Synthesis and Antimicrobial Activity of a New Class of Methyleneamine-Linked *bis*-Heterocycles

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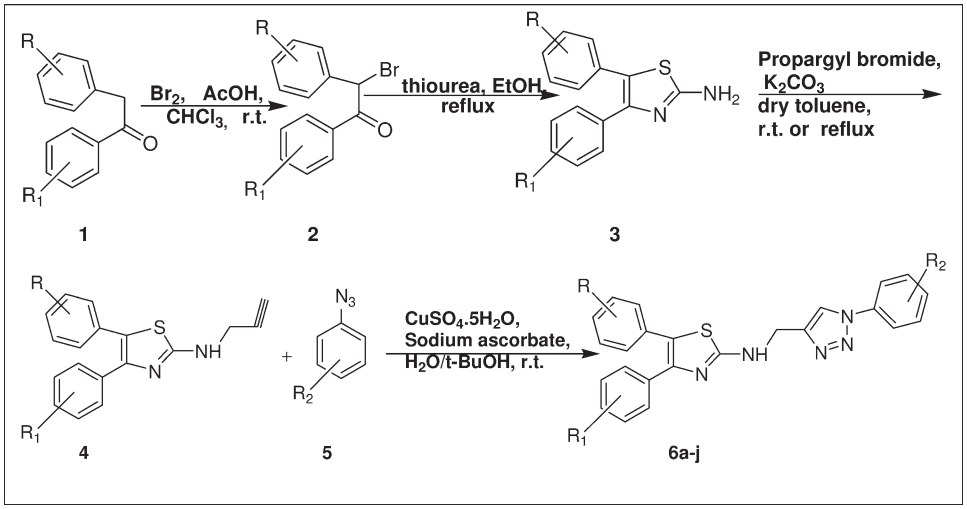

A new class of methyleneamine-linked bis-heterocycles that exhibit antimicrobial activity was synthesized. Bromination of **1** followed by condensation with thiourea gave **3**. The reaction of **3** with propargyl bromide in dry toluene under inert atmosphere led to the formation of **4**. Its subsequent reaction with different aromatic azides **5** using $CuSO_4.5H_2O$-sodiumascorbate system in a 2:1 mixture of water and tert-butylalcohol yielded the title compounds **6a–j** in good yields. The identities of these compounds were confirmed following elemental analysis, IR, ^1H, ^{13}C NMR, and mass spectral studies. All the title compounds exhibited pronounced *in vitro* antibacterial and antifungal activities.

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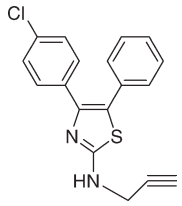
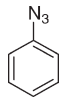
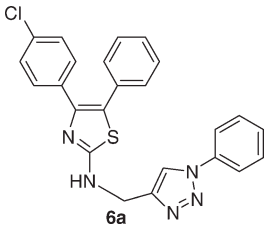
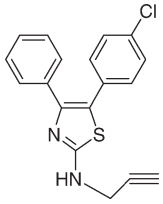
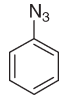
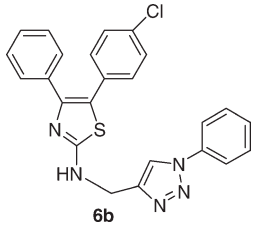
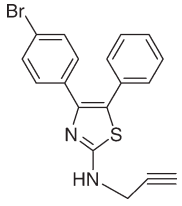
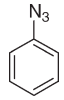
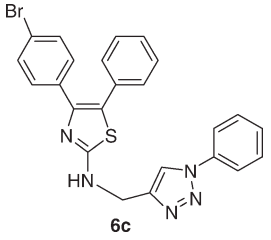
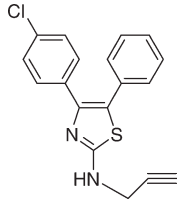
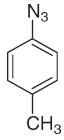
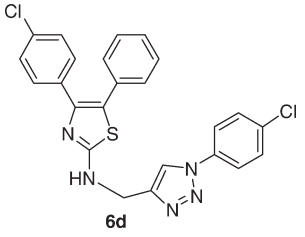
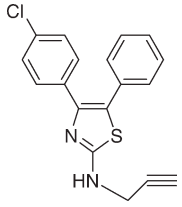
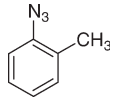
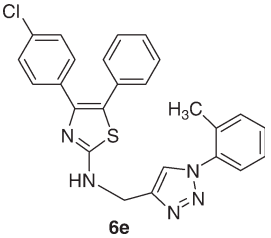
INTRODUCTION

