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Catalyst free synthesis of thiazole derivatives bearing azo imine linkageas anti-microbial agents

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Abstract: The present object deals with the synthesis and antimicrobial screening of a series of *1-(Substituted benzylidene)-2-(4-Substituted phenylthiazol-2-yl)hydrazine* **(5a–h, 8a-h).** The structures of synthesized compounds have been confirmed by spectral analysis, such asMass, IR, ^{1}H*NMR*and ^{13}C*NMR*.All the synthesized compounds were screened for *in vitro* antibacterial activity against some gram-positive (*Staphylococcus aureus, Streptococcus pyogenes*) and gram-negative (*Escherichia coli*, *Klebsila*) bacteria. The thiazole derivatives with a pharmacologically potent groupdiscovered in this article may provide valued therapeutic involvementin the treatment of microbial diseases, especially against bacterial and fungal infections.

Keywords: Thiazoles,Phenacyl bromide, Thiosemicarbazide

INTRODUCTION

Thiazoles derivatives have attached a great deal of interest due to their association with various kinds of biological properties, found in many potent biologically active molecules such as sulfathiazole (antimicrobial drug)[1], ritonavir (antiretroviral drug)[2], abafungin (antifungal drug)[3]and tiazofurin(antineoplastic drug)[4]. In date, the applications of thiazoles were found in drug development for the treatment of allergies[5], hypertension[6], inflammation[7, 8], schizophrenia[9], bacterial[10], *HIV* infections[11, 12], hypnotics[13] and more recently as an asfibrinogen receptor[14] antagonists, antithrombotic activity[15] and as new inhibitors of bacterial DNA gyrase B[16].Due to its wast range of applications, thiazoles are habitually included in the design or are used as a core structure for the synthesis of numerous chemical libraries[17].

Moreover, our current survey shows,a broad

range of traditional antibiotics have been well known and most of them are commercially available like metronidazole[18, 19] and secnidazole[20]. However, the major complication in the antimicrobial drug therapy has originated to be the drug resistance. Therefore, the spread of antibiotic resistance among pathogenic bacteria has become a serious mystery for the clinical managing of infectious diseases and resulted in a clear necessity for novel and better than traditional antibacterial agents[21]. To solve this severe medical tricky, the imperative task of looking for new types of antibacterial agents should be accomplished[22].

In current years, diverse targets in crucial areas of the bacterial cell cycle have been studied and correlative researches showed the outlook of finding a new approach against the challenge of drug resistance.Based on this challenge for the researcher, our group was designed and synthesized a new class of thiazole derivatives. According to the latest assessment, itpossesses a conspicuous place in the drug discovery process[23] and this ring structure is found in several well-known drugs which are given below with their biological importance ***(Figure 1)***. It can also be used in a scaffold bounding strategy[24] or as an amide isostere[25] during the course of probing structure activity relationships for lead optimization.

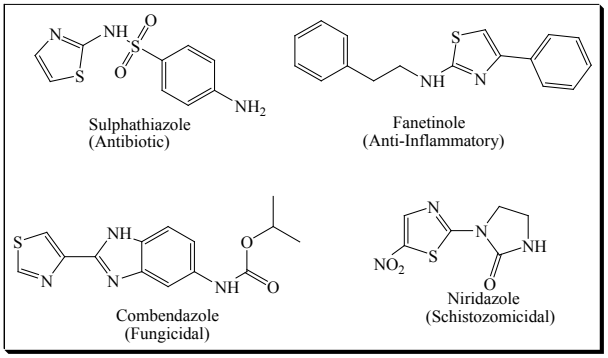


Figure 1: Drugs containing thiazole motif

MATERIAL AND METHODS

Chemicals and solvents were purchased from the Sigma-Aldrich Chemical Co., Merck chemical, Finar and spectrochem Ltd. The entire chemicals were used without further purification unless otherwise noted. Thin-layer chromatography was accomplished on 0.2 mm precoated plates of silica gel G60 F254 (Merck). Visualization was made under UV light (254 and 365nm) or with an iodine chamber. IR spectra were recorded on an IR Affinity-1S spectrophotometer (Shimadzu). ^{1}H (400 MHz) and ^{13}C (101.1 MHz) NMR spectra were recorded on a Bruker AVANCE II spectrometer in $CDCl_3$. Chemical shifts are expressed in δ ppms downfield from TMS as an internal standard. Mass spectra were determined using a direct inlet probe on a GCMS-QP 2010 mass spectrometer (Shimadzu). Melting points were measured in open capillaries and are uncorrected.

