www.jmscr.igmpublication.org
Impact Factor 5.244
Index Copernicus Value: 83.27
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v4i11.42

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Novel Thiazoles Derivatives Containing Methoxy-Napthyl Moiety as Potent Anti-Bacterial and Anti-Tubercular Agents and Its Characterization

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Abstract
Thiazoles and their derivatives have attracted continuing interest in both pharmaceutical and agrochemical industries and shows significant importance for the discovery of potent bioactive agents due to their various biological activities.
The present study reports the synthesis of novel 2-{2-[(6-methoxynaphthalen-2-yl) methylidene] hydrazinyl}-4-(aryl)-1, 3-thiazole (5a-5j) which was synthesized by acid hydrolysis of 6-methoxynaphthalene-2-carbaldehyde (1) and hydrazinecarbothioamide (2) which was refluxed for around 10 hours using alcohol as solvent, to yield (2E)-2-[(6-methoxynaphthalen-2-yl) methylidene] hydrazinecarbothioamide (Thiosemicarbozone) (3). The compound (3) was then condensed with different substituted phenacyl bromide (4) at 90°C for 8-9 hours .The structures of newly synthesized compounds were characterized by IR,[1]H-NMR,[13]C -NMR and mass spectroscopic studies, few of the synthesized compounds showed moderate anti-TB activities and compounds (5d) showed moderate activity against M.tuberculosis (H37 RV Strain).Among the compounds screened for antibacterial activity (5c), (5e), (5g) and (5h) showed excellent antibacterial activity.
Keywords: *1, 3- thiazoles, Anti-bacterial and Anti-tubercular activity studies.*

Thiazoles are the compounds with hetero atoms like sulphur and nitrogen and refer to a large family of derivatives. The compounds that contain thiazole moiety are synthesized from decades as they are found to exhibit various potential biological activities the structural modifications of these chemical scaffolds of 2-[(2*E*)-b]-4-(4-methoxyphenyl)-1,3-thiazole lead discovery of novel compound with enhanced pharmacological activity. The heterocyclic scaffolds having carbothioamide has not reported and hence a decision to synthesize novel compounds bearing this moiety had made and recent literature reviews that compounds with thiazole moiety are continuously drawing the interest in the field of research, as they are found in many potent biologically active compounds and exhibits broad range of pharmacological activity such as anti-inflammatory [1], anticancer [2] ,anti-protozoa [3], anti-oxidant [4], anti-tryposomal [5], Neuroprot-ective agents [6], anti-breast cancer [7], anti-

microbial [8], , anti-tumour [9,10], analgesic [11] and anticonvulsants [12].

Hence inspired from these reports from the present review of literature a plan to synthesize novel compounds bearing thiazole moiety (5a-5j) was taken up in this study.

MATERIALS AND METHODS

The reaction is carried out according to well defined procedure from the detailed review of literature [13-19]. The ((2*E*)-2-[(6-methoxynaphthalen-2-yl) methylidene] hydrazinecarbo-thioamide (*Thiosemicarbozone*) (3) was synthesized by acid hydrolysis of 6-methoxynaphthalene-2-carbaldehyde (1) and hydrazinecarbothioamide (2) which was refluxed for around 10 hours using alcohol as solvent, which was later condensed with different substituted phenacyl bromide (4) at 90°C for 8-9 hours to yield series of novel 2-{2-[(6-methoxynaphthalen-2-yl) methylidene] hydrazine-yl}-4-(aryl)-1,3-thiazole (5a-5j) .The structures of these novel compounds (5a-5j) were confirmed through spectral analysis .

General procedure for the synthesis of ((2*E*)-2-[(6-methoxynaphthalen-2-yl) methylidene] hydrazine-carbothioamide (3) :

The ((2*E*)-2-[(6-methoxynaphthalen-2-yl) methylidene] hydrazinecarbothioamide (Thiosemicarbozone) (3) was synthesized according to well defined procedure from the literature. The equimolar mixture of 6-methoxynaphthalene-2-carbaldehyde (1) and hydrazinecarbothioamide (2) was acid hydrolyzed by refluxing the mixture for around 10 hours using alcohol as solvent .The precipitated compound was filtered and recrystallized using hot ethanol.

