Synthesis, Characterisation and Antibacterial activity of 2-Aryl Benzothiazoles

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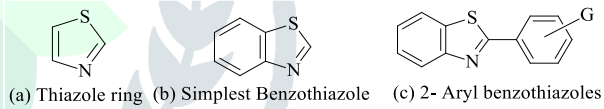
Abstract: *In this article, we have reported the synthesis of four different 2-aryl benzothiazoles namely 2-Phenyl-1, 3-benzothiazole, 2-(4-Chlorophenyl)-1, 3-benzothiazole, 2-(4-Bromophenyl)-1, 3-benzothiazole and 2-(3-Nitrophenyl)-1, 3-benzothiazole by using grinding method with minimum amount of the solvent. All the synthesised compounds were characterized by IR, ^{1}H- NMR and melting point analysis. We have also studied the antibacterial activity of these four prepared compounds against two gram negative bacterial strains namely Klebsiella sp. and Salmonella* sp *by Disk diffusion method. Amongst these four 2-aryl benzothiazoles, 2-(4-Chlorophenyl)-1, 3-benzothiazole have distinctive inhibitory property against Klebsiella sp. and 2-(4-bromophenyl)-1, 3-benzothiazole have inhibitory activity against Salmonella sp. for higher concentrations only.*

Key Words: 2-Aryl benzothiazoles, *Klebsiella* sp., *Salmonella* sp., Disk diffusion method, Antibacterial activity.

I. INTRODUCTION

Organic compounds have an enormous variety of structures and many of them have ring structures. If the ring system contains at least one element other than carbon atom is known as heterocyclic ring. The most common heteroatoms are generally nitrogen, oxygen and sulphur, but heterocyclic rings containing other hetero atoms are also widely known. Heterocyclic chemistry is a very important branch of organic chemistry and more than half of the organic compounds are heterocyclic compounds **[1]**. Heterocyclic compounds are very widely distributed in nature and are essential to life also in various ways **[2, 3]**. Most of the medicines, drugs and pharmaceuticals contain heterocyclic ring. Many natural products contain heterocycles, *for example*: antibiotics, alkaloids, flavones and vitamin B complexes etc. Besides the vast distribution of heterocycles in natural products, they are also the major components of biological molecules such as nucleic acids (DNA), haemoglobin, chlorophyll, amino acids, enzymes, genetic material etc. **[4, 5]**. Hence, the chemistry and biological study of heterocyclic compounds play an interesting field for a long time in medicinal chemistry **[6]**. A large number of heterocycles containing nitrogen and sulphur atom serve as a unique and versatile scaffolds for drug designing **[7]**. 1, 3-Benzothiazole and its derivatives are the N and S containing heterocycles that shows diverse medicinal activity **[8, 9]**. Benzothiazole consists of thiazole ring fused with benzene ring (**Fig. 1**). Thiazole is a five membered heterocyclic aromatic ring system having S and N as hetero atoms and also contain a C=N bond.

Fig. 1: Structures of (a) Thiazole ring (b) Simplest benzothiazole and (c) 2-Aryl benzothiazole



(a) Thiazole ring (b) Simplest Benzothiazole (c) 2- Aryl benzothiazoles

Various substituted benzothiazoles, mainly 2-phenyl and its derivatives possess multiple applications as drugs. They have been potentially used as antibacterial [**10]**, antifungal **[11, 12]**, antimicrobial **[13-18]**, antiparacites **[19]**, antitumor **[20-24]**, antidiabetic **[25],** anti-inflammatory **[26]**, anthelmintic **[27]**, antimalarial activity **[28]** etc. In addition to biological activities, benzothiazoles are also an important class of industrial chemicals. Many kinds of 2-substituted benzothiazoles are utilized as vulcanization accelerators in the manufacture of rubber, as fluorescent brightening agents in textile dyeing, and in the leather industry **[29-32]**.

II. REVIEW OF LITERATURE

In literature, many methods have been reported for the synthesis of 2-aryl benzothiazoles from 2-aminothiophenol. Although some of existing methods are effective methods but still various modifications of methodology and expensive catalysts are the subject of this synthesis. 2-Aminothiophenol is a versatile starting material for

the synthesis of different kind of 2-aryl benzothiazoles. 2-Aryl benzothiazoles can be synthesized by the condensation of substituted benzaldehydes **[8, 33]**, substituted aromatic carboxylic acids **[34, 35]**, substituted benzoyl chlorides, substituted aromatic esters and substituted aromatic nitriles **[36]** in presence of different catalysts. Devmurari *et al.* **[10]** synthesised 2-aryl benzothiazoles with good yield by treating 2-Aminothiophenol with substituted aromatic carboxylic acids in presence of polyphosphoric acid (**Fig. 2**). Similarly, the treatment of 2-aminothiophenol with substituted aromatic nitriles in presence of cerium (IV) ammonium nitrate to give corresponding 2-arylbenzothiazoles with excellent yield (**Fig. 2**) **[37]**.