General procedure for the preparation of (E)-1-Subsituted benzylidene thiosemicarbazide.

A 100 ml conical flask equipped with a magnetic stirrer and the septum was charged with a solution of thiosemicarbazide (**1**) (0.015M) and aldehyde (**3, 7**) (0.01M) was dissolved in a minimum quantity of methanol. It was than stirred at room temperature for 90 minutes under N_2 atmosphere. The progress of the reaction was monitored by thin layer chromatography. The reaction mixture was filtered, washed with cold methanol and dried. Compounds were directly used for the next step.

General procedure for the preparation of (E)-1-(Substituted benzylidene)-2-(Substituted phenylthiazol-2-yl) hydrazine.

To a mixture of compounds **(3, 7)** (10 mmol) and phenacyl bromide **(4)** (10.5 mmol) were dissolved in dried methanol. It was stirred for 10 hrs at room temperature. The reaction was monitored with thin layer chromatography and after completion of the reaction; the reaction

mixture was poured on crushed ice and was stirred at RT for 1 hr. The reaction mixture was filtered out and washed with water, crystallization was carried out using ethanol to afford analytically pure products **5a-h, 8a-h**.

(E)-1-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)benzylidene)-2-(4-(4-ethoxyphenyl) thiazol -2-yl)hydrazine. (5a)
Yield: 91%; mp 177 ^{o}C ; IR (cm^{-1}): 3350.20 (- NH Stretching of hydrazone) , 3029.50(C-H Stretching), 1577.77(C=N stretching), 1508.20 (Aromatic Ring skeleton), 1494.83 (C-H Bending), 1126.43(C-O bending), 1053.13(C-F stretching in aldehydic ring), 831.32(P-disubstituted aromatic ring); ^{1}H NMR (400 MHz, $CDCl_3$): 12.21 (1H, s), 7.97 (1H, s), 7.79-7.77 (2H, d, J= 8.36 Hz), 7.38 (1H, s), 7.24-7.20 (3H, m), 7.16-7.12 (2H, d, J= 16.96 Hz), 6.97-6.94 (1H, t, J= 8.48), 3.96-3.94 (2H, d, J= 6.80 Hz), 3.78 (3H, s), 1.26 (1H, dd, J= 13, 6 Hz), 0.60-0.58 (2H, d, J= 5 Hz), 0.38-0.37(2H, J= 4 Hz);^{13}C NMR (101 MHz, $CDCl_3$) δ 179.22, 172.36, 152.97, 150.60, 150.49, 144.88, 141.41, 141.00, 141.01, 140.01, 138.11, 132.71, 132.05, 132.26, 129.60, 125.61, 121.47, 121.34, 121.08, 119.95, 117.60, 116.09, 115.75, 113.52, 111.52, 111.09, 102.63, 74.98, 73.71, 54.05, 10.16, 3.32, 3.29; MS: *m/z* 445.13 (M).

(E)-1-(3-(Cyclopropylmethoxy)-4-(difluoromethoxy)benzylidene)-2-(4-(4-bromophenyl) thiazol -2-yl)hydrazine. (5e)
Yield: 72%; mp221 ^{o}C ; IR (cm^{-1}) 3330.30 (- NH Stretching of hydrazone) , 3030.30(C-H Stretching), 1566.20(C=N stretching), 1506.41 (Aromatic Ring skeleton), 1400.32 (C-H Bending), 1110.43(C-O bending), 1363.67(C-F stretching of aldehydic ring), 817.82(P-disubstituted aromatic ring), 590.30 (C-Br stretching of phenycyl ring); ^{1}H (400 MHz, $CDCl_3$) δppm:12.27 (1H, s), 7.86 (1H, s), 7.80-7.78 (2H, d, J= 8.39 Hz), 7.39 (1H, s), 7.22-7.18 (3H, m), 7.18-7.14 (2H, d, J= 16.91 Hz), 6.96-6.93 (1H, t, J= 8.51), 3.95-3.93 (2H, d, J= 6.81 Hz), 3.79 (3H, s), 1.31 (1H, dd, J= 13, 6 Hz), 0.63-0.61 (2H, d, J= 5 Hz), 0.40-0.38 (2H, J= 4 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.34, 150.64, 150.44, 141.59, 142.10, 141.09, 141.05, 135.59, 132.59, 129.10, 128.90, 128.30, 127.77, 126.50, 122.40, 119.89, 118.65, 116.05, 112.48, 111.33, 102.43, 71.77, 11.14, 4.31; MS: *m/z* 493.03 (M^{+}).