The development of simple, facile, and efficient synthetic methods for the synthesis of five-membered heterocycles from readily available reagents is one of the major challenges in organic synthesis. Among five-membered heterocycles, triazole and thiazole represent a class of compounds of great importance in biological chemistry. For instance, 1,2,3-triazole derivatives have received much attention because of their wide range of applications [1] as agents of anti-HIV [2], antimicrobial [3], and β_3-adrenergic antagonists [4]. Thiazole derivatives are gaining interest in recent years due to their broad spectrum of biological activities and molecules containing thiazole ring system are extensively found in the field of agrochemicals [5] in the synthesis of commercial agricultural fungicides, trifluzamide, and ethaboxam [6]. Because of their low toxicity, excellent biological activity as well as access of diverse derivatives, this class of *N*-hetero cyclic derivatives is widely studied [7]. Hence, it is thought that a worthwhile programme would be required to prepare molecules having both triazole and thiazole rings through the most popular method following 1,3-dipolar Huisgen cycloaddition reaction of azides with alkynes [1a,8]. However, the early Huisgen cycloaddition process needs a strong electron-withdrawing substituent either on azide or on alkyne and was often conducted at high temperature for a prolonged period of time and usually led to the isolation of mixture of 1,4- and 1,5-disubstituted-1,2,3-triazoles [1e,8]. The discovery that Cu(I) efficiently and regiospecifically unites terminal alkynes and aromatic azides, providing 1,4-disubstituted 1,2,3-triazoles under mild condition, was a welcome advance [9]. There are several reports in the literature for the synthesis of various combinations of bis-heterocycles, but no reports are available for the synthesis of bis-heterocycles encompassing 1,2,3-triazole and thiazole moieties. We, therefore, followed a convenient and regiocontrolled

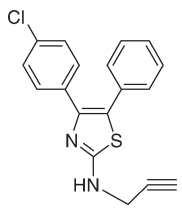
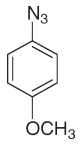
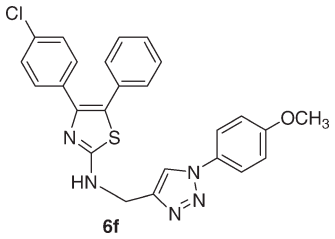
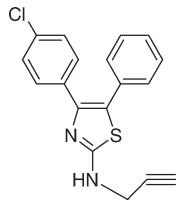
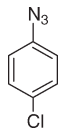
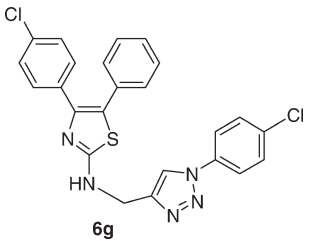
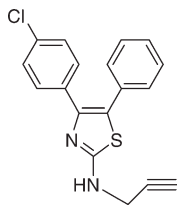
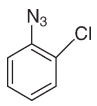
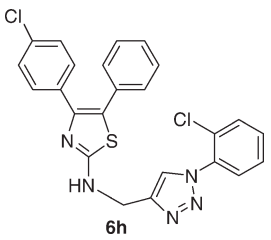
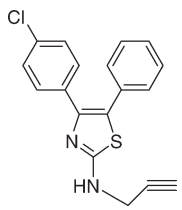
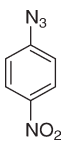
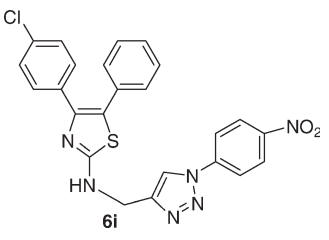
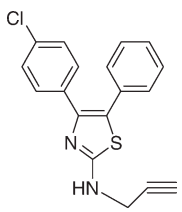
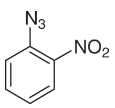
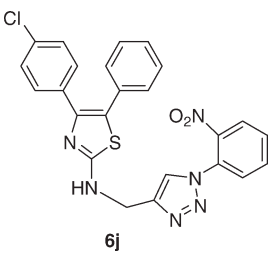
Table 1