General procedure for the synthesis of novel 2-{2-[(6-methoxynaphthalen-2-yl) methylidene] hydrazinyl}-4-(aryl)-1, 3-thiazole (5a-j):

The ((2*E*)-2-[(6-methoxynaphthalen-2-yl) methyldene] hydrazinecarbothioamide (*Thiosemicarbozone*) (3) was mixed with different substituted phenacyl bromide (4) and refluxed for about 8-9 hours at 90°C to yield series of novel 2-{2-[(6-methoxynaphthalen-2-yl) methylidene] hydrazinyl}-4-(aryl)-1,3-thiazole (5a-j).The precipitated solid was filtered under suction, washed and recrystallized from hot ethanol.

5a

IR (KBr,Cm^{-1}):3299.59(>NH),3112.61, 2936.51 (-C-H),1563.79(N=C<azomethine) , 1245.90(>C-S-). ^{13}C-NMR: 55.275, 55.109 (2C OCH_3), 158.781, 151.446, 140.155, 134.814, 129.917, 129.730 (6C phenyl), 128.267, 127.613, 168.092 (3C thiadiazole), 145.921 (1C adjacent to naphthalene), 157.984, 127.355, 126.827, 125.994, 124.478, 122.669, 121.234, 119.022, 113.958, 106.399 (10 C napthyl ring). ^{1}H NMR:3.791,3.895(6H,s,2-methoxy groups of naphthalene moiety and substituted benzene), 6.984 (2H,d,J=8.4-p-methoxy benzene group), 7.356 (2H,d,J=8.4,p-methoxy benzene group), 7.184 (1H,s,hydrogen of thiazole moiety), 7.867 (6H,m,napthoxy moiety), 8.152(1H,s,NH group adjacent to thiazole moiety), 12.016 (1H,s,CH adjacent to napthoxy moiety). LC-mass: [M^++1],(m/Z): 390.05.

5b

IR (KBr, Cm^{-1}): 3288.66(>NH), 3014.78, 2955.67 (-C-H), 1625.20 (N=C) ,1270.53(>C-S-).^{13}C-NMR: 20.772, 55.268 (2C methyl and methoxy), 157.984,136.762, 134.816, 132.046, 129.888, 129.734,(6C phenyl), 129.141,128.256, 168.111 (3C thiadiazole), 145.921 (1C adjacent to methoxy naphthalene), 151.446, 127.384 ,125.446, 124.334,123.112 , 122.653, 120.003, 119.030, 106.381, 102.605 (10 C napthyl ring). ^{1}H NMR:2.326 (3H, s, methyl group attached to benzene ring), 3.895 (3H, s, methoxy groups of naphthalene moiety),7.186(4H,d,methoxy benzene), 7.352(1H,s, hydrogen of thiazole moiety) ,7.870 (6H,m,napthoxy moiety) 8.163 (1H,s,NH group adjacent to thiazole moiety), 12.124 (1H,s,CH adjacent to napthoxy moiety).LC-mass:[M^++1],(m/Z):373.02.

5c

IR (KBr,Cm^{-1}):3309.14(>NH)3012.74,2942.20 (-C-H),1626.91(N=C),1269.30(>C-S-).830,728(C-

Cl,).^{13}C-NMR: 55.219 (1C methoxy) ,158.437, 152.456, 140.135, 134.814, 129.917, 129.730,(6C phenyl), 129.267, 128.613 (2C thiadiazole), 168.099, 145.921 (2C thiadiazole), 157.984, 127.355, 126.827, 125.994, 124.478, 122.669, 121.234, 119.022, 113.958, 106.399,(10 C napthyl ring).^{1}H NMR:3.865(3H, s, methoxy groups of naphthalene moiety),6.654(2H,s,chloro benzene), 7.763(1H,s, hydrogen of thiazole moiety) ,7.729 (6H,m,napthoxy moiety) 8.076(2H,d,J=8.8 chloro benzene moiety)8.158 (1H,s,NH group adjacent to thiazole moiety),12.124(1H,s,CH adjacent to napthoxy moiety).LC-mass:[M^{+}+1], (m/Z): 393.02/391.00.

