Synthesis, Characterization and Antibacterial Activity of Substituted Benzothiazole Derivatives

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***Abstract*-** Various substituted 2-aminobenzothiazoles have been synthesized cyclocondensation of various substituted anilines with ammonium thiocyanate in presence of bromine. The title product 5-[(1*E*)-*N*-(1,3-benzothiazol-2-yl)ethanimidoyl]-4-(furan-2-yl)-3,4-dihydropyrimidine-2(1*H*)-thione is synthesized by using 2-aminobenzothiazole. The structure of the synthesized compounds have been established on the basis of their spectral data. All micro-wave synthesized compounds results into good yield as compared to conventional method. Synthesized compounds were screened for their antibacterial activities.

***Index Terms*-** 2-Aminobenzothiazole, dihydropyrimidin-2-thiones and Antibacterial activity.

I. INTRODUCTION

Benzothiazole is a privileged bicyclic ring system. It contains a benzene ring fused to a thiazole ring.[1] The small and simple benzothiazole nucleus is present in compounds involved in research aimed at evaluating new products that possess interesting biological activities like antimicrobial, antitubercular[2], antitumor[3], antimalarial[4], antimicrobial[5], anthelmintic[6], antidiabetic[7], anticonvulsant[8], analgesic[9] and anti-inflammatory[10] activity. In addition, the benzothiazole ring is present in various marine or terrestrial natural compounds, which have useful biological activities. Due to their importance in pharmaceutical utilities, the synthesis of various benzothiazole derivatives is of considerable interest.

Today 3,4-dihydro-pyrimidin-2(1H)-ones (DHPM)and its derivatives have received considerable amount of attention due to its several biological activities such as antiviral, antibacterial, antitumor and anti-inflammatory properties[11]. Many of these compounds act as α-1a-antagonist calcium channel and antihypertensive agent [12,13]. Therefore the synthesis of this heterocyclic moiety has gained an immense importance in organic synthesis.

The Benzothiazole and Schiff base moieties are crucial functionalities due to their wide
Variety of biological activities and have a wide range of therapeutic properties. Keeping in view the importance of these organic moieties, a new series of 2-aminobenzothiazole containing novel Schiff bases derivatives were synthesized by sequential reaction. The structures of the synthesized compounds were confirmed by their analytical and spectral data. The synthesized compounds were evaluated for their in vitro antibacterial activity

against gram positive and gram negative bacteria. Synthesized compounds showed significant activity against microorganism, which can be correlated with the privileged heterocyclic scaffolds.

II. MATERIALS AND METHODS

All air reactions were carried out in oven dried (120^0C) or flame dried glassware. Analytical thin layer chromatography was performed with Merck silica gel plates (0.25mm thickness) with PF_{254} indicator. Compounds were visualized under UV lamp. Column chromatography was carried out using 60-120 mesh silica gel and technical grade solvents. ^{1}H-NMR spectra were recorded on at 200,300 and 400 MHz instruments with tetramethylsilane as an internal standard. IR spectra were recorded on Shimadzu Hyper IR Instruments.

III. EXPERIMENTAL

Synthesis of 2-amino -1, 3-benzothiazol (compound 1)

Compound **1** was prepared by reported method [19]. To a solution of (0.1 mol) of substituted Anilines and (0.4 mole) of Ammonium thiocyanate was dissolved in absolute ethanol containing 4 N HCl. To this mixture, bromine in glacial acetic acid was added and the reaction mixture was refluxed for 1 hour, then it was cooled in ice bath and basified with liquor ammonia to get the precipitate. The precipitate obtained was filtered washed with cold water and dried. The crude product was recrystallized from ethanol.

Synthesis of 1-[4-(furan-2-yl)-6-methyl-2-sulfanylidene-1, 2,3,4-tetrahydropyrimidin-5-yl]ethan-1-one (compound 2)

Furfuraldehyde (1mol), acetyl acetone (1mol) and thiourea (1.5 mol) taken in ethanol and added with few drops dilHCl and heated in water bath for 8 hrs. Then completion of reaction check with TLC (ethyl acetate + hexane 9:1) The reaction mixture pour with ice cold water solid filter wash with sufficient water and recrystallization from methanol

Synthesis of 5-[(1*E*)-*N*-(1,3-benzothiazol-2-yl)ethanimidoyl]-4-(furan-2-yl)-3,4-dihydropyrimidine-2(1*H*)-thione(compound 3)

3a. Conventional method:

In a round bottom flask, Compound Compound**1**(1mol), compound **2** (1 mol), dissolve in ethanol then add few drops of glacial acetic acid. The reaction mixture was reflux for about 8 hrs till the completion of the reaction. Progress of the reaction was checked with TLC (Hexane: Ethyl acetate – 4:1) Then it was cooled with ice cold water. It was filtered and washed with cold water and dried the crude product was recrystallized from ethanol.