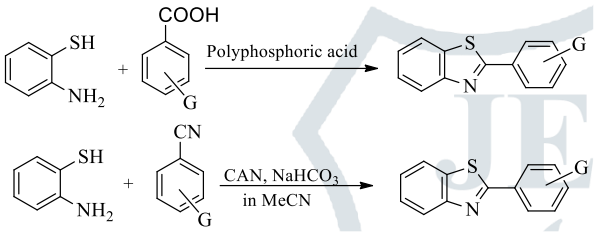


Fig. 2: Synthesis of 2-Aryl benzothiazoles from substituted aromatic acids and nitriles.

The simple condensation reaction of 2-aminothiophenol with substituted benzaldehyde in presence of different catalysts were reported by many authors such as (a) Rostamizadeh S *et al.* **[29]** , (b) Patil SS *et al.***[38]**, (c) Al-Qalaf F *et al.* **[39]** , (d) Guo HY *et al.* **[40]** , (e) Azarifar D *et al.* **[41]** and (f) Pratap UR *et al.* **[42]** are shown in **Fig. 3**.

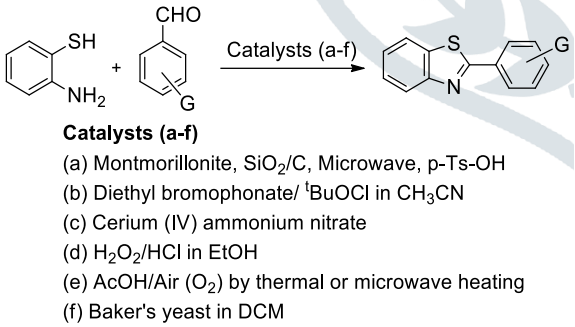


Fig. 3: Synthesis of 2-aryl benzothiazoles from substituted benzaldehydes.

Mn(III) triacetate is an excellent one-electron oxidant for radical cyclization of substituted thioformanilides to produce 2-substituted benzothiazoles under microwave irradiation **[18]**. 2-Aryl and 2-alkyl substituted benzothiazoles are also synthesized through intramolecular C(aryl)-S bond of N(2-chlorophenyl)benzothioamides forming-cyclization using Cu(II)-BINAM catalysed coupling using Cs_2CO_3 as a base in acetonitrile solvent (**Fig. 4**) **[43,44]**. Banerjee *et al.* **[8]** reported varieties of benzothiazole derivatives, can be prepared by the condensation reaction which is catalysed by green nanocatalyst ZnO in ethanol at nearly room temperature. Praveen C *et al.* [6] proposed the generality of the transformation of thiophenolic and phenolic schiff's bases to the corresponding benzothiazole and benzoxazole by treating PCC with a range of substituted and structurally diverse Schiff's bases. Treatment of Schiff's bases with silica gel supported PCC (1:1 equiv) in CH_2Cl_2 afforded the oxidized products in good to excellent yields.

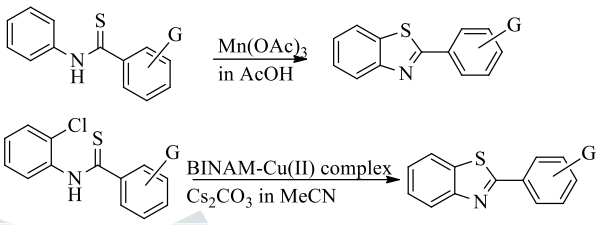


Fig. 4: Synthesis of 2-arylbenzothiazoles from substituted thioformanilides, N-(2-chlorophenyl) benzothioamides.