5d

IR (KBr, Cm^{-1}):3305.05(>NH) 3015.59, 2937.87(-C-H), 1626.23(N=C),1269.15 (>C-S-).695.84 (C-Br). ^{13}C-NMR: 55.484 (1C methoxy), 163.379, 135.804, 131.356, 130.785, 130.494, 130.232, (6C phenyl), 130.185, 128.805, 188.706 (3C thiadiazole), 145.921 (1C adjacent to naphthalene) ,158.898, 127.483, 127.333, 126.143, 125.127, 124.466, 120.972, 119.450, 113.851, 106.089 (10 C napthyl ring).^{1}H NMR:3.871(3H, s, methoxy groups of naphthalene moiety),6.987(2H,s,bromo benzene),7.174(1H,s, hydrogen of thiazole moiety) ,7.762(6H,m,napthoxy moiety), 8.069(2H,d,J=8.8 bromo benzene moiety),8.158 (1H,s,NH group adjacent to thiazole moiety),12.124(1H,s,CH adjacent to napthoxy moiety).LC-mass:,[M^{+}+1],(m/Z): 438.12/435.13.

5e

IR (KBr,Cm^{-1}):3308.5(>NH)3013.92,2948.32(-C-H),1625.50(N=C),1272.32 (>C-S-).1505.88 (NO_2,4-nitro phenyl moiety) ^{13}C-NMR: 60.522 (1C methoxy) , 163.302,151.446 147.445 140.155 135.017 134.955,(6C phenyl), 133.478 132.858, 173.895 (3C thiadiazole),145.921 (1C adjacent to naphthalene), 153.805, 132.664, 131.556 , 129.315 , 127.887 , 124.300 , 113.702 , 112.642, 111.345, 106.122 (10 C napthyl ring).^{1}H NMR:3.898(3H, s, methoxy groups of naphthalene moiety),7.354(1H,s, hydrogen of thiazole moiety) ,7.872(6H,m,napthoxy moiety) 8.128(2H,d,J=8.8 nitro benzene moiety),8.188 (1H,s,NH group adjacent to thiazole moiety), 8.314(2H,d,J=8.0 nitro benzene moiety),12.273(1H,s,CH adjacent to napthoxy moiety).LC-mass:,[M^{+}+1],(m/Z):.405.01.

5f

IR (KBr,Cm^{-1}):3298.23(>NH),3100.41,2934.05(-C-H stretch),1684.07(N=C),1260.30(>C-S-). ^{13}C-NMR: 55.267 (1C methoxy) , 158.053, 147.332 , 143.445, 142.190, 140.675, 134.904,(6C 3 phenyl), 129.760, 129.714,168.643 (3C thiadiazole) ,146.193 (1C adjacent to naphthalene), 148.556, 128.231, 127.603, 127.407, 126.300 ,124.051, 122.641, 119.040, 108.439, 106.395.(10 C napthyl ring).^{1}H NMR:3.898 (3H, s, methoxy groups of naphthalene moiety),7.287(1H,s, hydrogen of thiazole moiety) , 8.567 (1H,s,NH group adjacent to thiazole moiety) ,12.107(1H,s,CH adjacent to napthoxy moiety).8.043(4H,m, napthyl moiety) ,8.004, 8.345(2H,s, napthyl moiety), 7.980 (2H, s, methoxy napthoxy moiety) ,8.426 (2H, d, J=8.8 – methoxy napthoxy moiety), 8.288, 8.304(2H, s,-methoxy napthoxy moiety).LC-mass:, [M^{+}+1], (m/Z):409.02.