(E)-1-(3-Phenoxybenzylidene)-2-(4-(4-methoxyphenyl)thiazol-2-yl)hydrazine.(8a)
Yield: 92%; mp142 ^{o}C ; IR (cm^{-1}) 3320.48 (- NH Stretching of hydrazone) , 3030.30(C-H Stretching), 1645.30(C=N stretching), 1510.26 (Aromatic Ring skeleton), 1440.83 (C-H Bending), 1215.30(C-O bending), 827.46(P-disubstituted aromatic ring); ^{1}H (400 MHz, $CDCl_3$) δppm: 8.02 (1H, s), 7.78-7.76 (2H, d, J=8.72), 7.46-7.41 (4H, m), 7.29 (1H, s), 7.20-7.16 (2H, m), 7.08-7.06 (2H, d, J= 7.8 Hz), 7.02-7.00 (2H, t, J= 2 Hz), 3.78 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.01, 159.98, 155.41, 152.37, 143.25, 142.01, 132.85, 130.30, 129.21, 129.03, 124.66, 124.49, 123.06, 122.31, 120.60, 120.25, 115.07, 55.45; MS: *m/z* 401.12 (M^{+}).

(E)-1-(3-phenoxybenzylidene)-2-(4-(4-bromophenyl)thiazol-2-yl)hydrazine. (8e)
Yield: 74%; mp232 ^{o}C; IR (cm^{-1}) 3320.99 (- NH Stretching of hydrazone) , 3038.30(C-H Stretching), 1670.05(C=N stretching), 1585.89 (Aromatic Ring skeleton), 1436.97 (C-H Bending), 1215.15(C-O bending), 825.53(P-disubstituted aromatic ring), 650.01(C-Br stretching of phenacyl ring); ^{1}H (400 MHz, $CDCl_3$) δppm: 8.06 (1H, s), 7.76-7.74 (2H, d, J=8.71), 7.45-7.40 (4H, m), 7.39 (1H, s), 7.21-7.17 (2H, m), 7.10-7.08 (2H, d, J= 7.7 H), 7.04-7.02 (2H, t, J= 2.2 Hz), 3.79 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.15, 156.80, 156.05, 149.09, 145.50, 141.55, 131.22, 130.21, 129.02, 122.19, 118.29, 115.44, 112.53, 112.17, 118.56, 118.27, 110.31; MS: *m/z* 449.02 (M^{+}).

RESULTS AND DISCUSSION

To date, use of less hazardous chemicals and solvent is a green chemistry approach which is more preferred by most chemists. As a target of that we prefer routesfor the synthesis of a target scaffold by using polar solvents like methanol at roomtemperature.

Due to the simple reaction procedure and easy to accomplished final product according to the mechanism***(Figure 2)***, we select this route to accomplish this task. Our key intermediate **(3, 7)** was formed by simple stirring at room temperature on condensation between two different aldehyde **(2, 6)** and thiosemicarbazide **(1)**. The final compounds **(5a-h, 8a-h)** was formed by ring formation between intermediate **(3, 7)** and various phenacyl bride **(4)** using methanol and stirring for appropriate time ***(Reaction Scheme).*** All synthesized compounds were obtained at higher yield as compared to traditional way ***(Table 1)***.

