

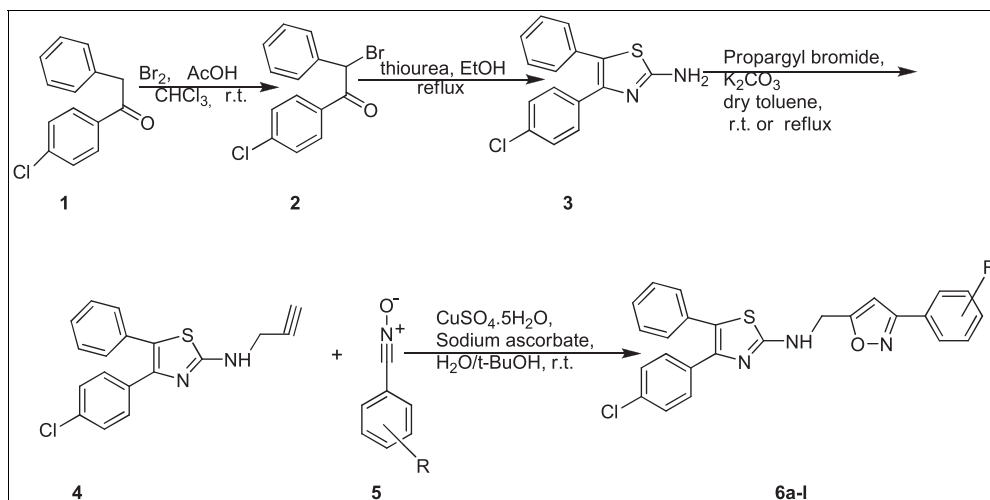
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A new class of methyleneamine-linked bis-heterocycles that exhibit antimicrobial activity was synthesized. Bromination of **1** followed by condensation with thiourea gave **3**. The reaction of **3** with propargyl bromide in dry toluene under inert atmosphere led to the formation of **4**. Its subsequent reaction with different nitrile oxides using $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ –sodium ascorbate system in a 2:1 mixture of water and *tert*-butyl alcohol yielded the title compounds **6a–l** 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 synthesis of five-membered heterocycles from readily available reagents is one of the major challenges in organic synthesis. Among five-membered heterocycles, isoxazole and thiazoles represent a class of compounds of great importance in biological chemistry. Bis-heterocyclic compounds with suitable alkyl spacer constitute an important class and have been under study for various types of activities, preferably antitumor [1] and antimicrobial [2], based on the DNA-binding affinity and enzyme-inhibiting actions. For instance, isoxazole-containing natural and non-natural compounds are interesting because of their biological activities [3] as fungicides [4], herbicides [5], or as nicotinic acetylcholine receptor ligands [6], and also isoxazoles have long been targeted in synthetic investigations for their known biological activities and pharmacological properties, which includes hypoglycemic [7], analgesic [8], anti-inflammatory [9,10], antiviral [11], antitubulin

[12], antibacterial [13], and immunomodulating activities [14], and have also been used as dyes, electric-insulating oils, and high-temperature lubricants [15–24]. Thiazole derivatives were gaining synthetic 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 [25], such as commercial agricultural fungicides trifluzamide and ethaboxam [26]. Because of its low toxicity, excellent biological activity, as well as ready access of diverse derivatives, this class of *N*-heterocyclic derivatives is widely studied [27]. Hence, it is thought that a worthwhile program would be required to prepare molecules having both isoxazole and thiazole rings through the most popular method following 1,3-dipolar cycloaddition reaction of nitrile oxides with terminal alkynes [28]. 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 isoxazole and thiazole moieties. We, therefore, followed a convenient and

regiocontrolled approach for the synthesis of this new class of isoxazole-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-amino-thiazole derivatives **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 nitrile oxides **5** using CuSO₄·5H₂O–sodium ascorbate system in a 2:1 mixture of water and *tert*-butyl alcohol led to the formation of **6a–l** in good yields. The reactions were monitored by thin layer chromatography (TLC; EtOAc:hexane, 1:4). The chemical structures of **6a–l** were confirmed by elemental analysis and spectral data (IR, ¹H, ¹³C NMR, and mass spectra).

Characteristic IR absorption bands were observed for C–N, N–O, C=N, C–S, and NH at 1037–1089, 1415–1477, 1518–1547, 719–774, and 3342–3392 cm^{−1}, respectively [29]. The aromatic hydrogens resonated as multiplets at δ 7.02–8.05.