Synthesis of methyleneamine-linked bis-heterocycles.

Entry	*N*-Substituted propargyl amine	Azide	*bis*-Heterocycle[a]	Reaction time (h)	Yield (%)
1			 **6a**	23	85[b]
2			 **6b**	26	78[b]
3			 **6c**	24	81[b]
4			 **6d**	21	87[b]
5			 **6e**	26	90[b]

(*Continued*)

Table 1
(*Continued*)

Entry	*N*-Substituted propargyl amine	Azide	*bis*-Heterocycle[a]	Reaction time (h)	Yield (%)
6			 **6f**	28	95[b]
7			 **6g**	23	89[b]
8			 **6h**	26	81[b]
9			 **6i**	32	78[b]
10			 **6j**	27	82[b]

[a] All products were characterized by IR, ^{1}H, ^{13}C NMR, and mass spectrometry.
[b] Yields obtained after recrystallization.

approach for the synthesis of new class of triazole-based bis-heterocycles.

RESULTS AND DISCUSSION

Bromination of the ketone **1** followed by condensation with thiourea in ethanol or methanol gave rise to the 4,5-diaryl-2-aminothiazole derivative **3**. Reaction of **3** with propargyl bromide at room temperature under dry and inert conditions in the presence of potassium carbonate afforded the corresponding *N*-substituted propargyl amines **4**. Further reaction of **4** with different aromatic azides **5** using $CuSO_4 \cdot 5H_2O$-sodiumascorbate system in a 2:1 mixture of water and tert-butylalcohol led to the formation of **6a–j** in good yields. The reactions were monitored by thin-layer chromatography. The chemical structures of **6a–j** were confirmed by elemental analysis and spectral data (IR, ^1H, ^{13}C NMR, and mass spectra).

Characteristic IR absorption bands were observed for C—N, N—N, N=N, C=N, C—S, and NH at 1030–1083, 1405–1476, 1537–1580, 1515–1689, 610–710, and 3248–3389 cm^{-1}, respectively [10]. The aromatic hydrogens resonated as multiplets at δ 6.89–8.12. The formation of bis-heterocycles has been unequivocally established through the characteristic chemical shift value of the triazole proton (5-CH) at δ = 8.30–8.38 in contrast to the appearance of 4-CH signal at δ =7.50–7.75 in the case of 1,5-disubstituted triazoles [10]. The yields were higher when the azides contained electron-donating groups (**6d**, **6e**, and **6f**; Table 1).

EXPERIMENTAL

All melting points were determined in open capillary tubes on Mel-Temp apparatus (Laboratory Devices, Cambridge, MA), and are uncorrected. Infrared spectra (υ_{max} in cm^{-1}) were recorded as KBr pellets on a Perkin-Elmer 283 double-beam spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on ABX 400 MHz spectrophotometer operating at 400 MHz for ^1H NMR, and 100 MHz for ^{13}C NMR using DMSO-d_6 as solvent. The ^1H and ^{13}C NMR chemical shifts were referenced to tetra methyl silane.

Typical experimental procedures.