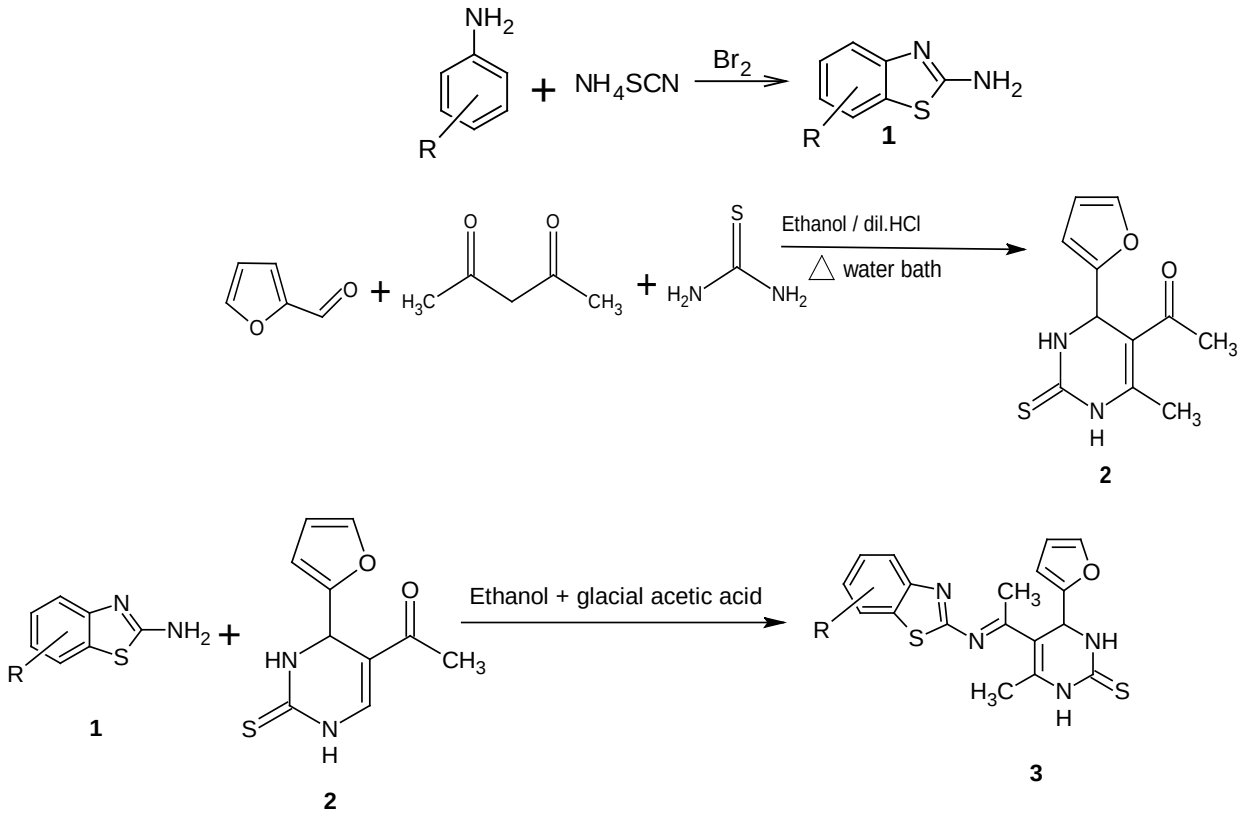
3b. Microwave irradiation method:

A mixture of Compound **1**(1mol), compound **2** (1 mol), and few drops of DMF were added in a hard glass tube and irradiated in microwave oven at appropriate power and time Completion of the reaction was monitored by

TLC, mixture was cooled and poured with ice cold water. And the resulting Solid filtered dried and recrystallized from ethanol.

5-[(1*E*)-*N*-(1,3-benzothiazol-2-yl)ethanimidoyl]-4-(furan-2-yl)-3,4-dihydropyrimidine-2(1*H*)-thione IR (KBr) cm^{-1}: 3294 (-NH);;1612 (C=C); 1535(C=C), 817,748, (Ar-CH), ^{1}H-NMR (DMSO d6) δ: 9.0 (1H, NH), 1.2(3H,t,CH_3),4.0(2H,q,OCH_2CH_3),2.2 (3H,s,CH_3),2.3(3H, s,CH_3-N),5.37 (1H, d,CH), 6.2, (1H,d,Ar-CH)6.4, (1H,d,Ar-CH),6.8(1H,d,Ar-CH), 7.1-7.6(3H,m , Ar-H), MS:- m/z = 368.47(m+)

Figure 1: Schematic representation of Benzothiazole



Where R=H, -Cl. CH_3, -Cl, $-NO_2$, $-OC_2H_5$ etc.

