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One pot Synthesis of Novel Thiazole Derivatives as Potential Antimicrobial Agents

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Abstract: The presented work deals with the synthesis and antimicrobial screening of*N-substitutedal-kylidine/benzylidine-2-(4-substitutedphenylthiazol-2-yl)hydrazine***(5a-5e, 8f-8j)**.*The structures of synthe-sizedthiazole derivatives have been confirmed by spectral analysis, such asIR,Mass, ^{1}HNMRand ^{13}CNMR. Allthe synthesized compounds were screened for their *in vitro* antibacterial activity against different strains of bacteria such as *S.aureus*, *E.coli and P.aeruginosa*.

Keywords: Thiazole,Anti-microbial agents, PMR, CMR.

Introduction

Nowadays, we are observing that microbes and also microorganism resistance to multiple antibacterial and antifungal agents have become a serious problem for increasing of serious infections all over the world. Based on the above facts, need and considerable interest in the discovery of new chemical entities and novel lead structures which will act as antimicrobial agents [1-2].

Thiazoles and their derivatives havea greatdeal of interest due to their various kinds of biological properties and their usefulness as medicines are also well established [3-4]. It is also found inmany potent biologically active molecules and gives variety of biological activities suchas in the treatment of Allergies[5], Schizophrenia[6], Hypertension[7], Inflammation[8], HIV[9], Diabetes[10-11], Cancer[12], Convulsant[13], Microbial[14-18]agents.

For the synthesis of several biological molecules thiazole moiety is a key pharmacophore because of its low toxicity and also the synthesis of thiazole derivatives from thiosemicarbazone is of particular interest in medicinal chemistry due to their ease of synthesis, good yields, low cost, and the possibility of obtaining a wide diversity

of derivatives, allowing the modulation of pharmacokinetics and optimization of biological activity. In addition, this class of heterocyclic compounds has demonstrated great potential as antimicrobial agents with a broad spectrum of action against different types ofbacteria [19].
From the above-cited effect of thiazole and need of new anti-infectious agents, we have planned the synthesis of thiazole derivatives and their evaluation against different microbes to check their potency.

Experimental

Material

Chemicals and solvents were purchased from the Merck chemical, Sigma-Aldrich Chemical Co. and Spectrochem Ltd. The all entire chemicals were used without further purification. Thin-layer chromatography was accomplished on 0.2 mm precoated plates of Silica gel G60 F254 (Merck). IR spectra were recorded on an "IR Affinity-1S spectrophotometer (Shimadzu)". ^{1}H (400.1 MHz) and ^{13}C (100.6 MHz) NMR spectra were recorded on a "Bruker AVANCE III spectrometer" in DMSO-d_6. Chemical shifts are expressed in δ ppm downfield from TMS. Mass spectra were determined by direct inlet probe on a "GC-MS-QP 2010 mass spectrometer (Shimadzu)". Melting points were measured in ''Digital Auto Melting point Apparatus (Labtronics)".

Method of synthesis

General Procedure for the synthesis of various *N-substituted alkylidine/benzylidine-2-(4-substitutedphenylthiazol-2-yl)hydrazine*

In anRBF, suspension of2-Methylbut-2-enal**(2)**or 4-hydroxy-3-(prop-2-yn-1-yloxy)benzaldehyde**(6)**(1 mmol) and thiosemicarbazide **(1)**(1 mmol) in methanol was stirred at room temperature (RT) for 2 hr. The completion of the reaction was monitored by thin layer chromatography using Hexane: Ethyl acetate (7:3) as a mobile phase. The product was isolated by pouring onto crushed ice-water, filters and dried it. The dried product was used for the next step**(Int-3 & Int-7)**. The mixture of **(Int-3 & Int-7)** (1 mmol) and varioussubstituted phenacyl bromide(1.4 mmol) in methanol and stirred for 10 hrat RT, filtered and washed with cold water. The isolated products were crystallized in ethanol affording desired products **5a-5e** and**8f-8j** in good yield **(Reaction Scheme1)**.