Crucial intermediate thiosemicarbazone **(3, 7)** have been confirmed by spectroscopic analysis, such as ^{1}H *NMR* and mass analysis, which is further supported by IR spectral studies. In IR spectrum structure of **3, 7** absence of absorption band at 1720 cm^{-1} gives confirmation about

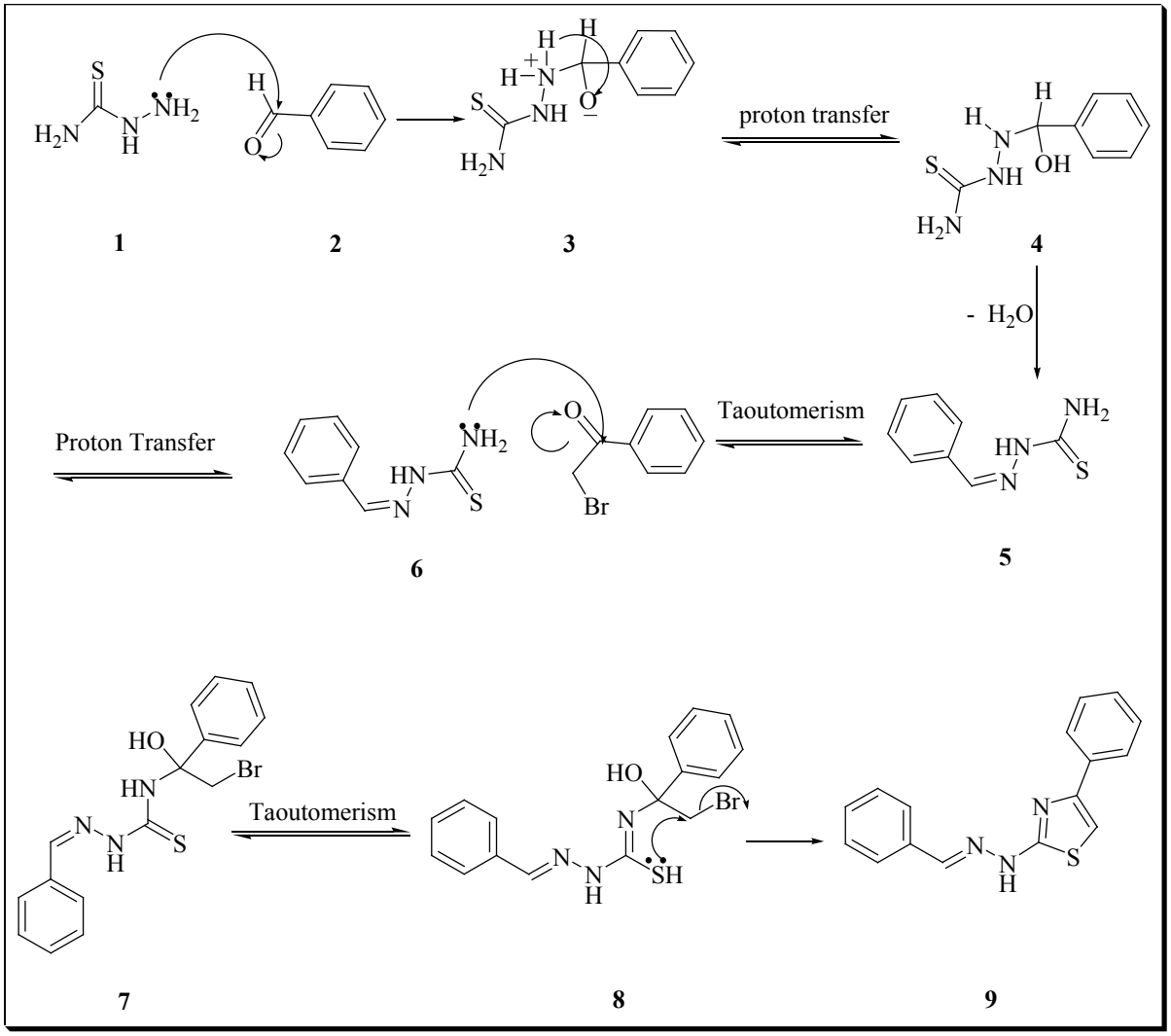
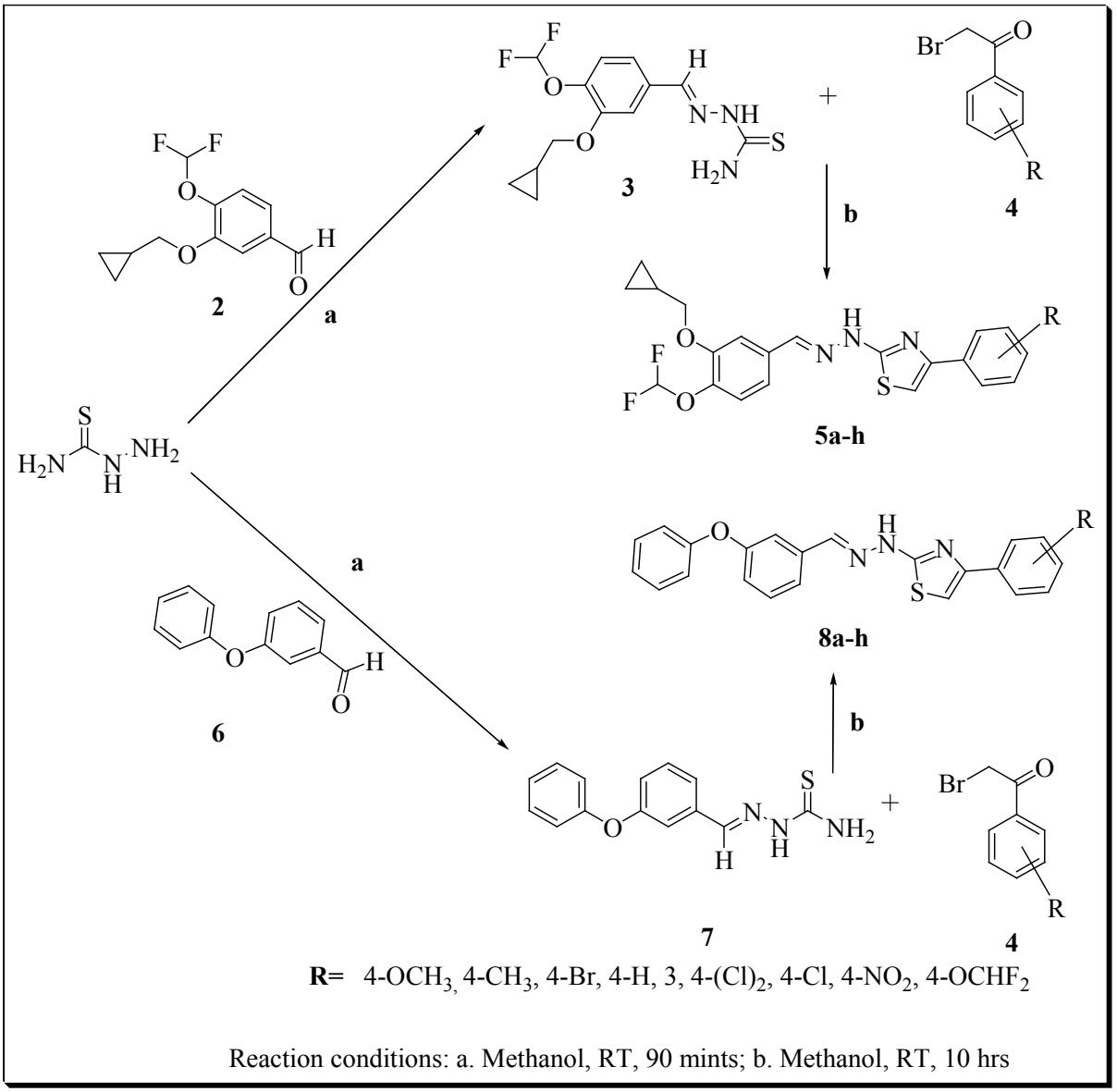


