Synthesis and Antimicrobial Evaluation of Some Novel Sulfonamide Derivatives Containing Thiazole Moiety†

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Abstract : In the present study, synthesis of some novel thiazole containing sulfonamide analog have been carried out. Reaction of 4-(2-{[(3-Ethyl-4-methyl-2-oxo-2,5-dihydro-1H-pyrrol-1-yl)carbonyl] amino}ethyl) benzenesulfonyl chloride and 3-aminoacetophenone in acetone for 36 hours afforded N-(2-{4-[(3-acetylanilino)sulfonyl]phenyl}ethyl)-3-ethyl-4-methyl-2-oxo-2,5-dihydro-1H-pyrrole-1-carboxamide (sulfonamide), while reaction of various aniline with hydrochloric acid yields aniline hydrochloride. Which was further reacted with ammonium thiocyanate to obtain various phenyl thioureas. To obtain thiazole, (N-(2-{4-[(3-acetylanilino)sulfonyl]phenyl}ethyl)-3-ethyl-4-methyl-2-oxo-2,5-dihydro-1H-pyrrole-1-carboxamide) i.e. sulfonamide was reacted with different phenyl thioureas in presence of iodine and recrystallised from methyl ethyl ketone. The synthesized compound was characterized for structural confirmation by IR, ^{1}H NMR and elemental analysis. The antimicrobial activity of these synthesized compounds were examined by the broth dilution method. Bacterial strains such as gram-negative bacteria (*Escherichia coli),* and gram-positive bacteria (*Staphylococcus aureus)* were used.

I. INTRODUCTION

Thiazole derivatives reported to possess broad spectrum of pharmacological activities like analgesic [1], antidiabetic [2], anthelmintic, anticancer[3], antifilarial[4], antifungal and antibacterial[5], CNS depressant[6], antitumoral activites[7], anti-inflammatory [8], antihyperlipidemic[9], antihypertensive [10] and several other biological properties [11]. Thiazoles are also used as synthetic intermediates in numerous biologically active compounds [12,13].

II. LITERATURE REVIEW

One pot synthesis of substituted imidazo-pyridines and thiazoles from styrenes by NBS in water was reported by Shinde M et al.[14]. Zali-boeini H et al.[15] carried out a novel one-pot reaction for the synthesis of thiazole derivatives from α-haloketones, thioamides, and ammonium acetate at 110°C under microwave irradiation under solvent-free conditions**.** Valiveti A.K. et al.[16] synthesized 4-substituted-2-amino thiazoles from bromo-acetaldehyde derivative and thiourea. Suzuki et al.[17] reported the synthesis 5-substituted aminothiazole-4-carboxylic acid by the reaction of methyl α-isocyanoacetate with a proper isothiocyanate in the presence of potassium tertiary butoxide in THF at room temperature. Takaya and Takasugi[18] prepared 2-anilino-4-carbethoxy-5-phenylthiazole by the condensation of α-haloketoester with phenylthiourea . El-Subbagh and Al-Obaid[19] prepared a series of 2,4-disubstituted thiazole derivatives bearing N-cyclohexyl or N-butyl thioureido synthon at 2-position and N-substituted thiosemicarbazone moiety at 4-position and these compounds were tested for antitumor activity. Zhao D et al.[20] synthesized 2,4,5 -trisubstituted thiazoles via the reaction of thioureas and α-nitroepoxides under mild conditions at room temperature. Liu Y et al.[21] carried out the synthesis of 2,4-disubstituted thiazoles from carboxylic acids or anhydrides and β-azido disulfides. Brown et al.[22] synthesized a series of 2,4-diaryl-5-thiazole acetic acid as a potent anti-inflammatory agent. Pappalardo et al.[23] prepared 2-arylvinyl-5-phenylthiazoles and tested them for antibacterial activity. Zitouni et al.[24] synthesized thiazole derivatives of triazoles and screened for their antifungal and antibacterial activity.

III. MATERIALS AND METHODS

Materials: Reagent-grade chemicals were purchased from Merck. All the reagents and solvents were used without further purification. Melting points were determined on a Fisher–Johns melting point apparatus and are uncorrected. IR spectra were obtained on a Shimadzu FTIR 8400 spectrometer.^{1}H NMR spectra were recorded on Bruker Avance Ⅱ 400 NMR Spectrometer. The bacterial strains Gram positive bacteria: *Staphylococcus aureus* and Gram negative bacteria: *Escherichia coli* were used.