Substituted benzothiazoles have shown a wide spectrum of biological activities. Yadav *et al.* **[45]** has screened antibacterial activity of 2-substituted benzothiazoles against *S. Aureus, S. Epidermidis, P. Aeruginosa, E. Coli* by disk diffusion method using DMF as a solvent. Devmurari *et al.* **[10]** reported some 2-phenyl substituted benzothiazoles, which are more active against gram positive microorganism (*Staphylococcus aureus, Bacillus cereus*) than the gram negative bacteria (*Klebsiella pneumoniae, Escherichia coli*). Singh *et al.* **[46]** evaluated antibacterial activity of benzothiazole derivatives against two Gram positive bacterial strains *Staphylococcus aureus* and *Enterococcus faecalis* and four Gram-negative bacterial strains: *Escherichia coli, Salmonella typhi, Pseudomonas aeruginosa*, and *Klebsiella pneumonia*, using the method recommended by National Committee for Clinical Laboratory Standards (NCCLS). Shi *et al.* **[24]** reported that 2-(4-aminophenyl) benzothiazoles display potent inhibitory properties in a range of cell types *in vitro* and shows selective effects, particularly against breast cancer cell lines. Liu *et al.* **[11]** reported some benzothiazole derivatives shows antifungal activity against a number of microorganisms (*C. Albicans, C. Glabrata, C. Neoformans, T. rubrum and M. Gypseum*). Mahran *et al.* **[19]** reported benzothiazole derivatives were subjected to in vivo antiparasitic evaluation against *Trichenilla spiralis.* Venkatesh *et al.* **[26]** reported some 2-aminobenzothiazole derivatives, active as anti-inflammatory agents. In view of the above observations, the synthesis 2-aryl benzothiazoles

and then antibacterial activity study of the prepared compounds have been taken as the aim in this small article. Four different 2-aryl benzothiazoles were prepared by grinding method using minimum amount of the solvent **(Fig. 5)**. Two gram negative bacterial strains viz *Klebsiella* sp., *Salmonella* sp were taken to study the antibacterial activity of the prepared compounds.

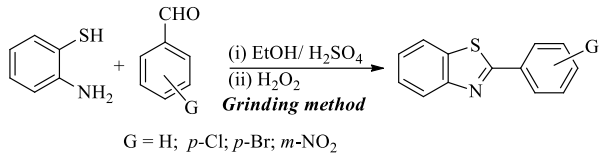


Fig. 5: Proposed scheme of preparation of 2-aryl benzothiazoles

III. EXPERIMENTAL

(A) Materials and methods:

The reagents and solvents used in this work were procured from commercial sources and utilised without further purification. Melting points were measured on an Electrothermal melting point apparatus and are uncorrected.The infrared spectra were obtained with KBr pellets in the range of 4000 cm^{-1}- 450 cm^{-1} using Perkin Elmer Fourier transform (FT-IR) spectrophotometer. The bands obtained in the IR spectra reveal the functional groups present. NMR spectra were recorded on a Bruker 300 MHz FT-NMR spectrometer with $CDCl_3$ as a solvent and using tetramethylsilane (TMS) as an internal standard.

(B) General procedure of preparation of 2-aryl benzothiazoles:

8 mmol of 2-aminothiophenol, 8 mmol of aldehydes or substituted aldehydes and a minimum amount of ethanol were mixed in a pestle in an open mortar with thoroughly ground. To it, added 4 drops of dil. HCl and ground the mixture for 2-3 minutes. Then added 1 mL of H_2O_2 to the mixture and ground the mixture for 20 minutes. The reaction was monitored by TLC. The product was washed with distilled H_2O and was recrystallized with alcohol

2-Phenyl-1, 3-benzothiazole (P1): m.p. 110-111 ^oC (Li.t m.p.: 112-116 ^oC); % yield 95.5; IR (KBr), ν_{max}, cm^{-1}: 3 064.84 cm^{-1} (Ar C-H), 1588.92 cm^{-1} (C=C str.),1478.88 cm^{-1}(C=N str.) 1314.22 cm^{-1} (Ar. C-N str.) 623.51 cm^{-1} (C-S); ^1H NMR($CDCl_3$, 300MHz) (δ in ppm, J in MHz): δ=7.267-7.428 (m, 1H) δ=7.487-7.521 (m, 4H) δ=7.917 (d, 1H, *J*=7.8) δ=8.080-8.125 (m, 3H)