Preparation of aromatic azides. Aromatic aniline (5 g, 0.0537 mole) dissolved in concentrated HCl or H_2SO_4 and kept in ice bath at 0–5°C. In another flask, $NaNO_2$ (7.4 g, 0.1074 mole) was dissolved in water, cooled to 0°C, and added to aniline in acid at 0°C that resulted change in color of the reaction mixture. A mixture of NaN_3 (13.9 g, 0.2148 mole) and sodium acetate (44 g, 0.537 mole) in crushed ice at 0°C was added slowly to the above reaction mixture. The resulting precipitate was filtered and dried.

[4-(4-Substitutedphenyl)-5-(4-substitutedphenyl)-thiazol-2-yl]-(1-substitutedphenyl-1H-[1,2,3]triazol-4-ylmethyl)-amine 6a–j. To a well-stirred solution of ketone **1** (8 g, 0.035 mole) in acetic acid (70 mL), a solution of bromine (5.57 g, 0.035 mole) in acetic acid (15 mL) was added dropwise during 20 min. Stirring was continued for ~24 h, the separated solid was filtered and recrystallized from 95% ethanol to furnish **2** at an yield 86%. To this intermediate **2** (4 g, 0.017mole) in ethanol (30 mL), thiourea (2 g, 0.026 mole) was added and refluxed for 8 h, and the reaction progress was monitored by TLC. The solvent was evaporated under reduced pressure, and solid was recrystallized from 95% ethanol to get sharp crystals of **3** (79%). To a solution of **3** (2 g, 0.0069 mole) in dry toluene (10 mL), a cooled solution of propargyl bromide (0.99 g, 0.0083 mole) was added dropwise in the presence of K_2CO_3 (1.15 g, 0.0083 mole) under nitrogen atmosphere. The reaction mixture was refluxed on water bath at 110°C for 8 h, and the reaction progress was monitored by TLC. The toluene and propargyl bromide were removed by distillation, and the residue was washed with sodium bicarbonate (5% w/v) followed by cold water. The crude product was dried and recrystallized from 95% ethanol to get crystals of **4** (89%).

To a well-stirred solution of **4** (1 g, 0.003 mole), in 5 mL of tertiary butanol and water mixture (1:1), copper sulphate (0.004 mole), and sodium ascarbate (0.28 mole) were added. After 15 min, aromatic azide **5** (0.055 mmole) was added to the above reaction mixture and allowed to stir for 28–32 h. The reaction progress was monitored by TLC. The resulting mixture was diluted with water and extracted with ethyl acetate (2 × 20 mL). The organic layer was dried over anhydrous sodium sulphate and evaporated under reduced pressure to afford a crude product, which on recrystallization using EtOAc/hexane yielded crystalline solids **6a–j**.

[4-(4-Chlorophenyl)-5-phenyl-thiazol-2-yl]-(1-phenyl-1H-[1,2,3]triazol-4-ylmethyl)-amine (6a). M.p. 186–187°C; ^1H NMR (DMSO-d_6): δ 8.32 (1H, s, CH), 7.96–6.98 (14H, m, Ar-H), 4.58 (2H, s, CH_2), 4.21 (1H, brs, NH); ^{13}C NMR data: 173.3, 158.1, 149.5, 137.3, 135.4, 133.1, 132.8, 129.4, 129.0, 128.5, 128.1, 127.0, 103.2, 53.6; IR (KBr) cm^{-1}: 3315, 2980, 2875, 2369, 1571, 1434, 1383, 1139, 1025, 868; LCMS *m/z*: 444 (M^++1); Anal. Calcd. for $C_{24}H_{18}ClN_5S$: C, 64.93; H, 4.09; N, 15.79; S, 7.29. Found C, 64.87; H, 4.01; N, 15.72; S, 7.22.