Spectral Analysis

2-(2-(2-Methylbut-2-en-1-ylidene)hydrazinyl)-4-phenylthiazole. (5a)

This compound was obtained as off white colored powder; Yield: 85%; mp (melting point): 188 °C; IR (cm^{-1}):3350.50 (-NH Stretching of Hydrazone), 3043.70(C-H Stretching), 1650.80(C=N Stretching), 1506.46 (Aromatic ring skeleton), 1440.83 (C-H Bending);^{1}H NMR (DMSO-d_6, 400.1 MHz) δ:1.78-1.80 (6H, d, -CH_3), 5.84-5.86 (1H, s, -CH), 7.25-7.30 (2H, m, -Ar-H), 7.37-7.41 (2H, t, -CH_2), 7.67 (1H, s, -Ar-H), 7.82-7.84 (2H, d, -Ar-H), 11.78 (1H, s, -NH); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ: 128.55, 125.43, 13.94, 10.71; Mass (m/z): 257.1.

2-(2-(2-Methylbut-2-en-1-ylidene)hydrazinyl)-4-(p-tolyl)thiazole. (5b)

This compound was obtained as off white colored powder; Yield: 88%; mp: 193 °C; IR (cm^{-1}):3350.50 (-NH Stretching of Hydrazone), 3040.73 (C-H Stretching), 1655.70 (C=N Stretching), 1610.46 (Aromatic ring skeleton), 1445.73 (C-H Bending), 894 (Aromatic C-H mono substitution);^{1}H NMR (DMSO-d_6, 400.1 MHz) δ:1.78-1.84 (3H, t, -CH_3), 2.50 (3H, s, -CH_3), 5.85-5.87 (1H, d, -CH), 7.33 (1H,

s, -CH), 7.44-7.46 (2H, d, -CH), 7.67 (1H, s, -CH), 7.84-7.86 (2H, d, -CH), 11.79 (1H, s, -NH); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ: 168.60, 149.19, 146.72, 133.60, 133.40, 132.16, 131.77, 128.55, 127.13, 103.98,13.94, 10.78; Mass (m/z): 271.1.

2-(2-(2-Methylbut-2-en-1-ylidene)hydrazinyl)-4-(4-chlorophenyl)thiazole. (5c)

This compound was obtained as off white colored powder; Yield: 85%; mp: 192 °C; IR (cm^{-1}):3410.50 (-NH Stretching of Hydrazone), 3010.50 (C-H Stretching), 1650.60 (C=N Stretching), 1570.60 (Aromatic ring skeleton), 1445.73 (C-H Bending), 895 (Aromatic C-H mono substitution);^{1}H NMR (DMSO-d_6, 400.1 MHz) δ:1.78-1.80 (3H, d, -CH_3), 1.84 (3H, s, -CH_3), 5.85 (1H, s, -CH), 7.33 (1H, s, -CH), 7.44-7.46 (2H, d, -Ar-H), 7.67 (1H, s, -Ar-H), 7.84-7.86 (2H, d, -Ar-H), 11.79 (1H, s, -NH); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ: 168.60, 149.19, 146.72, 133.60, 133.40, 132.16, 131.77, 128.55, 127.13, 103.98,13.94, 10.78; Mass (m/z): 290.9

2-(2-(2-Methylbut-2-en-1-ylidene)hydrazinyl)-4-(4-bromophenyl)thiazole.(5d)

This compound was obtained as off white colored powder; Yield: 90%; mp: 198 °C; IR (cm^{-1}):3340.50 (-NH Stretching of Hydrazone), 3040.63 (C-H Stretching), 1655.60 (C=N Stretching), 1510.46 (Aromatic ring skeleton), 1445.73 (C-H Bending), 894 (Aromatic C-H mono substitution);^{1}H NMR (DMSO-d_6, 400.1 MHz) δ:1.78-1.80 (3H, d, -CH_3), 1.84 (3H, s, -CH_3), 5.85-5.87 (1H, d, -CH), 7.34-7.36 (1H, d, -CH), 7.57-7.59 (2H, d, -Ar-H), 7.67 (1H, s, -CH), 7.77-7.79 (2H, d, -Ar-H), 11.79 (1H, s, -NH); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ: 168.61, 149.23, 146.72, 133.93, 133.40, 132.17, 131.46, 127.45, 120.37, 104.07,13.94, 10.69; Mass (m/z): 334.8.

