds were supported by physical data (Table 1) and following spectral analysis

Only three compounds i.e. BT<sub>1</sub>, BT<sub>2</sub> and BT<sub>4</sub> were taken for spectral studies. The results showed the presence of compounds which were predicted in the synthetic scheme.

### 2-(6-acetamidobenzo[d]thiazol-2-ylcarbamoyl) benzoic acid: BT<sub>1</sub>

IR( $\nu$  cm<sup>-1</sup>): 1649.14 (amide C=O, str), 2854.65 (aliphatic C-H, str), 3527.80 (N-H, str), 3115.04 (Ar CH, str), 1556.55 (Ar C=C, str), 1400.32 (C-N, str), 1219.01 (C-S, str), 727.16 (C-S-C, str), 1602 (C=N, str), 3292.49 (carboxylic O-H, str), 1728.22 (carboxylic C=O, str), 1369.46 (CO-H, bend), <sup>1</sup>H NMR (DMSO- *d*<sub>6</sub>)  $\delta$ : 2.024- Singlet, -CH<sub>3</sub> (3H), 7.245-7.693- Multiplet, Aromatic protons (7H), 8.007- Singlet, -NH-C=O (1H), 9.876- Singlet, -NH-C=O (1H), 13.245- Singlet, -OH (1H), LC-MS:  $m/z$  355.24 (M<sup>+</sup>).

### N-((E)-2-(4-methoxybenzylideneamino)benzo[d]thiazol-6-yl)acetamide: BT<sub>2</sub>

IR( $\nu$  cm<sup>-1</sup>): 1658.78 (amide C=O, str), 2850.79 (aliphatic C-H, str), 3527.80 (N-H, str), 3273.20 (Ar C-H, str), 1406.11 (C-N, str), 1261.45 (C-S, str), 765.74 (C-SC, str), 1649.14 (C=N, str), 2933.73 (methoxy CH, str), 1161.45 (C-O-C str), <sup>1</sup>H NMR (DMSO- *d*<sub>6</sub>)  $\delta$ : 2.025- Singlet, -CH<sub>3</sub> (3H), 3.356- Singlet, -OCH<sub>3</sub> (3H), 7.256-7.764- Multiplet, Aromatic protons (7H), 9.876- Singlet, -NH-C=O (1H), 10.594- Singlet, -N=CH (1H), LC-MS:  $m/z$  325.12 (M<sup>+</sup>).

### N-(2-(((1Z)-(4-chlorophenyl)methylene)amino)-1,3-benzothiazol-6-yl)acetamide: BT<sub>4</sub>

IR( $\nu$  cm<sup>-1</sup>): 1681 (amide C=O, str), 2960.73 (aliphatic CH, str), 3377.36 (NH, str), 3080.32 (Ar C-H, str), 1404.18 (C-N, str), 1371.39 (CS, str), 731.02 (C-S-C, str), 1631.78 (C=N, str), 1055 (C-Cl, str), <sup>1</sup>H NMR (DMSO- *d*<sub>6</sub>)  $\delta$ : 2.024- Singlet, -CH<sub>3</sub> (3H), 6.894-8.002- Multiplet, Aromatic protons (7H), 9.875- Singlet, -NH-C=O (1H), 10.356- Singlet, -N=CH (1H), LC-MS:  $m/z$  329.13 (M<sup>+</sup>).

Synthesized compounds have been evaluated for antibacterial activity by standard method against *Staphylococcus aureus* (gram +ve) and *Escherichia coli* (gram -ve). Mean zone of inhibition of the compounds were compared with different concentration of standard drugs

like Ertapenam (10 mcg/disk), Netilmicin (30 mcg/disk) and Streptomycin (100 mcg/ml) and DMSO as the control. All the tested compounds have been shown to exhibit significant antibacterial activity. The results were presented in Table 2. The figure of zone of inhibition of the compound against E.coli is given in figure.1.

**Table 1: Physical data of the compounds.**

| Compound code   | Molecular formula   | Molecular weight | Percentage yield | m.p( <sup>0</sup> c)    | Rf   | Solvent system           |
|-----------------|---|------------------|------------------|-------------------------|------|--------------------------|
| BT <sub>1</sub> | C <sub>17</sub> H <sub>13</sub> N <sub>3</sub> O <sub>4</sub> S | 355.37           | 65.5%,           | 121- 123 <sup>0</sup> C | 0.75 | Chloroform: ethanol(7:3) |
| BT <sub>2</sub> | C <sub>17</sub> H <sub>15</sub> N <sub>3</sub> O <sub>2</sub> S | 325.39           | 68.75%           | 223-225 <sup>0</sup> C  | 0.83 | Chloroform: ethanol(7:3) |
| BT <sub>3</sub> | C <sub>16</sub> H <sub>12</sub> N <sub>4</sub> O <sub>3</sub> S | 340.36           | 65.52%           | 180-182 <sup>0</sup> C  | 0.73 | Chloroform: ethanol(7:3) |
| BT <sub>4</sub> | C <sub>16</sub> H <sub>12</sub> ClN <sub>3</sub> OS             | 329.81           | 63%              | 222-224 <sup>0</sup> C  | 0.62 | Chloroform: ethanol(7:3) |
| BT <sub>5</sub> | C <sub>17</sub> H <sub>15</sub> N <sub>3</sub> OS               | 309.39           | 62.65%           | 220-223 <sup>0</sup> C  | 0.74 | Chloroform:ethanol (7:3) |