2-(4-Chlorophenyl)-1,3-benzothiazole (P2): m.p. 116-117 ^oC (Li.t m.p.: 118-120 ^oC); % yield 92.1; IR (KBr), ν_{max}, cm^{-1}: 3055.19 cm^{-1} (Ar C-H str.), 1597.11cm^{-1} (C=C str.), 1474.63 cm^{-1}(C=N str.), 1315.16 cm^{-1} (Ar. C-N str.),756.47 cm^{-1} (C-Cl str.), 617.84 cm^{-1}(C-S str.); ^1H NMR($CDCl_3$, 300MHz) (δ in ppm, J in MHz): δ=7.389-7.543 (m, 4H), δ=7.922 (d, 1H, *J*=7.5), δ=8.027-8.091 (m, 3H)

2-(4-Bromophenyl)-1, 3-benzothiazole (P3): m.p. 130-132 ^oC (Li.t m.p.: 132-136 ^oC); % yield 95.5; IR (KBr), ν_{max}, cm^{-1}: 3058.02 cm^{-1} (Ar C-H str.), 1607.11 cm^{-1} (C=C str.), 1475.58 cm^{-1} (C=N str.), 1314.12 cm^{-1} (Ar. C-N str.), 617.85 cm^{-1} (C-S str.), 548.44 cm^{-1} (C-Br str.); ^1H NMR($CDCl_3$, 300MHz) (δ in ppm, J in MHz): δ=6.907-6.957 (m, 1H), δ=7.0605 (d, 1H, *J*=8.1), δ=7.244-7.262 (m, 2H), δ=7.343-7.406 (m, 3H), δ=8.645 (s, 1H)

2-(3-Nitrophenyl)-1, 3-benzothiazole (P4): m.p. 184-185 ^oC (Li.t m.p.: 186-188 ^oC); % yield 95.5; IR (KBr), ν_{max}, cm^{-1}: 3086.37 cm^{-1} (Ar C-H str.), 1621.45cm^{-1} (C=C str.), 1530.75 & 1346.15 cm^{-1} (NO_2), 1460.81 cm^{-1} (C=N str.) 1312.49 cm^{-1} (Ar. C-N str.), 698.07 cm^{-1} (C-S str.); ^1H NMR($CDCl_3$, 300MHz) (δ in ppm, J in MHz): δ=7.255-7.496 (m,1H), δ=7.540-7.588 (m, 1H), δ=7.684-7.737 (m, 1H), δ=7.970 (d, 1H, *J*= 7.8), δ=8.1335 (d, 1H, *J*= 8.1), δ=8.344-8.370 (m, 1H), δ=8.441 (d, 1H, *J*=7.8), δ=8.951 (s, 1H).

(C) Antibacterial Analysis by Disc Diffusion Method:

The compounds were screened for their antimicrobial activity by Disc Diffusion method **[32-34]** against two gram negative bacterial strains namely *Klebsiella* sp. and *Salmonella* sp. Antibacterial activity was tested by the filter paper disc diffusion technique. Nutrient Agar (NA) was used as the bacteriological medium. The test solutions of the compounds were prepared in chloroform for the study. The synthesized compounds were tested at different concentrations 0.5, 1.0, 1.5, 2.0, 5.0, 10.0 and 20.0 mg/mL to find out the minimum concentration of the compounds required for inhibiting the growth of bacteria. Ampicillin (10 μg/mL) was taken as the positive control for antibacterial activity and sterile double distilled water was used as negative control. 20 mL sterile melted autoclaved nutrient agar poured in a sterile petri dish and allowed to solidify. Then the bacterial samples were inoculated in the NA medium by mixing one mL of inoculum. Then the test solutions, the standard drugs, and the blank were impregnated in Whatman filter paper discs (diameter of 7 mm), placed on the solidified medium in the petri dish, and left undisturbed for 2 hour at room temperature. The petri dishes were then incubated at 32 ^0C for 24 hour and the zone of inhibition for the test samples, standard (positive control), and distilled water (negative control) were measured.