Table I: Synthesis 3a-j under conventional and microwave heating.

Entry	R	Conventional heating		Microwave heating			mp. ^oC
		Time in Hours	% Yields*	Microwave power in Watt	Time in min.	% yield*	
3a	H	8	55	300	3	90	97

3b	6-OC_2H_5	8	56	300	3.5	89	195
3c	5-NO_2	8	53	450	5	85	228
3d	6-CH_3	8	58	300	3	92	235
3e	4-Cl	8	61	300	3.5	88	179
3f	4,6,7-Tri Cl	8	63	450	4	91	135
3g	5-CH_3	8	65	300	3	94	175
3h	4-NO_2	8	54	300	5	86	170
3i	6- NO_2	8	58	450	5	87	174
3j	5,6–di-CH_3	8	66	300	4	95	175

*****Yields refer to purified compounds

IV. ANTIBACTERIAL BIOASSAY

0.4% of the MIC (minimum inhibitory concentration) of all the final products were prepare in dimethyl formamide solvent and tested against one gram +ve (Escherichia coli) and one gram –ve bacteria (Staphylococcus aureus). The composition of nutrient agar medium was bactotryptone (4g), Broth (3.9 g) less than 2%, NaCl (2.9 g) in 100 ml of water (0.9%). After 18h the exponentially growing culture of the 2 bacteria in nutrient broth at 37^0C were diluted in sterile broth. From each of these diluted culture, 1ml was added to 100ml sterilized and cooled nutrient agar media to give a final bacterial. The plates were set at room temperature and later dried at 37^0C for 20h. Paper discs (6mm, punched from whatmann No. 41 paper) used for the assays. Discs were socked in DMF and placed on the inoculated agar media at regular intervals of 6-7 cm, care was taken to ensure that excess solution was not on the discs. All the samples were taken in triplicates. The plates were incubated at 37^0C in an inverted fusion. Activity as determined by zone showing complete inhibition (mm). Growth inhibition was calculated with reference to positive control.

V. RESULTS

The structure of synthesized compounds was confirmed by IR, ^{1}H NMR, GC-MS analysis. Compounds (3a-j) were screened against twopathogenic bacteria. One gram negative strains viz.., Escherichia coli and one Gram positive stains viz.., Staphylococcus aureus following agar well diffusion procedure as per the reference. The antibacterial activity of the synthesized benzothiazole 3a-3j was corrected with the zone of inhibition of erythromycin as a standard control. (Table 2). The bacterial test result for the newly synthesized benzothiazole analogues revealed that most of the compounds exhibited moderated to good activity against Gram

+ve(Staphylococcus aureus) and Gram –ve bacteria (Escherichia coli). Staphylococcus aureus: compounds 3a and 3g exhibited maximum activity while the other compounds displayed moderate activity. And in case of Escherichia coli, compounds 3f and 3jexhibited good to excellent activity while the reaming compounds displayed moderate and less activity. As all compounds showed antibacterial activity against the bacteria tested. In indicates that this basic moiety can be a potential scaffold for anti bacterial drugs. It may be suggested that the amino benzothiazole derivative with a suitable R group may lead to a good antibacterial agent for all the Escherichia coli and Staphylococcus aureus bacterial strains. Thus further lead optimization is required to get wide spectrum of activity.

Table 2: Result of Antibacterial Bioassay of compounds

Compound No.		**Zone of Inhibition (mm)**	
		Gram -ve	**Gram +ve**
	R	**E.coli**	**S. aureus**
3a	H	12	11
3b	6-OC_2H_5	10	09
3c	5-NO_2	11	10
3d	6-CH_3	13	10
3e	4-Cl	13	10
3f	4,6,7-Tri Cl	15	12
3g	5-CH_3	12	11
3h	4-NO_2	13	08
3i	6- NO_2	11	09
3j	5,6 –di CH_3	14	11
Standard	Erythromycin	24	22

VI. CONCLUSION

Substituted derivatives of 5-[(1*E*)-*N*-(1,3-benzothiazol-2-yl)ethanimidoyl]-4-(furan-2-yl)-3,4-dihydropyrimidine-2(1*H*)-thiones (3a-3j) were prepare from commercially available 2- amino benzothiazole. Compounds (3a-j) were also synthesized by microwave irradiation method. Yields of microwave assisted synthesis were high. Synthesized compounds were tested for Gram positive and Gram Negative bacterial cultures. All the compounds were found to exhibit good to moderate antibacterial activity.

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