Synthesis of (N-(2-{4-[(3-acetylanilino)sulfonyl]phenyl}ethyl)-3-ethyl-4-methyl-2-oxo-2,5-dihydro-1H-pyrrole-1-carboxamide) (Sulfonamide)

4-(2-{[(3-Ethyl-4-methyl-2-oxo-2,5-dihydro-1H-pyrrol-1-yl)carbonyl]amino} ethyl) benzenesulfonyl chloride (0.1 mole, 37.06 g) was taken in acetone (345 mL) under stirring in 3 necked round bottom flask. 3-Aminoacetophenone (0.1 mole, 13.5 g) was added into it in portions and this reaction mass was stirred for 36 hr at 25-30^{0}C. After completion of reaction, acetone was removed and water was added for transforming it into a solid. The obtained solid was recrystallised from methyl ethyl ketone.
M.P. : 148-152°C, Yield : 88%

Synthesis of phenyl thiourea

Aniline (2.68 mole, 250 g) and toluene (1250 mL) were taken into a 2 litre 3-necked round bottom flask and stirred at room temperature. It was cooled to 15-20°C and at this temperature, hydrochloric acid (35%) (4.07 mole, 465 g) was added slowly to reaction mass. Reaction mass was maintained at room temperature for 1 hr. Then it was cooled to 0-5°C and reaction mass was filtered, yielding aniline hydrochloride.

Aniline hydrochloride (2.66 mole, 345 g) and ammonium thiocyanate (2.20 mole, 168 g) was charged in isopropyl alcohol (2070 mL) at room temperature into a 3 litre 3-necked round bottom flask. Reaction mass was heated for reflux (3 hr). Then reaction mass was filtered in hot condition and the obtained filtrate was collected and again charged to round bottom flask. It was concentrated by distillation, and cooled to room temperature. Then reaction mass was chilled to 0-5°C for 1 hr and filtered, which yielded phenyl thiourea.

Similarly, other eleven phenyl thioureas were synthesized by using various anilines. The results are summarized in Table 1.

Table 1. Various thioureas synthesized using different anilines

S. No.	Aniline	Phenyl thiourea	Mol. formula	Mol. weight	Yield (%)	M.P. (ºC)
1	2-Chloroaniline	2-Chlorophenyl thiourea	$C_7H_7ClN_2S$	186.58	54	141
2	4-Chloroaniline	4-Chlorophenyl thiourea	$C_7H_7ClN_2S$	186.58	56	178
3	2,6-Dimethylaniline	2,6-Dimethyphenyl thiourea	$C_9H_{12}N_2S$	180.15	58	193
4	4-Fluoroaniline	4-Fluorophenyl thiourea	$C_7H_7FN_2S$	170.12	53	163
5	3-Chloroaniline	3-Chlorophenyl thiourea	$C_7H_7ClN_2S$	186.58	57	138
6	4-Nitroaniline	4-Nitrophenyl thiourea	$C_7H_7N_3O_2S$	197.11	51	206
7	2,4-Dimethylaniline	2,4-Dimethylphenyl thiourea	$C_9H_{12}N_2S$	180.15	56	178
8	4-Methylaniline	4-Tolylphenyl thiourea	$C_8H_{10}N_2S$	166.14	59	180

9	4-Methoxylaniline	4-Methoxyphenyl thiourea	$C_8H_{10}N_2OS$	182.13	53	211
10	2-Methoxylaniline	2-Methoxyphenyl thiourea	$C_8H_{10}N_2OS$	182.13	55	152
11	2-Methylaniline	2-Methylphenyl thiourea	$C_8H_{10}N_2S$	166.14	58	156

Synthesis of thiazole (N-{2-[4-({3-[2-anilino-1,3-thiazol-4-yl]anilino}sulfonyl)phenyl]ethyl}-3-ethyl-4-methyl-2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxamide) (AF-12)

N-(2-{4-[(3-Acetylanilino)sulfonyl]phenyl}ethyl)-3-ethyl-4-methyl-2-oxo-2,5-dihydro-1H-pyrrole-1-carboxamide (0.01 mole, 46.92 g) and phenyl thiourea (0.02 mole, 3.04 g) was added to chloroform (50 mL) and stirred. Iodine crystals (0.01 mole, 2.53 g) were added into it with stirring and reaction mass was heated to reflux for 12 hr. It was filtered and the obtained crystals were added to water (60 mL). Reaction mass was heated to reflux and filtered. The filtrate thus obtained was cooled and basified with ammonium hydroxide for obtaining solid crystals, which was separated by filtration, washed with water and dried. Finally, it was recrystallised from methyl ethyl ketone.