[4-Phenyl-5-(4-chlorophenyl)-thiazol-2-yl]-(1-phenyl-1H-[1,2,3]triazol-4-ylmethyl)-amine (6b). M.p. 202–203°C; ^1H NMR (DMSO-d_6): δ 8.30 (1H, s, CH), 7.94–6.91 (14H, m, Ar-H), 4.52 (2H, s, CH_2), 4.22 (1H, brs, NH); ^{13}C NMR data: 173.5, 158.7, 149.1, 137.2, 135.6, 133.0, 132.2, 129.5, 129.0, 128.3, 128.1, 127.0, 103.2, 53.6; IR (KBr) cm^{-1}: 3325, 2986, 2871, 2363, 1579, 1437, 1385, 1142, 1026, 869; LCMS *m/z*: 444 (M^++1); Anal. Calcd. for $C_{24}H_{18}ClN_5S$: C, 64.93; H, 4.09; N, 15.79; S, 7.29. Found C, 64.88; H, 4.04; N, 15.73; S, 7.26.

[4-(4-Bromophenyl)-5-phenyl-thiazol-2-yl]-(1-phenyl-1H-[1,2,3]triazol-4-ylmethyl)-amine (6c). M.p. 231–233°C; ^1H NMR (DMSO-d_6): δ 8.38 (1H, s, CH), 8.11–7.28 (14H, m, Ar-H), 4.43 (2H, s, CH_2), 4.27 (1H, brs, NH); ^{13}C NMR data: 176.9, 160.2, 153.5, 148.6, 143.1, 140.3, 137.5, 133.1, 132.0, 129.4, 129.0, 103.2, 52.3; IR (KBr) cm^{-1}: 3248, 2987, 2346, 1568, 1467, 1324, 1191, 1065, 976, 875; LCMS *m/z*: 487 (M^+), 488 (M^++1); Anal. Calcd. for $C_{24}H_{18}BrN_5S$: C, 59.02; H, 3.78; N, 14.34; S, 6.60. Found C, 59.02; H, 3.71; N, 14.28; S, 6.57.

[4-(4-Chlorophenyl)-5-phenyl-thiazol-2-yl]-(1-p-tolyl-1H-[1,2,3]triazol-4-ylmethyl)-amine (6d). M.p. 191.5–193°C; ^1H NMR (DMSO-d_6): δ 8.35 (1H, s, CH), 7.99–6.89 (13H, m, Ar-H), 4.51 (2H, s, CH_2), 4.19 (1H, brs, NH), 2.73 (3H, s, CH_3); ^{13}C NMR data: 175.1, 159.3, 153.8, 149.2, 144.2, 141.6, 137.0,

Table 2

Antibacterial activity (MIC) of **6a–j**.

Compound	Antibacterial activity (MIC, μg mL^{-1})				
	P. aeruginosa	*S. aureus*	*E. coli*	*S. faecalis*	*P. acnes*
6a	90	90	90	90	90
6b	75	75	–	75	75
6c	40	40	40	75	75
6d	75	50	75	75	50
6e	50	–	75	75	50
6f	25	25	25	25	25
6g	20	20	20	20	20
6h	22	22	22	22	22
6i	75	50	30	30	30
6j	50	50	25	25	25
Ciprofloxacin	12	12	12	12	12

MIC, minimum inhibition concentration.

132.7, 132.0, 129.5, 129.1, 104.8, 51.3, 22.9; IR (KBr) cm^{-1}: 3389, 2976, 2391, 1515, 1409, 1312, 1176, 1034, 987, 799; LCMS *m/z*: 458 (M^++1); Anal. Calcd. for $C_{25}H_{20}ClN_5S$: C, 65.60; H, 4.43; N, 15.32; S, 7.01. Found C, 65.56; H, 4.40; N, 15.29; S, 7.00.