**Table 2: Antibacterial activity of compounds.**

| Compound               | Mean Zone Of Inhibition In mm |     |     |                 |     |     |
|------------------------|-------------------------------|-----|-----|-----------------|-----|-----|
|                        | S.aureus(Gram+Ve)             |     |     | E.coli(Gram-Ve) |     |     |
|                        | 50                            | 100 | 150 | 150             | 300 | 500 |
| BT <sub>1</sub>        | 28                            | 32  | 35  | 26              | 29  | 35  |
| BT <sub>2</sub>        | 26                            | 29  | 33  | 29              | 32  | 36  |
| BT <sub>3</sub>        | 23                            | 26  | 30  | 26              | 30  | 33  |
| BT <sub>4</sub>        | 29                            | 31  | 34  | 27              | 29  | 32  |
| BT <sub>5</sub>        | 24                            | 27  | 29  | 28              | 31  | 35  |
| Ertapenam(10mcg/disc)  | 43                            |     |     | 27              |     |     |
| Netilmicin(30mcg/disc) | 29                            |     |     | 21              |     |     |
| Streptomycin100μg/ml   | 24                            |     |     | 23              |     |     |
| DMSO                   | -                             |     |     | -               |     |     |

- indicates no zone of inhibition



**Figure:-1 Zone of inhibition of the compound against E.coli.**

## CONCLUSION

The research work was oriented towards the finding of newer derivatives of benzothiazole with enhance antibacterial activity. The different derivatives were synthesized. The synthesized derivatives showed very good antibacterial activities against previously reported derivatives of benzothiazole.

## ACKNOWLEDGEMENT

The author is thankful to Department of Chemistry, Magadh University, Bodh Gaya, Gaya, Bihar, India for providing research facilities and encouragement and to my friends those helped me to complete this research.

## REFERENCES

1. Prabhu Padmavathi P., Shastryb C. S., Pande Sushant Sudhir, Selvama T. Panneer, Design, synthesis, characterization and biological evaluation of Benzothiazole-6 carboxylate derivatives, *Res. Pharm.* 2011; 1(2): 6-12.
2. Rajeeva B, Srinivasulu N, Shantakumar S., Synthesis and antimicrobial activity of some new 2-substituted benzthiazole derivatives, *Eur J Chem.* 2009; 6(3): 775-779.
3. Bhusari KP., Synthesis and antitubercular activity of some substituted 2-(4-amino phenylsulphonamido) benzothiazoles, *Ind J Hetero Chem.* 2000; 9: 213-216.
4. Himaja M, Munirajasekar D, Malisunli, Synthesis and anthelmenthic activity of 2-amino-6-substituted benzthiazoles, *Int Res J of Pharm.* 2011; 2(1): 114-117.
5. Singh SP, Vaidya RK, Synthesis and anti-inflammatory activity of some 2-(4'-butyl-3', 5'-dimethyl pyrazol-1'-yl)-6-substituted benzothiazoles and 4- butyl-1-(6'-substituted-2'-benzothiazolyl) -3-methyl pyrazol-5-ols, *Ind J Chem.* 1986; 25: 288-291.

6. Akhilesh G, Swati R, Synthesis and anti-inflammatory study of fluoroben zothiazole derivatives, *J Chem Pharm Res.* 2010; 2(5): 244-258.
7. Vishawanth SD, Pasha S, Balasubramaniam V, Nagendra A, Perumal P, Suthakaran R, Synthesis of some substituted benzthiazole derivatives and its analgesic activity, *Int J Chem Tech Res.* 2009; 1(14): 1224-1231.
8. Mariappan G, Prabhat P, Sutharson L, Banerjee J, Pantangia U, Nath S., Synthesis and antidiabetic evaluation of benzthiazole derivatives, *J Kor Chem Soc.* 2012; 56(2): 31-45.
9. Xuan-Hong Shi, Zhao Wang, Yong Xia, Ting-Hong Ye, Mei Deng and You-Zhi Xu., Synthesis and biological evaluation of novel benzthiazole-2-thiol derivatives as potential anticancer agents, *Molecules.* 2012; 17(1): 3933-3944.
10. Sekar V, Balbudhe D, Sivakumar P, Perumal P, Synthesis, characterisation and invitro anticancer evaluation of some 6-substituted 2-aminobenzothiazole derivatives, *Int J Pharm Res Dev.* 2011; 4(03): 332-337.
11. Yadav AG, Patil VN, Asrondkar AL, Naik AA, Ansulkar PV, Bobade AS, Chowdhary AS, Antioxidant and antimicrobial activities of pyrazolyl-benzthiazole derivatives using vilsmeier-haack reaction, *Ras J Chem.* 2012; 5(1): 117-120.
12. Cruickshank R, Duguid JP, Marmoin BP Swan HA, *The practice of medical microbiology*, XII ed. London: Churchill livingstone, 1975.