5g

IR (KBr,Cm^{-1}):3308.92 (>NH),3014.21,2947.52 (-C-H) ,1625.44 (N=C) ,1270.70 (>C-S-),842 (C-Cl). ^{13}C-NMR: 55.968 (1C methoxy),142.234, 141.184,141.297, 137.342, 136.476, 135.562, 134.616,133.790, 132.846,130.112, 129.888, 128.734,(12C biphenyl) 129.941,129.256 (3C atoms of thiadiazole moiety)168.091(1C atom of C=N in thiadiazole moiety), 145.921 (1C adjacent to naphthalene), 156.446, 127.384 ,126.446, 125.334,124.112 , 121.653, 120.003, 118.030, 115.381, 111.605 (10 C napthyl ring).^{1}H NMR:3.767 (3H, s, methoxy groups of naphthalene moiety),7.327(1H,s, hydrogen of thiazole moiety) , 8.157 (1H,s,NH group adjacent to thiazole moiety) ,12.071(1H,s,CH adjacent to napthoxy moiety),7.973(4H,m, napthoxy moiety),

7.880, 7.980(2H, s, napthoxy moiety), 8.426(2H, d, J=8.8 -2,4-di chloro benzene moiety), 8.288(1H, s,- 2,4-di chloro benzene moiety).LC-mass:,[M^++1],(m/Z):427.94/425.76.

5h

IR (KBr, Cm^{-1}):3299.32(>NH), 3012.92,2954.17(-C-H) ,1625.41(N=C),1270.15 (>C-S-).

^{13}C-NMR: 55.784 (1C methoxy), 164.379, 136.804, 132.356, 131.785, 131.494, 131.232, (6C phenyl) ,131.185, 129.805 , 188.706 (3C thiadiazole), 145.981 (1C adjacent to naphthalene) 158.898, 127.483, 127.333, 126.143, 125.127, 124.466, 120.972, 119.450, 113.851, 106.089. (10 C napthyl ring).^{1}H NMR:3.788 (3H, s, methoxy groups of naphthalene moiety),7.287 (1H,s, hydrogen of thiazole moiety) , 8.347 (1H,s,NH group adjacent to thiazole moiety), 12.098(1H,s,CH adjacent to napthoxy moiety) .8.043(5H,m, biphenyl moiety), 8.004(1H,s, biphenyl moiety), 8.667(3H,m, biphenyl moiety) ,7.880, 7.980(2H, s, napthoxy moiety), 8.426(2H, d, J=8.8 - napthoxy moiety), 8.288,8.304(2H, s, napthoxy moiety).LC-mass:,[M^++1], (m/Z): 436.04.

5i

IR (KBr,Cm^{-1}):3304.01(>NH)3015.16,2939.64(-C-H),1625.42(N=C),1269.11(>C-S-),1087 (C-F).^{13}C-NMR: 56.168 (1C methoxy), 141.984, 141.897, 137.542, 136.776, 135.762, 134.816, 133.890, 132.046, 129.888, 129.734(10C napthyl group) ,129.141,128.256 ,168.091 (3C atoms of thiadiazole moiety), 145.921 (1C adjacent to naphthalene), 151.446, 127.384 ,125.446, 124.334 ,123.112 , 122.653, 120.003, 119.030, 106.381, 102.605 (10 C napthyl ring).^{1}H NMR:3.898(3H, s, methoxy groups of naphthalene moiety),7.714 (1H,s, hydrogen of thiazole moiety) , 8.188 (1H,s,NH group adjacent to thiazole moiety) ,12.274(1H,s,CH adjacent to napthoxy moiety). 7.873 (3H,m, napthoxy moiety)7.216, 7.350, 7.980(3H, s, napthoxy moiety) 8.126(2H, d, J=8.8 fluoro benzene moiety), 8.288(2H, d, J=8.8 fluoro benzene moiety).LC-mass:[M^++1], (m/Z): 378.02/377.98.