[4-(4-Chlorophenyl)-5-phenyl-thiazol-2-yl]-(1-o-tolyl-1H-[1,2,3]triazol-4-ylmethyl)-amine (6e). M.p. 170–172.5°C; ^{1}H NMR (DMSO-d_6): δ 8.33 (1H, s, CH), 7.96–6.91 (13H, m, Ar-H), 4.52 (2H, s, CH_2), 4.21 (1H, brs, NH), 2.71 (3H, s, CH_3); ^{13}C NMR data: 174.9, 159.1, 153.6, 149.2, 144.6, 141.1, 137.5, 132.8, 132.2, 129.5, 129.2, 104.6, 51.1, 22.4; IR (KBr) cm^{-1}: 3392, 2979, 2392, 1519, 1419, 1318, 1179, 1035, 988, 801; LCMS *m/z*: 458 (M^++1); Anal. Calcd. for $C_{25}H_{20}ClN_5S$: C, 65.60; H, 4.43; N, 15.32; S, 7.01. Found C, 65.58; H, 4.41; N, 15.28; S, 7.05.

[4-(4-Chlorophenyl)-5-phenyl-thiazol-2-yl]-[1-(4-methoxyphenyl)-1H-[1,2,3]triazol-4-ylmethyl]-amine (6f). M.p. 139–141°C; ^{1}H NMR (DMSO-d_6): δ 8.32 (1H, s, CH), 7.92–7.09 (13H, m, Ar-H), 4.63 (2H, s, CH_2), 4.21 (1H, brs, NH), 3.93 (3H, s, OCH_3); ^{13}C NMR data: 174.2, 165.8, 151.0, 145.3, 136.5, 136.0, 130.7, 129.3, 128.6, 127.1, 114.8, 58.3, 52.9; IR (KBr) cm^{-1}: 3298, 2985, 2843, 2371, 1579, 1489, 1388, 1071, 835; LCMS *m/z*: 474 (M^++1); Anal. Calcd. for $C_{25}H_{20}ClN_5OS$: C, 63.35; H, 4.23; N, 14.78; S, 6.77. Found C, 63.36; H, 4.21; N, 14.79; S, 6.70.

[4-(4-Chlorophenyl)-5-phenyl-thiazol-2-yl]-[1-(4-chlorophenyl)-1H-[1,2,3]triazol-4-ylmethyl]-amine (6g). M.p. 271–271.5°C; ^{1}H NMR (DMSO-d_6): δ 8.37 (1H, s, CH), 8.02–7.27 (13H, m, Ar-H), 4.57 (2H, s, CH_2), 4.17 (1H, brs, NH); ^{13}C NMR data: 176.7, 162.8, 160.3, 157.0, 149.3, 138.9, 136.5, 133.1, 129.3, 128.5, 123.1, 114.6, 52.9; IR (KBr) cm^{-1}: 3318, 2935, 2341, 1581, 1478, 1368, 1011, 879; LCMS *m/z*: 479 (M^++1); Anal. Calcd. for $C_{24}H_{17}Cl_2N_5S$: C, 60.25; H, 3.58; N, 14.64; S, 6.70. Found C, 60.36; H, 3.50; N, 14.69; S, 6.73.

[4-(4-Chlorophenyl)-5-phenyl-thiazol-2-yl]-[1-(2-chlorophenyl)-1H-[1,2,3]triazol-4-ylmethyl]-amine (6h). M.p. 168–169°C; ^{1}H NMR (DMSO-d_6): δ 8.35 (1H, s, CH), 8.01–7.26 (13H, m, Ar-H), 4.53 (2H, s, CH_2), 4.19 (1H, brs, NH); ^{13}C NMR data: 175.9, 162.9, 160.5, 157.6 , 149.1, 138.6, 135.8, 133.7, 129.6, 127.5, 124.1, 115.6, 52.7; IR (KBr) cm^{-1}: 3323, 2937, 2348, 1578, 1471, 1361, 1015, 882; LCMS *m/z*: 479 (M^++1); Anal. Calcd. for $C_{24}H_{17}Cl_2N_5S$: C, 60.25; H, 3.58; N, 14.64; S, 6.70. Found C, 60.38; H, 3.52; N, 14.72; S, 6.76.