Figure 2: Proposed reaction mechanism for the formation of thiazoles

formation of product. Moreover the presence of stretching band at 1640 cm^{-1} and 1250 cm^{-1} confirms the formation of the thiazole ring due to C=N and C-O bond respectively. Presence of –NH group was confirmed by stretching band at 3300 cm^{-1}. ^1H *NMR* spectrum of **3, 7** give confirmation about the presence of imine group proton at δ 7.30 ppm. Thiazole ring proton gives singlet at 7.20 δppm confirms ring formation.

All the synthesized compounds were screened for their antibacterial activity against Gram-positive *(S. aureus, S. pyogenes)* and Gram negative *(E. coli, P. aeruginosa)* bacteria, using ciprofloxacin, chloramphenicol, nystatin and itraconazole as the reference antibacterial agent. Antifungal activity was carried out using selected fungal strain *(C. albicans, A. niger)*. Results were expressed in **minimum inhibition concentration (MIC)*(Table 2)***.



Reaction Scheme: Synthesis of (E)-1-Subsituted benzylidene thiosemicarbazide **3, 7** and (E)-1-(Substituted benzylidene)-2-(4-Substituted phenylthiazol-2-yl) hydrazine **5 a-h, 8 a-h.**

All the newly synthesized compounds evaluate against Gram –ve and Gram +ve strains at two different concentrations (10 µg/ml and 5 µg/ml) as a zone of inhibition. For zone of inhibition Cefazolin and ampicillin were used as a control drug***(Table 3)***. After obtaining positive results, MIC was determined for these series.

By assessment of biological data, we come to conclude that some of our synthesized compounds give moderate to higher activity as compared to standard drug. In some cases there are degree of variation from control compounds due to structure interaction property and function group variations.

From the result of biological evaluation, some of the compounds tested were found to have moderate antibacterial and antitubercular activity. Remaining most of the compounds gives higher activity. From the **Table 2**, it can be observed that compounds**5f** and **8f** showed moderate activity againstmost of the antibacterial and anti-fungal agents due to the absence of any donating or withdrawing group. It is observed that compounds **5a, 5d, 5h, 8a** and **8d** are active against gram + ve bacterial strain due to presence of donating group as well halogen group in to the molecule. Compounds **5a, 5e, 5g, 8a, 8c, 8g** and **8h** are remarkably active against gram –ve bacterial strain due to more preferably presence of halogen atoms. Most of the compounds are active against anti-fungal strain except**5f, 8c** and **8f** due to function group effects. By observing **Table 3**, it is clear that at low concentration compounds are active and high

Code	R	M.F.	M.W.	Yield (%)	m.p. ^{o} C	Rf
5a	4-OCH_3	$C_{22}H_{21}F_2N_3O_3S$	445.13	91	177	0.55
5b	4-CH_3	$C_{22}H_{21}F_2N_3O_2S$	429.13	87	169	0.51
5c	4-Cl	$C_{21}H_{18}ClF_2N_3O_2S$	449.08	87	188	0.61
5d	4-NO_2	$C_{21}H_{18}F_2N_4O_4S$	460.1	79	147	0.57
5e	4-Br	$C_{21}H_{18}BrF_2N_3O_2S$	493.03	72	221	0.48
5f	H	$C_{21}H_{19}F_2N_3O_2S$	415.12	86	173	0.60
5g	3, 4- Cl	$C_{21}H_{17}Cl_2F_2N_3O_2S$	483.04	76	207	0.52
5h	4-$OCHF_2$	$C_{22}H_{19}F_4N_3O_3S$	481.11	70	179	0.62
8a	4-OCH_3	$C_{23}H_{19}N_3O_2S$	401.12	92	142	0.50
8b	4-CH_3	$C_{23}H_{19}N_3OS$	385.12	89	183	0.56
8c	4-Cl	$C_{22}H_{16}ClN_3OS$	405.07	88	206	0.49
8d	4-NO_2	$C_{22}H_{16}N_4O_3S$	416.09	80	227	0.47
8e	4-Br	$C_{22}H_{16}BrN_3OS$	449.02	74	234	0.52
8f	H	$C_{22}H_{17}N_3OS$	371.11	91	168	0.50
8g	3, 4- Cl	$C_{22}H_{15}Cl_2N_3OS$	439.03	77	213	0.58
8h	4-$OCHF_2$	$C_{23}H_{17}F_2N_3O_2S$	437.1	73	210	0.51