5j

IR (KBr, Cm^{-1}):3301.12(>NH), 3013.14, 2948.35(-C-H), 1626.70(N=C) ,1629.92(>C-S-).^{13}C-NMR: 20.772, 60.522 (2C methyl and methoxy group), 133.478 132.858 , 173.895 (3C atoms of thiadiazole moiety,145.921 (1C adjacent to naphthalene moiety) 153.805, 132.664, 131.556, 129.315, 127.887, 124.300, 113.702, 112.642, 111.345, 106.122 (10 C napthyl ring).^{1}H NMR:2.436 (3H, s, methyl group attached to thiazole ring),3.879 (3H, s, methoxy groups of naphthalene moiety),7.365(1H,s, hydrogen of thiazole moiety) , 8.265(1H,s,NH group adjacent to thiazole moiety) ,12.563(1H,s,CH adjacent to napthoxy moiety),8.013(2H,d,J=8.4, napthoxy moiety) ,7.880, 7.980(2H, s, napthoxy moiety), 8.426(2H, d, J=8.8 - napthoxy moiety).LC-mass: [M^++1], (m/Z):297.07.

Anti- bacterial activity

The micro-organisms were collected from the institute of microbial technology, Chandigarh, India. The antimicrobial activity of novel compounds 5a-5j were screened *in vitro* by disc diffusion method (zone of inhibition test) using Ciprofloxacin an antibiotic as a reference standard against two gram positive *(Staphylococcus aureus* (MTCC-7443), *Bacillus subtilius* (MTCC-441*))* and two gram negative *(Escherichia coli* (MTCC-725), *Klebsiella pneumonia* (MTCC-1739)).

The colonies of the microbial strains were inoculated on nutrient agar plates with the help of sterile loop and visually adjusted the turbidity with broth to broth to match that of 0.5 McFarland standards. The excess of the inoculums was removed by rotating the sterile swab dipped in to the inoculum against the wall of the tube against it approximately 60^{o}C between streaking, the procedure is repeated three times to ensure even distribution. After 3 mins sterile discs of the size 6mm diameter were aseptically impregnated with the test compounds at a concentration 50µg/ml.

The plates were incubated at 37^0C for 24h.The compounds that produce distinct circular zones of inhibition around the discs .the diameter of clear zone indicate the anti-bacterial activity.

Antitubercular activity

All the synthesized compounds were evaluated for their anti-tubercular activity by Micro plate Alamar Blue Assay (MABA) the bacterial strain M.tuberculosis (H37 RV strain) was used for the screening.

The 96 wells plate of outer perimeter was inoculated with 200µl of sterile water and 100µl of middle brook 7H9 broth and serial dilution of compound were made directly on plate The final drug concentration tested were 100 to 3.12 µg/ml, the plates were sealed with parafilm and incubated at 37^oC for 5 days. Later 25µl of freshly prepared mixture of Alamar Blue reagent and10%tween 80 in 1:1 ratio was added and incubated for 24 hours .A blue colour in the well was interpreted as no bacterial growth and pink colour as bacterial growth. The antibiotic drugs such as pyrazinamide, streptomycin and ciprofloxacin was used as reference standard, whose standard values are 3.12µg/ml, 6.25µg/ml and 3.125µg/ml respectively.

RESULTS AND DISCUSSION

The reagents used in the reaction were derived from the commercial sources. Melting points of the compounds (5a-5j) were determined by the open capillary method and it was uncorrected. The purity of novel compounds was confirmed by observing single spot on TLC plate, Merck silica gel 60 F_{254}coated alumina plates. The structures of these novel compounds (5a-5j) were confirmed through spectral studies. The IR spectra (cm^{-1}) were recorded on a Shimadzu-FTIR 577 infrared spectrometer in KBr pellets. The ^{1}H-NMR and ^{13}C-NMR spectra was recorded on Brucker AMX-400(400MHz) spectrometer using $CdCl_3$-d as solvent and TMS as the internal standard. The mass spectra were recorded on Perkin –Elmer 018444Y, triple quadrapole LC/MS spectrometer. The data is included in characterization Table-1.