M.P. : 149-150°C, Yield : 68%

Similarly, other eleven thiazoles were synthesized by using various phenyl thioureas. The results are summarized in Table 2.

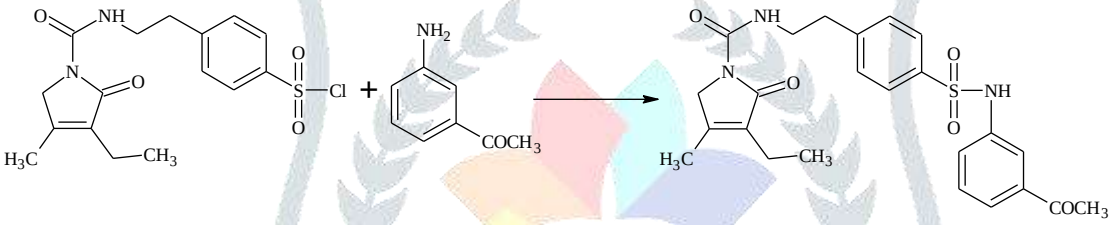
Table 2. Various thiazoles synthesized using different phenyl thioureas

S. No.	**Comp. Code**	**Phenyl thiourea used**	**Molecular formula of thiazole**	**Molecular weight**	**Yield (%)**	**M.P. (°C)**
1	AF-1	2-Chlorophenyl thiourea	$C_{31}H_{30}ClN_5O_4S_2$	635.84	71	120-122
2	AF-2	4-Chlorophenyl thiourea	$C_{31}H_{30}ClN_5O_4S_2$	635.84	66	135-143
3	AF-3	2,6-Dimethylphenyl thiourea	$C_{33}H_{35}N_5O_4S_2$	629.41	69	144-145
4	AF-4	4-Fluorophenyl thiourea	$C_{31}H_{30}FN_5O_4S_2$	619.38	73	103-107
5	AF-5	3-Chlorophenyl thiourea	$C_{31}H_{30}ClN_5O_4S_2$	635.84	69	130-137
6	AF-6	4-Nitrophenyl thiourea	$C_{31}H_{30}N_6O_6S_2$	646.37	72	143-149

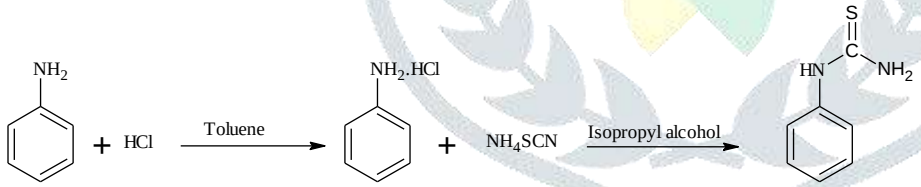
7	AF-7	2,4-Dimethylphenyl thiourea	$C_{33}H_{35}N_5O_4S_2$	629.41	68	147-149
8	AF-8	4-Methylphenyl thiourea	$C_{32}H_{33}N_5O_4S_2$	615.40	66	127-128
9	AF-9	4-Methoxyphenyl thiourea	$C_{32}H_{33}N_5O_5S_2$	631.39	69	149-153
10	AF-10	2-Methoxyphenyl thiourea	$C_{32}H_{33}N_5O_5S_2$	631.39	73	144-145
11	AF-11	2-Methylphenyl thiourea	$C_{32}H_{33}N_5O_4S_2$	615.40	70	149-151

Reaction Schemes:

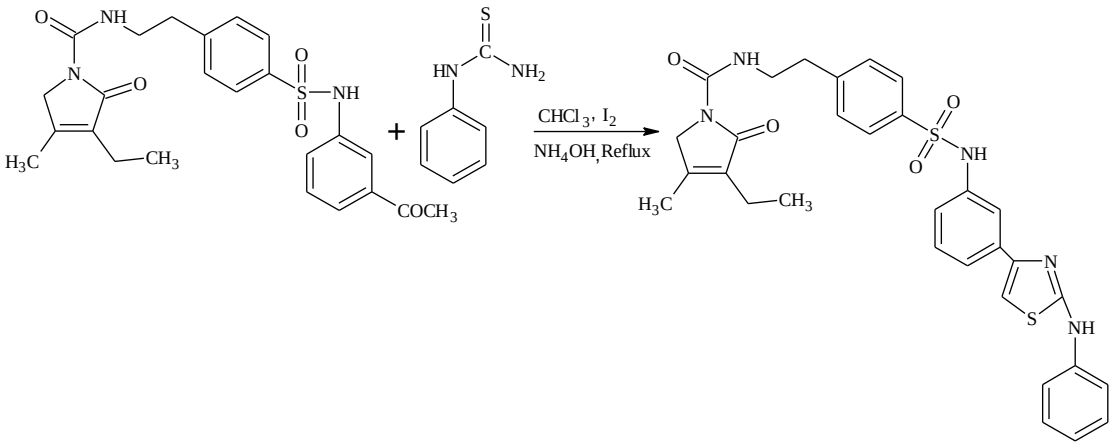
Synthesis of sulfonamide (N-(2-{4-[(3-acetylanilino)sulfonyl]phenyl}ethyl)-3-ethyl-4-methyl-2-oxo-2,5-dihydro-1H-pyrrole-1-carboxamide)



Synthesis of phenyl thiourea



Synthesis of thiazole (N-{2-[4-({3-[2-anilino-1,3-thiazol-4-yl]anilino}sulfonyl)phenyl]ethyl}-3-ethyl-4-methyl-2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxamide) (AF-12)



All the synthesized thiazoles were analyzed for their elemental composition and results are reported in Table 3.

Table 3. Elemental analysis of synthesized compounds

S. No.	Comp. Code	Comp. formula	C (%)		H (%)		N (%)	
			Calc.	Found	Calc.	Found	Calc.	Found
1	AF-1	$C_{31}H_{30}ClN_5O_4S_2$	60.04	60.01	4.88	4.87	11.29	11.28
2	AF-2	$C_{31}H_{30}ClN_5O_4S_2$	60.04	60.01	4.88	4.86	11.29	11.29
3	AF-3	$C_{33}H_{35}N_5O_4S_2$	62.93	62.88	5.60	5.57	11.12	11.10
4	AF-4	$C_{31}H_{30}FN_5O_4S_2$	60.08	60.13	4.88	4.90	11.30	11.27
5	AF-5	$C_{31}H_{30}ClN_5O_4S_2$	58.53	58.57	4.75	4.76	11.01	11.02
6	AF-6	$C_{31}H_{30}N_6O_6S_2$	57.57	57.51	4.68	4.65	12.99	13.00
7	AF-7	$C_{33}H_{35}N_5O_4S_2$	62.93	62.89	5.60	5.62	11.12	11.10
8	AF-8	$C_{32}H_{33}N_5O_4S_2$	62.42	62.39	5.40	5.40	11.37	11.38
9	AF-9	$C_{32}H_{33}N_5O_5S_2$	60.84	60.81	5.26	5.24	11.09	11.08
10	AF-10	$C_{32}H_{33}N_5O_5S_2$	60.84	60.89	5.26	5.28	11.09	11.10
11	AF-11	$C_{32}H_{33}N_5O_4S_2$	62.42	62.37	5.40	5.37	11.37	11.35
12	AF-12	$C_{31}H_{31}N_5O_4S_2$	61.88	61.81	5.19	5.16	11.64	11.63

Characterization: Infra-red data of compound (AF-1) and (AF-10) are reported in Tables 4 and 5, respectively

Table 4: IR spectral data of compound N-{2-[4-({3-[2-(2-chlorophenyl)-2,3-dihydro-1,3-thiazol-4-yl]anilino}sulfonyl)phenyl] ethyl}-3-ethyl-4-methyl-2-oxo-2,5-dihydro-1H-pyrrole-1-carboxamide (AF-1)

S. No.	Functional group (vibrational mode)	Frequency (cm^{-1}) (standard)	Frequency (cm^{-1}) (observed)
1	C-S str.	710-570	689.57
2	C-N str.	1342-1266	1312.60
3	C-N str. (aromatic amines)	1335-1250	1282.71
4	C=O str. (carbonyl)	1760–1665	1747.57
5	N-H str.	3400–3250	3322.50
6	C-H str. (aromatics)	3100-3000	3093.92