2-(2-(2-Methylbut-2-en-1-ylidene)hydrazinyl)-4-(4-methoxyphenyl)thiazole. (5e)

This compound was obtained as off white colored powder; Yield: 86%; mp: 197 °C; IR (cm^{-1}):3350.50 (-NH Stretching of Hydrazone), 3040.73 (C-H Stretching), 1655.70 (C=N Stretching), 1510.46 (Aromatic ring skeleton), 1445.73 (C-H Bending), 894 (Aromatic C-H mono substitution);^{1}H NMR (DMSO-d_6, 400.1 MHz) δ:1.78-1.80 (6H, d, -CH_3), 3.84 (3H, s, -CH_3), 5.83-5.85 (1H, d, -CH), 7.03-7.05 (2H, d, -Ar-H), 7.34 (1H, s, -CH), 7.55-7.57 (2H, d, -Ar-H), 7.87 (1H, s, -Ar-H), 11.89 (1H, s, -NH); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ: 168.60, 149.19, 146.72, 133.60, 133.40, 132.16, 131.77, 128.55, 127.13, 103.98,55.90, 13.94, 10.78; Mass (m/z): 286.9.

4-((2-(4-(4-chlorophenyl)thiazol-2-yl) hydrazono)methyl)-2-(prop-2-yn-1-yloxy) phenol. (8g)

This compound was obtained as off white colored powder; Yield: 91%; mp: 199 °C; IR (cm^{-1}):3330.10 (-NH Stretching of Hydrazone), 3010.73 (C-H Stretching), 1654.60 (C=N Stretching), 1520.36 (Aromatic ring skeleton), 1444.70 (C-H Bending), 895 (Aromatic C-H mono substitution), 660 (aromatic C-H di substitution), 1126.44 (C-O bending), 3304.17 (-OH Stretching);^{1}H NMR (DMSO-d_6, 400.1 MHz) δ:4.60 (1H, s, -CH), 4.67 (2H, s, -CH_2), 4.80 (1H, s, -OH), 7.02-7.03 (1H, d, -Ar-H), 7.23-7.25 (1H, d, -Ar-H), 7.31 (1H, s, -Ar-H), 7.39 (1H, s, -Ar-H), 7.45-7.47 (2H, d, -Ar-H), 7.86-7.88 (2H, d, -Ar-H), 7.95 (1H, s, -Ar-H), 12.14 (1H, s, -NH); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ: 168.36, 149.53, 144.43, 142.26, 140.52, 133.51, 131.86, 128.98, 1288.59, 127.18,120.69, 117.61, 113.54, 104.38, 92.34, 63.98; Mass (m/z): 382.8.

4-((2-(4-(4-bromophenyl)thiazol-2-yl) hydrazono)methyl)-2-(prop-2-yn-1-yloxy)

phenol.(8h)

This compound was obtained as off white colored powder; Yield: 91%; mp: 198 °C; IR (cm^{-1}):3340.10 (-NH Stretching of Hydrazone), 3030.73 (C-H Stretching), 1655.60 (C=N Stretching), 1535.36 (Aromatic ring skeleton), 1440.60 (C-H Bending), 894 (Aromatic C-H mono substitution), 655 (aromatic C-H di substitution),1136.54 (C-O bending), 3310.17 (-OH Stretching); ^{1}H NMR (DMSO-d_6, 400.1 MHz) δ:4.61 (1H, m, -CH), 4.68 (1H, s, -CH_2), 4.80 (1H, s, -OH), 7.24-7.26 (2H, m, Ar-H), 7.32 (1H, s, Ar-H), 7.41 (1H, s, Ar-H), 7.60-7.62 (2H, d, Ar-H), 7.79-7.81 (2H, d, Ar-H), 7.79-7.81 (2H, d, Ar-H), 7.99 (1H, d, Ar-H), 12.01 (1H, s, -NH); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ: 158.00, 155.64, 154.04, 151.46, 147.74, 140.58, 136.21, 122.97, 119.66, 118.45,116.10, 115.88, 115.33, 115.26, 32.74, 25.37, 25.27, 24.66, 9.97, 3.22; Mass (m/z): 428.7.