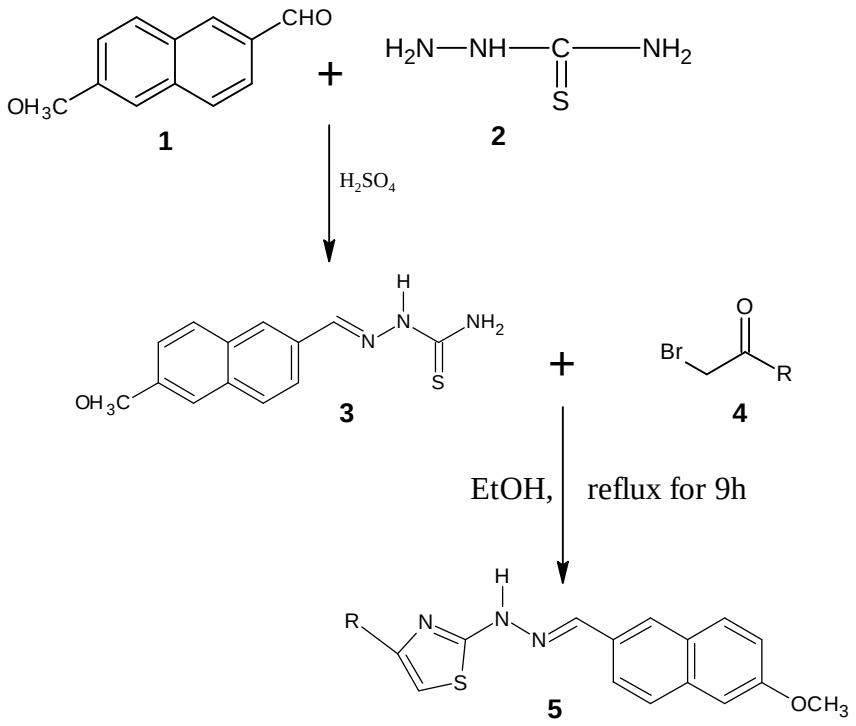
The correct sequence of the reaction scheme for the synthesis of the target compounds are shown in the figure 1.The literature studies of the thiazole derivatives indicated that the thiazole derivatives show enormous biological activities, hence inspired by this, it was decided to synthesize a series of novel thiazole derivates and screened for it various biological activities.

All the synthesized compounds were screened for the anti- bacterial activity by the disc diffusion method (ZOI test).The target compounds showed different results for the anti-bacterial screening .i.e. most of the compounds exhibit satisfactory results but few of the compound showed promisingly good results.. Analysis showed that the compound 5h found to be extremely sensitive towards both gram positive and gram negative bacteria for the test strains used where as compound 5c and 5g were sensitive towards only one kind of bacterial strain and the compound 5e was sensitive towards only gram negative bacteria and showed maximum inhibition in case of E.*coli* bacterial strain. Hence the above mentioned compounds can be considerd as drug candidates for the bacterial infections. The results obtained in the anti- bacterial activity is summarized in Table-2.

All the synthesized compounds were screened for the *in vitro* anti-tubercular activities and are presented in the Table-3.Among the tested compounds 5d showed good and remaining compounds exhibited moderate Anti- TB activity. The relative potency indicates that novel compounds (5a-5j) tested in the present study are not as effective as that of the standard compounds pyrazinamide, streptomycin and ciprofloxacin drugs but target compounds may be considered as Anti –TB agent.

TABLE -1: CHARACTERIZATION DATA OF THE NOVEL SYNTHESISED NOVEL COMPOUNDS.