[4-(4-Chlorophenyl)-5-phenyl-thiazol-2-yl]-[1-(4-nitrophenyl)-1H-[1,2,3]triazol-4-ylmethyl]-amine (6i). M.p. 212–213°C; ^{1}H NMR (DMSO-d_6): δ 8.38 (1H, s, CH), 8.12–7.19 (13H, m, Ar-H), 4.59 (2H, s, CH_2), 4.27 (1H, brs, NH); ^{13}C NMR data: 178.1, 162.3, 160.5, 158.3, 149.9, 138.0, 137.2, 136.5, 133.7, 129.0, 127.5, 124.6, 115.6, 54.9; IR (KBr) cm^{-1}: 3309, 2987, 2365, 1591, 1434, 1398, 1039, 982, 834; LCMS *m/z*: 489 (M^++1); Anal. Calcd. for $C_{24}H_{17}Cl_2N_6O_2S$: C, 58.95; H, 3.50; N, 17.19; S, 6.56. Found C, 58.95; H, 3.57; N, 17.32; S, 6.61.

[4-(4-Chlorophenyl)-5-phenyl-thiazol-2-yl]-[1-(2-nitrophenyl)-1H-[1,2,3]triazol-4-ylmethyl]-amine (6j). M.p. 190–192°C; ^{1}H NMR (DMSO-d_6): δ 8.32 (1H, s, CH), 8.03–7.38 (13H, m, Ar-H), 4.62 (2H, s, CH_2), 4.31 (1H, brs, NH); ^{13}C NMR data: 178.4, 162.6, 161.0, 158.7, 149.8, 139.0, 137.2, 136.5, 133.3, 129.2, 127.7, 123.8, 114.6, 53.9; IR (KBr) cm^{-1}: 3312, 2994, 2363, 1590, 1431, 1389, 1037, 984, 839; LCMS *m/z*: 489 (M^++1); Anal. Calcd. for $C_{24}H_{17}Cl_2N_6O_2S$: C, 58.95; H, 3.50; N, 17.19; S, 6.56. Found C, 58.99; H, 3.58; N, 17.34; S, 6.69.

Antibacterial activity. Thiazole and triazole derivatives are known to be potent antimicrobial agents [11–13]. The

Table 3

Antifungal activity of **6a–j**.

Compound	Zone of inhibition (in mm)	
	C. albicans	*A. niger*
6a	12	10
6b	19	17
6c	14	16
6d	14	16
6e	12	14
6f	28	17
6g	14	13
6h	11	12
6i	09	11
6j	13	25
Clotrimazole (10 μg cup^{-1})	27	19

compounds synthesized in the present study (**6a** through **6j**) were, therefore, screened for their antibacterial activity against human pathogenic bacteria such as *Pseudomonas aeruginosa, Staphylococcus aureus, Escherichia coli, Streptococcus faecalis, and Propionibacterium acnes*. The minimum inhibition concentration was determined using the dilution method [14]. DMF was used as a blank and Ciprofloxacin as standard, and the results are presented in Table 2.

An examination of the data reveals that all the compounds showed antibacterial activity ranging from 20 to 90 μg mL^{-1}. Of the 10 compounds, **6f** to **6h** exhibited pronounced antibacterial activity, and the inhibitory activity among these three compounds followed the increasing order: **6g**>**6h**>**6f**. Compounds **6c**, **6i**, and **6j** showed differential activity toward the test pathogenic bacteria. Thus, the relative activity of compound **6c** was more toward *P. aeruginosa, E. coli*, and *S. aureus*, and that of **6i** and **6j** against *E. coli*, *P. acnes,* and *S. faecalis*. The results clearly indicate that the presence of methoxy/chloro group at the phenyl ring increases the antibacterial activity. However, the activity was the maximum for a compound with two chloro groups.

Antifungal activity. The compounds **6a–j** were screened also for their antifungal activity (Table 3) against *Candida albicans* and *Aspergillus niger* using fungicide Clotrimazole in DMF as the standard [15]. All the compounds exhibited moderate to high-antifungal activity when compared with that of the reference compound. Most of the compounds exerted high activity against the tested fungi.

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