Table 5: IR spectral data of compound N-{2-[4-({3-[2-(2-methoxyphenyl)-1,3-thiazol-4-yl]anilino}sulfonyl)phenyl]ethyl}-3-ethyl-4-methyl-2-oxo-2,5-dihydro-1H-pyrrole-1-carboxamide (AF-10)

S. No.	Functional group (vibrational mode)	Frequency (cm^{-1}) (standard)	Frequency (cm^{-1}) (observed)
1	C-S str.	710-570	690.54
2	C-N str.	1342-1266	1315.50
3	C-N str. (aromatic amines)	1335-1250	1279.81
4	C=O str (carbonyl)	1760–1665	1747.57
5	N-H str	3400–3250	3320.57
6	C-H str. (aromatics)	3100-3000	3099.71

^{1}H NMR spectral data of compound 3-ethyl-4-methyl-N-{2-[4-({3-[2-(4-nitroanilino)-1,3-thiazol-4-yl]anilino}sulfonyl)phenyl]ethyl}-2-oxo-2,5-dihydro-1H-pyrrole-1-carboxamide (AF-6)

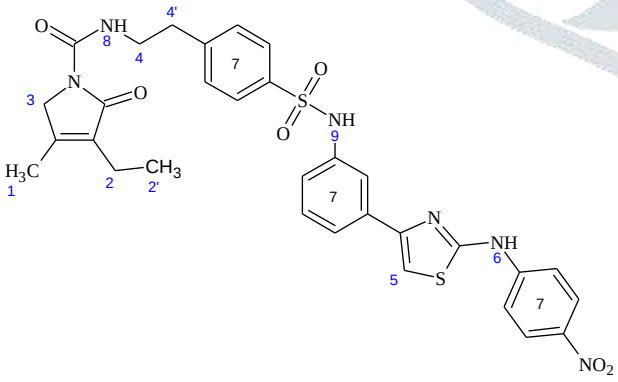


Table 6. ^{1}H NMR spectral data of compound (AF-6)

S. No.	Signal position	Relative no. of proton	Multiplicity	Assignment
1	2.49	3H	singlet	$-CH_3$ [1]
2	2.00	2H	triplet	$-CH_2$ [2]
3	2.25	3H	quartet	$-CH_3$ [2']
4	2.75	2H	triplet	$-CH_2$ [3]

5	2.65	2H	doublet, triplet	- CH_2 [4]
6	2.90	2H	quartet	- CH_2 [4']
7	8.08	1H	singlet	-CH [5]
8	10.07	1H	singlet	-NH [6]
9	6.89 - 8.08	12H	multiplet	-Ar-H [7]
10	7.62	1H	doublet	-CONH [8]
11	7.37	1H	singlet	-SO_2NH [9]

Antimicrobial activity: The antibacterial activity has been determined by using broth dilution method. All the synthesized compounds were screened for their antibacterial activity against a variety of bacterial strains such as gram-negative bacteria *(Escherichia coli)*, and gram-positive bacteria (*Staphylococcus aureus*). Gentamycin, ampicillin, chloramphenicol, ciprofloxacin and norfloxacin were used as standard drugs. Results are reported in Table 7 and Fig. 1.

Table 7. Antibacterial activity of synthesized compounds

Zone of inhibition (mm)			
S. No.	**Compound No.**	***E. coli***	***S. aureus***
		MTCC 443	**MTCC 96**
1	AF-1	250	500
2	AF-2	250	250
3	AF-3	50	250
4	AF-4	125	250
5	AF-5	250	100
6	AF-6	250	500
7	AF-7	25	1000
8	AF-8	500	250
9	AF-9	1000	500
10	AF-10	50	500
11	AF-11	100	125
12	AF-12	125	250
Standard drugs			
S. No.	**Drug** ($mg\ mL^{-1}$)	***E. coli*** MTCC 443	***S. aureus*** MTCC 96
13	Gentanmycin	0.05	0.25
14	Ampicillin	100	250
15	Chloramphenicol	50	50
16	Ciprofloxacin	25	50
17	Norfloxacin	10	10