Compd.	R	Mol. Formula	M. W	M. P ^{0}C
5a	-(4-(OCH_3) -Ph)	$C_{22}H_{19}N_3O_2S$	389.470	207-209
5b	-(4-(CH_3) -Ph)	$C_{22}H_{19}N_3OS$	373.470	217-220
5c	-(4-(Cl) -Ph)	$C_{22}H_{16}ClN_3OS$	393.889	115-118
5d	-(4-(Br) -Ph)	$C_{21}H_{16}BrN_3OS$	438.340	222-223
5e	-(4-(NO_2) -Ph)	$C_{21}H_{16}N_4O_3S$	404.442	218-221
5f	-($C_{10}H_8$)	$C_{25}H_{19}N_3OS$	409.502	178-181
5g	-(3,4-(Cl)$_2$ -Ph)	$C_{21}H_{15}Cl_2N_3OS$	428.334	204-206
5h	-(Ph-Ph)	$C_{27}H_{21}N_3OS$	435.540	136-137
5i	-(4-(F) -Ph)	$C_{21}H_{16}FN_3OS$	377.434	242-250
5j	-CH_3	$C_{16}H_{15}N_3OS$	297.374	238-240



R= 4-OCH_3-Ph; 4-Me-Ph; 4-Cl-Ph; 4-Br-Ph; 4-NO_2-Ph; 4-F-Ph;C_6H_5-Ph ; 3,4(Cl)$_2$-Ph; Ph-Ph; CH_3

Figure 1: Synthetic route for the preparation of target compounds (5a-5j)

TABLE -2: ANTI-BACTERIAL ACTIVITY OF STANDARD AND TEST COMPOUNDS.

Compd.	Diameter of inhibition Zone			
	Gram positive bacteria		Gram negative bacteria	
	Staphylococcus aureus	*Bacillus subtilius*	*Escherichia coli*	*Klebsiella pneumonia*
5a	11mm	12mm	16mm	12mm
5b	10mm	20mm	12mm	19mm
5c	20mm	15mm	30mm	22mm
5d	16mm	11mm	10mm	12mm
5e	16mm	13mm	27mm	18mm
5f	11mm	9mm	-	19mm
5g	22mm	28mm	29mm	17mm
5h	21mm	22mm	26mm	24mm
5i	10mm	14mm	12mm	16mm
5j	12mm	16mm	16mm	16mm
Ciprofloxacin	26mm	30mm	32mm	28mm

[A]Mean values of 3 trails. '0' indicates no sensitivity (zone of inhibition <7mm)

TABLE-3: ANTI-TUBERCULAR ACTIVITY OF THE SYNTHESIZED COMPOUNDS AGAINST REFERNCE STANDARDS.

SAMPLES	100 µg/ml	50 µg/ml	25 µg/ml	12.5 µg/ml	6.25 µg/ml	3.12 µg/ml
5a	S	S	R	R	R	R
5b	S	S	R	R	R	R
5c	S	S	S	R	R	R
5d	S	S	S	S	S	R
5e	S	S	R	R	R	R
5f	S	S	R	R	R	R
5g	S	S	R	R	R	R
5h	S	S	R	R	R	R
5i	S	S	R	R	R	R
5j	S	S	R	R	R	R

S-Sensitive R-Resistant

CONCLUSION

The screening studies of the antibacterial and anti-tubercular activity studies of the synthesized novel compounds proved to be potent agents for the respective studies. In conclusion, a series of novel thiazoles were synthesized which were analyzed for anti-bacterial and anti-tubercular activities. Presence of electron withdrawing groups like Chlorine and nitro groups at the para position of the phenyl ring attached to the thiazole nucleus as substituent are responsible for the good anti-bacterial and moderate anti-tubercular activity. A further study of these compounds with special reference to therapeutic index for the drug is going on.

ACKNOWLEDGEMENTS

The authors express their heartfelt thanks to, The head ,NMR research center ,SAIF –cochin-22 for 1H-NMR,13C-NMR spectroscopy and FT-IR analysis, Syngenta Goa for Mass spectroscopy, Maratha mandal's NGH institute of dental sciences and research center, Belgaum for Microbiological activities.

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