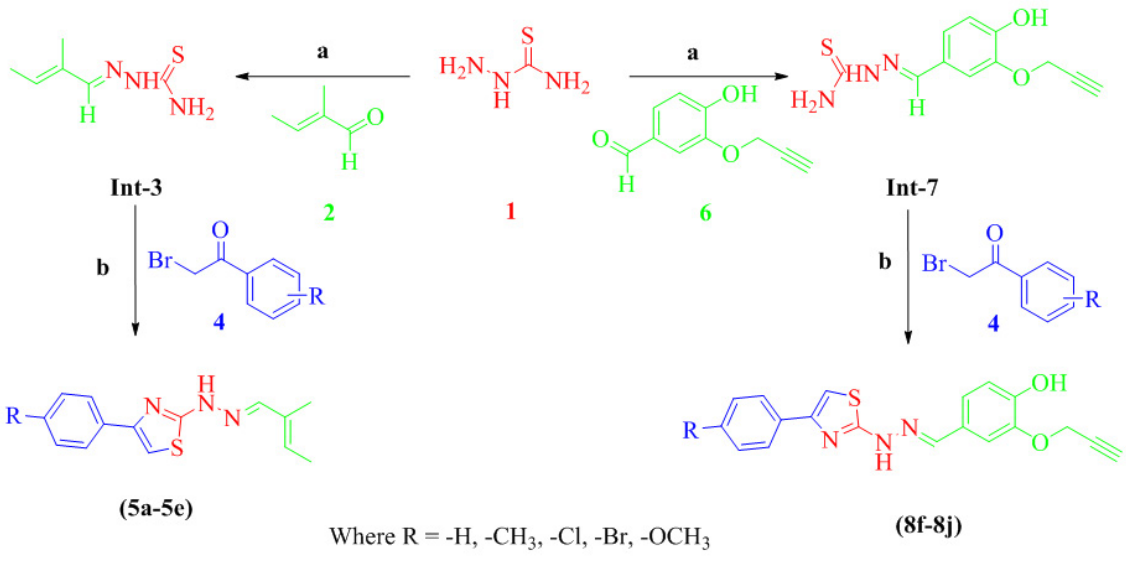
4-((2-(4-(p-tolyl)thiazol-2-yl)hydrazono) methyl)-2-(prop-2-yn-1-yloxy)phenol. (8i)

This compound was obtained as off white colored powder; Yield: 90%; mp: 215 °C; IR (cm^{-1}):3430.10 (-NH Stretching of Hydrazone), 3010.53 (C-H Stretching), 1655.40 (C=N Stretching), 1520.56 (Aromatic ring skeleton), 1440.70 (C-H Bending), 894 (Aromatic C-H mono substitution), 654 (aromatic C-H di substitution), 1128.40 (C-O bending), 3304.20 (-OH Stretching); ^{1}H NMR (DMSO-d_6, 400.1 MHz) δ:2.32 (3H, s, -CH_3), 4.60 (1H, s, -CH), 4.67 (2H, s, -CH_2), 4.80 (1H, s, -OH), 7.01-7.03 (1H, d, -Ar-H), 7.20-7.24 (4H, m, -Ar-H), 7.30 (1H, s, -Ar-H), 7.73-7.75 (2H, d, -Ar-H), 7.94 (1H, s, -Ar-H), 12.11 (1H, s, -NH); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ: 158.00, 155.64, 154.04, 151.46, 147.74, 140.58, 136.21, 122.97, 119.66, 118.45,116.10, 115.88, 115.33, 115.26, 32.74, 25.37, 25.27, 24.66, 9.97, 3.22; Mass (m/z): 363.0.

Result and Discussion

Synthetic aspects

In the present work, all the new thiazole derivatives **5a-e and 8f-j were** synthesized by two-step economically and industrially



Reaction Conditions: a. Methanol, RT, 2 hr, stirring; **b.** Methanol, RT, 10 hr, stirring

Reaction Scheme 1: Preparation of various substituted thiazole adducts **(5a-5e,8f-8j)**

adaptable routes. In the first step, there was a coupling between thiosemicarbazide **(1)**and aldehyde **(2**or **6)**in a polar protic media to afford **Int-3** and **Int-7**, which later on condensation with different phenacyl bromide in methanol at RT and furnished desired product**(5a-e, 8f-j)** respectively**.(Reaction Scheme 1)**