Table 1 Physical parameters of 5a-h and 8a-h

Compounds and standard drugs	Antibacterial activity				Antifungal activity	
	Minimum inhibitory concentration µg/ml				Minimum inhibitory concentration µg/ml	
	Gram +Ve Bacteria		Gram -Ve Bacteria			
	S. aureus	*S.pyogenes*	*E.coli*	*P.aeruginosa*	*C.albicans*	*A.niger*
Ciprofloxacin	7.8	7.8	15.62	15.62	-	-
Chloramphenicol	7.8	7.8	7.8	7.8	-	-
Nystatin	-	-	-	-	31.25	31.25
Itraconazole	-	-	-	-	15.62	15.62
5a	**9.7**	11.22	**15.64**	**15.60**	**16.62**	**31.60**
5b	11.7	17.25	22.36	**7.81**	**31.50**	**32.05**
5c	31.25	45.67	32.30	31.20	**15.75**	70.05
5d	**8.00**	**9.01**	31.50	61.50	**16.52**	72.25
5e	15.72	17.28	**16.02**	60.80	**31.50**	**16.75**
5f*	16.52	62.65	31.22	31.50	45.67	65.50
5g	15.84	19.58	**15.80**	65.25	**32.10**	62.72
5h	**7.81**	**9.25**	**7.81**	62.50	**32.25**	**32.75**
8a	**8.81**	11.25	**15.80**	**15.75**	**16.30**	**16.25**
8b	12.0	21.58	31.50	**15.70**	**15.90**	**16.55**
8c	31.00	**7.81**	1**6.80**	31.10	68.80	75.25
8d	**7.98**	**7.8**	30.60	**16.25**	**16.72**	**32.25**
8e	19.12	31.98	31.05	**7.50**	**16.75**	**31.50**
8f*	15.90	51.63	31.10	60.00	65.50	75.25
8g	15.92	15.50	**15.82**	**16.25**	**32.25**	**32.50**
8h	30.25	62.55	**16.00**	**7.95**	**31.50**	**32.75**

Table 2: Antimicrobial and antifungal screening of compounds as a MIC (5a-h and 8a-h)

$_*$ = compounds show lowest activity

concentration results are variable compared to standards drugs. At low concentration compounds **5c, 8a, 8c** and **8h** gives better results against gram +ve bacterial strain. It is interesting to note that most of the compounds are inactive against anti-fungal strain in a zone of inhibition.

		E. Coli. Gram -Ve		Klebsila Gram -Ve		Streptococcus Gram +Ve		Staphylococcus Gram +Ve	
		Cefazolin				Ampicillin			
Antibiotic	L	9		15		17		15	
	H	10		19		20		19	
Chemical Compound	5a(L)	13	14	10	12	11	12	0	0
	5a(H)	15	16	11	12	9	11	0	0
	5b(L)	14	14	16	17	11	10	0	0
	5b(H)	14	15	11	11	10	10	0	0
	5c(L)	11	10	12	11	12	11	0	0
	5c(H)	15	15	12	12	10	11	0	0
	5d(L)	12	15	12	12	7	11	0	0
	5d(H)	12	14	11	13	9	10	0	0
	5e(L)	12	14	11	11	9	12	0	0
	5eH)	14	14	11	14	9	10	0	0
	5f(L)	14	14	11	11	8	10	0	0
	5f(H)	12	13	11	13	9	11	0	0
	5g(L)	12	14	11	11	9	12	0	0
	5g(H)	14	14	11	14	9	10	0	0
	5h(L)	14	14	11	11	8	10	0	0
	5h(H)	12	13	11	13	9	11	0	0
	8a(L)	10	11	16	16	10	10	0	0
	8a(H)	12	14	11	12	8	10	0	0
	8b(L)	12	13	13	11	9	10	0	0
	8b(H)	13	13	11	13	9	9	0	0
	8c(L)	11	10	17	18	9	11	0	0
	8c(H)	13	14	11	11	7	8	0	0
	8d(L)	13	15	12	12	9	9	0	0
	8d(H)	12	13	11	12	8	10	0	0
	8e(L)	13	13	12	12	8	9	0	0
	8e(H)	13	13	10	12	9	8	0	0
	8f(L)	13	13	12	12	10	10	0	0
	8f(H)	13	12	10	13	8	7	0	0
	8g(L)	12	13	13	11	9	10	0	0
	8g(H)	13	13	11	13	9	9	0	0
	8h(L)	11	11	15	16	9	11	0	0
	8h(H)	13	14	11	11	7	8	0	0

Table 3: Antimicrobial screening of compounds as a Zone of inhibition (5a-h and 8a-h)

CONCLUSION

In this short article, we developan easy way to synthesized various thiazole derivatives and check their potency as an antibacterial as well as anti-fungal agents. By observing activity data, many of compounds are active and may enhance activity by changing various substituents.

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