IV. RESULTS AND DISCUSSION:

In this section, the preliminary characterization of the prepared benzothiazoles using basic techniques such as ^{1}H NMR and IR spectroscopy, TLC and melting point determination has been discussed. The IR and ^{1}H NMR spectra of the recrystallized benzothiazoles are shown in Figures (SM1-SM4 in supplementary data). In the IR spectra, the weak stretching frequency of $C_{sp}{}^2$–H of aromatic rings appears in the range 3200–2900 cm^{-1}. The C=C bond of aromatic rings appear at ~1600 cm^{-1} as weak or medium band. The aromatic C=N stretching frequency generally appears at 1600-1750 cm^{-1} but in thiazole ring the $\nu_{C=N}$ absorption appears in the range of 1470-1690 cm^{-1}. The aromatic C-N stretching frequency appears at 1246–1351 cm^{-1}. The C-S stretching frequencies occur at 600-700 cm^{-1}. Two strong intense IR frequency for symmetric and antisymmetric stretching of NO_2 group exhibits ~1550 and ~1350 cm^{-1} respectively. The C-Cl and C-Br stretching frequency occurs at 540-785 cm^{-1} and 510-650 cm^{-1} respectively. The C=N stretching frequencies of thiazole ring for all the four investigated compounds occur at ~1460.81 -1478.88 cm^{-1} whereas the aromatic C-N stretching frequencies are observed at ~1312.49-1315.16 cm^{-1}. The C-S stretching frequencies of the products occur in the range of 617.84- 698.18 cm^{-1}. The C-Cl stretching frequency of compound P2 occurs at 756.33 cm $^{-1}$ whereas the C-Br str. frequency of compound P3 occurs at 548.44 cm^{-1} cm^{-1}.The -NO_2 group of compound P4 absorbs at 1530.75 and 1346.15 cm^{-1} for antisymmetric and symmetric stretching respectively. All the prepared compounds have only aromatic hydrogens and hence give the signals within 6.5-8.5 ppm in ^{1}H NMR spectra.

In the present work, the synthesis has been carried out by grinding method by using minimum amount of the solvent. Under this condition, the product yield is quite good, reaction time is very less and isolation of the product is also easy. An additional advantageous feature of the present work is that here simple technique like TLC has been used to monitor the course or progress of the reactions. Furthermore, the common spectroscopic tools such as NMR and IR have been used to characterize the products. Determination of melting point via the simple laboratory set-up has also been used as the supportive way to investigate the products. The method reported here for the synthesis of benzothiazoles is very simple and effective in terms of short reaction time, excellent yields, and the formation of one product as measured by TLC. It is also consistent with the green chemistry approach because it does not need heating or microwave irradiation. It occurs at room temperature and is free from organic solvents during separation of the product.

Antibacterial activity of the prepared compounds were studied against *Klebsiella* sp. and *Salmonella* sp. The ZOI of blank disc of 7 mm of diameter has been used as negative control against two bacteria. The ZOI of the tested compounds are shown in **Table I** and **Table II**. The mean ZOIs of the compounds against the two bacteria are plotted in **Fig. 6 and Fig. 7**. The pictures of antibacterial study were found as shown in **Fig. 8.** Among the four compounds, 2-(4-chlorophenyl)-1, 3-benothiazole (P2) was found to inhibit the growth of *Klebsiella* sp. for all the concentrations (1.0, 1.5, 2.0,5, 10, and 20 mg/mL) except 0.5 mg/mL and 2-(4-bromophenyl)-1,3-benothiazole (P3) showed inhibitory activity against *Salmonella* sp. for higher concentrations i.e 10 and 20 mg/mL only. The zone of inhibition (ZOI) for the standard Ampicillin was found to be 19.1 mm against Klebsiella sp. and 18.7 mm for *Salmonella* sp. The sensitivity of our prepared compounds was found be much lower as compared to the standard drug.

Table I: ZOI produced by all the tested compounds against *Klebsiella* sp

Conc. (mg/mL)	ZOI P1(mm)	Mean ± SD	ZOI of P2(mm)	Mean ± SD	ZOI of P3(mm)	Mean ± SD	Z O I of P4(mm)	Mean ± SD
0.5	7	7±0	7	7±0	7	7±0	7	7±0
	7		7		7		7	
1.0	7	7±0	7.1	7.15±0.05	7	7±0	7	7±0
	7		7.2		7		7	
1.5	7	7±0	8.1	8.15±0.05	7	7±0	7	7±0
	7		8.0		7		7	
2.0	7	7±0	8.6	8.55±0.05	7	7±0	7	7±0
	7		8.5		7		7	
5.0	7	7±0	8.5	8.55±0.05	7	7±0	7	7±0
	7		8.6		7		7	
10.0	7	7±0	8.7	8.7±0	7	7±0	7	7±0
	7		8.7		7		7	
20.0	7	7±0	9	8.94±0.06	7	7±0	7	7±0
	7		8.8		7		7	

Table II: ZOI produced by all the tested compounds against *Salmonella* sp.