Spectral elucidation

The structures of the entire synthesized scaffold were confirmed by spectroscopic techniques,such as IR, ^{1}H NMR, ^{13}C NMRand mass analysis. On the basis of IR frequencies, we come to concluded that the characteristic absorption bands at ~3300 cm^{-1}confirmed–NH group.Characteristics values at~1640 cm^{-1} and ~1250 cm^{-1}were also givenconfirmations to the formation of the thiazole ring due to C=N and C-O bond respectively. Furthermore, the absence of C=S frequency from the intermediate step to the final step also give an idea regarding the formation of thiazole ring. ^{1}H NMRspectrum of all derived compoundsshowed signals at11.78-12.11 δppm due to –NH group,1.78-1.80 δppmdue to the presence of –CH_3group and highly desheildedproton at ~4.80δppm gives confirmation of –OH group respectively. Thiazole ring proton gives a signal at ~7.33 δppm confirms the ring formation. Mass spectrums of all the derived molecules were in good agreement with respect to their molecular ion peak and fragmentation pattern.

Anti-microbial assay

All the synthesized thiazole derivatives were screened for their antibacterial activity against Gram-positive *(S.aureus)* and Gram-negative *(E. coli, P. aeruginosa)* bacterial strains, usinggentamycin,ampicillin, chloramphenicol and ciprofloxacin as the reference standard antibacterial agents. The protocol used for the screening was described by the guidelines in NCCLS-approved standard document M7-A4, Broth Dilution Method to evaluate the antibacterial activity [20]

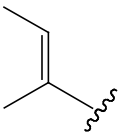
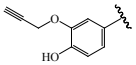
Antibacterial activity MIC (µg/ml)					
Sr. No.	**R_1**	**R_2**	*E.coli* **MTCC 442**	*P. aeruginosa* **MTCC 441**	*S.aureus* **MTCC 96**
5a		–H	100	250	125
5b		4-CH_3	**75**	100	100
5c		4-Cl	200	250	100
5d		4-Br	200	200	100
5e		4-OCH_3	**62.5**	**50**	**75**
8f		–H	200	200	250
8g		4-CH_3	**62.5**	100	500
8h		4-Cl	100	100	100
8i		4-Br	200	200	250
8j		4-OCH_3	**75**	**62.5**	**50**
Standard Drug	GENTAMYCIN		0.05	1	0.25
	AMPICILLIN		100	--	250
	CHLORAMPHENICOL		50	50	50
	CIPROFLOXACIN		25	25	50

Table 1: Antimicrobial screening of compounds as a MIC (5a-e and 8f-j)

The thiazole derivatives **5a-e and 8f-j** with an extended alkyl/aryl chain exhibited significant antimicrobialactivity compared to the referencesubstances gentamycin,ampicillin, chloramphenicol and ciprofloxacin. Correlation of anti-microbial study was made by two aldehyde groups *i.e.*(E)-2-methylbut-2-enal**(2)** and 4-hydroxy-3-(prop-2-ynyloxy) benzaldehyde**(6)**.It was demonstrated that in both the case efficient donating part on the phenyl ring may serve as good agents in medicinal chemistry. The results from table 1 shows that the methoxygroup at 4-position increase of antimicrobial potency in both types of compounds. On theother hand, a minor increase in antimicrobial activity was achieved with the methyl group as it has less electron donation power than that of –OCH_3. Among

both structural isomers which differ from each othersolely in the 4thposition of phenacyl moiety at the heterocycles 1,3-thiazole, compound. **Table 1** also summarized that none of the electron withdrawing part contributes to enhancing the biological activity. It was concluded that the compounds **5e** and **8j** exhibited MIC in the range of **50-75µg/ml** against used gram positive and gram negative strains and found to be most active. While that of compounds **5b** and **8g** were found to active only in *E.coli* strain with MIC values **75** and **62.5µg/ml**.

Conclusion

In the course of this study, we developed an efficient way to synthesized diversely substituted thiazole derivatives in moderate to good yield by two-step protocol. The remarkable biological activity observed compared to standard drugs in compounds **5b, 5e, 8g, and 8j** against gram positive and gram negative bacteria which supports the SAR study of synthesized compounds. The results described here, merits furtherinvestigations in our laboratories using a forward chemical geneticapproach for finding lead molecules as antimicrobial agents.

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