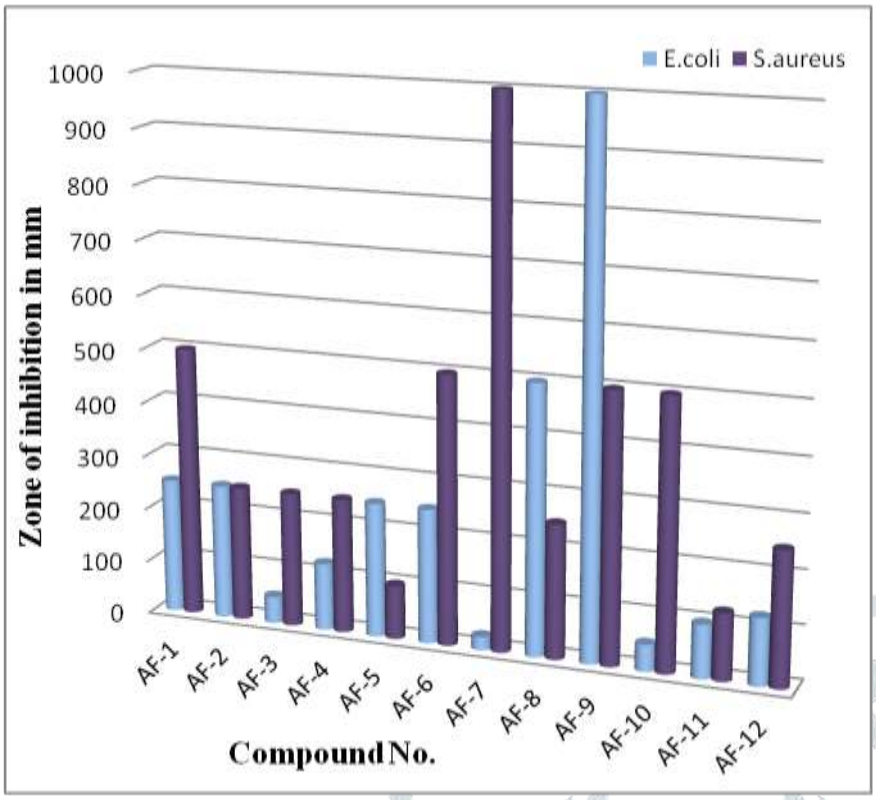


Fig.1. Antibacterial activity of synthesized compounds

IV. RESULTS AND DISCUSSION

RESULTS: Twelve thiazoles bearing sulfonamide group have been synthesized. All the synthesized compounds are tested for their antibacterial activity against gram negative (*Escherichia coli*) and gram positive (*Staphylococcus aureus*) bacteria strains by measuring zone of inhibition in mm, revealing that all compounds have considerable antibacterial activity, Out of all these synthesized compounds (AF-6–AF-10), showed strong antibacterial activity with respect to reference standard.

DISCUSSION: The substituted thiazole derivative having sulfonamide moieties are already known for different biological activities. As per the result of the screening, it is clearly indicated that the synthesized compound of the scheme (AF-1–AF-12) are having good antibacterial activity equipotent with the standard drugs. From the obtained results; one can reveal that the synthesized thiazole derivatives can be a rich source for the exploitation. Therefore, in search of new compound, which are biologically compound, one can explore the possibility in this area by introducing different functional group as substituent's, which may result into better pharmacological active compounds.

Synthesized compounds were purified by recrystallisation using methyl ethyl ketone. These compounds were confirmed by IR spectra, which showed the expected bands for the characteristic groups such as C–S, C–N and aromatic moiety. The presence of peaks in the region 689.57 and 690.54 indicates the presence of C-S, while peaks at 1312.60 and 1315.50 indicates the existence of C–N moiety in the compounds (AF-1) and (AF-10).
The structure of compound (AF-6) was confirmed by ^{1}H NMR which revealed the aromatic protons appeared as multiple peaks within the range 6.89 - 8.08 δ ppm, proton of CONH at 7.62 δ ppm and SO_2NH appeared at 7.37 δ ppm.

V. CONCLUSION

The substituted thiazole derivative having sulfonamide moieties are already known for different biological activities. It is clearly indicated by this study that the synthesized compounds are having good antibacterial activity, which is equipotent with the standard drugs. From the above results; one can see that the synthesized thiazole derivatives can be rich source for further exploitation. Therefore, in search of new generation of the active compound, it may be useful to explore the possibility in this area by making or introducing different substituent's.

VI. AKNOWLEDGEMENT

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