Conc. (mg/mL)	ZOI of P1(mm)	Mean ± SD	ZOI of P2(mm)	Mean ± SD	Z OI of P3 (mm)	Mean ± SD	Z OI of P4(mm)	Mean ± SD
0.5	7	7±0	7	7±0	7	7±0	7	7±0
	7		7		7		7	
1.0	7	7±0	7	7±0	7	7±0	7	7±0
	7		7		7		7	
1.5	7	7±0	7	7±0	7	7±0	7	7±0
	7		7		7		7	
2.0	7	7±0	7	7±0	7	7±0	7	7±0
	7		7		7		7	
5.0	7	7±0	7	7±0	7	7±0	7	7±0
	7		7		7		7	
10.0	7	7±0	7	7±0	7.5	7.55±0.05	7	7±0
	7		7		7.6		7	
20.0	7	7±0	7	7±0	8.5	8.55±0.05	7	7±0
	7		7		8.6		7	

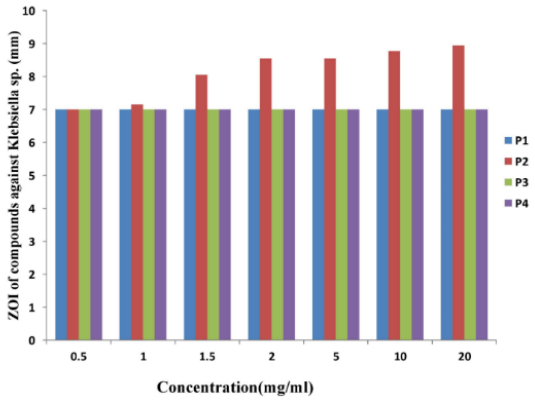


Fig. 6: Plot of Mean ZOI of compounds against concentrations for *Klebsiella* sp

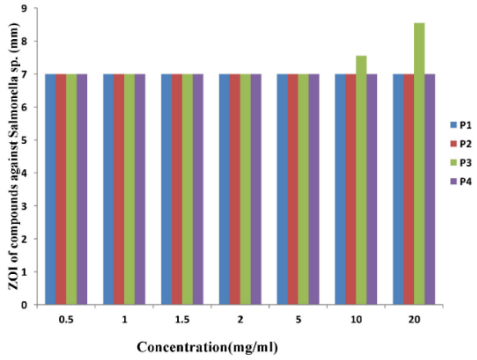
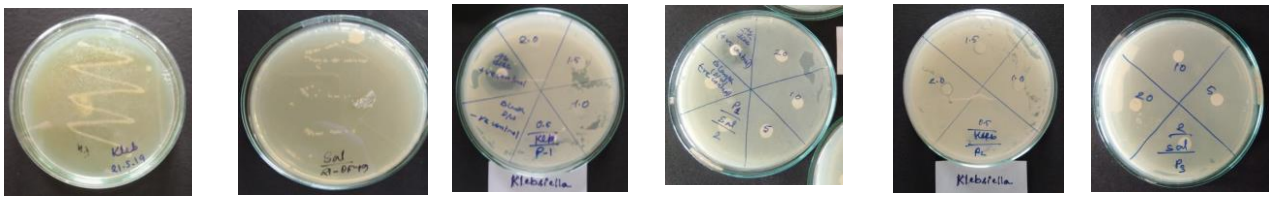


Fig. 7: Plot of Mean ZOI of compounds against concentrations for *Salmonella* sp



(a) (b) (c) (d) (e) (f)

Fig. 8: Pictures of antibacterial study; **(a)** Growth of *Klebsiella* sp **(b)** Growth of *Salmonella* sp. **(c)** ZOI of **P1**, Ampicillin, blank disk against *Klebsiella* sp.**(d)** ZOI of **P1**, Ampicillin, blank disk against *Salmonella* sp. **(e)** ZOI of **P2** against *Klebsiella* sp **(f)** ZOI of **P3** against *Salmonella* sp.

V. CONCLUSION

This methodology is very simple and efficient for the synthesis of 2-Aryl benzothiazoles. All the four compounds have been synthesised by grinding method using minimum amount of the solvent. The main advantages of this procedure are the less reaction time, easy isolation of the products and excellent yields. Out of four prepared compounds, 2-(4-chlorophenyl)-1, 3-benzothiazole (**P2)** was found to inhibit the growth of *Klebsiella* sp. for all the taken concentrations except 0.5 mg/mL whereas 2-(4-bromophenyl)-1, 3-benzothiazole **(P3)** showed inhibitory activity against *Salmonella* sp. for higher concentrations only. However, the bacterial activity of the tested compounds was found to be less than the standard ampicillin.

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