Under the optimized conditions, a variety of substituents, aromatic compounds, were readily used in this transformation. Both electron-rich and electron-poor aromatic groups were tolerated in 1,3-dipolar cycloaddition reaction. Generally, the reaction was highly dependent on both electronic and steric effects. An evident steric effect was observed when we compared the yield of simple nitrile oxides with that of substituted nitrile oxides (entries 1–12). On whole, the better yields were obtained with simple nitrile oxides in a short period (entry 1). But interestingly, aromatic nitrile oxides bearing electron-withdrawing substituent, such as Cl, F, and NO₂ group at *p*-position afforded the product in prolonged period (**6f**, **6i**, and **6j**; Table 1). The formation of 3,5-disubstituted isoxazole has been unequivocally established through the characteristic chemical shift value of the isoxazole proton 4-CH at δ 6.90–7.05 in contrast to the appearance of 3-CH signal at δ 7.50–7.75 in the case of 4,5-disubstituted isoxazoles [29]

EXPERIMENTAL

Column chromatography was carried out on silica gel. All melting points were determined in open capillary tubes on Mel-Temp apparatus (Laboratory Devices, Cambridge, MA, USA) and are uncorrected. Infrared spectra ($\nu_{\max}$ in cm^{−1}) were recorded as KBr pellets on a Perkin-Elmer 283 double-beam spectrophotometer. ¹H and ¹³C NMR spectra were recorded on ABX 400 MHz spectrophotometer operating at 400 MHz for ¹H NMR, and 75 MHz for ¹³C NMR using CDCl₃ as solvent. The ¹H and ¹³C NMR chemical shifts were referenced to tetra methyl silane (TMS).

Typical experimental procedure

[4-(4-Substituted phenyl)-5-(4-substituted phenyl)-thiazol-2-yl]-(3-substituted phenyl isoxazole-5-ylmethyl)-amine **6a–l**. To a well-stirred solution of ketone **1** (8 g, 0.035 mol) in acetic acid (70 mL), a solution of bromine (5.57 g, 0.035 mol) in acetic acid

(15 mL) was added drop-wise during 20 min. Stirring was continued for about 24 h. The separated solid was filtered and recrystallized from 95% ethanol to furnish (**2**) at a yield of 86%. To this intermediate (4 g, 0.017 mol) in ethanol (30 mL), thiourea (2 g, 0.026 mol) was added and refluxed for 8 h, and the reaction progress was monitored by TLC. The solvent was evaporated under reduced pressure, and the solid was recrystallized from 95% ethanol to obtain sharp crystals of (**3**) (79%). To a solution of (**3**) (2 g, 0.0069 mol) in dry toluene (10 mL), a cooled solution of propargyl bromide (0.99 g, 0.0083 mol) was added drop-wise in the presence of K₂CO₃ (1.15 g, 0.0083 mol) 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 obtain crystals of (**4**) (89%).

To a well-stirred solution of **4** (1 g, 0.003 mol), in 5 mL of *tertiary* butanol and water mixture (2:1), copper sulfate (0.004 mol) and sodium ascorbate (0.28 mol) were added. After 15 min, aromatic nitrile oxides (**5**) (0.055 mmol) was added to the aforementioned reaction mixture and stirred for 17–34 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 sulfate and evaporated under reduced pressure to afford a crude product that upon recrystallization using EtOAc/hexane (1:4) yielded title compounds **6a–l**.

[4-(4-Chlorophenyl)-5-phenyl-thiazol-2-yl]-(3-phenyl-isoxazole-5-ylmethyl)-amine (**6a**). Semi solid; IR ν (cm^{−1}): 3360, 3032, 2983, 2852, 2365, 2342, 1632, 1537, 1467, 1330, 1269, 1121, 949, 851, 728; ¹H NMR (400 MHz, CDCl₃): δ 7.19–7.81 (m, 14H), 6.84 (s, 1H), 4.72 (s, 2H), 4.06 (br s, 1H); ¹³C NMR (75 MHz, CDCl₃) 173.19, 162.91, 155.23, 152.00, 148.71, 147.32, 136.91, 133.83, 131.35, 129.80, 129.31, 129.01, 128.59, 128.00, 127.03, 103.23, 106.06, 53.81; MS (EI) *m/z*: (M⁺ + 1) 444; Anal. Calcd. for C₂₅H₁₈ClN₃OS: C, 67.64; H, 4.09; Cl, 7.99; N, 9.47; S, 7.22. Found: C, 67.71; H, 4.03; Cl, 7.91; N, 9.56; S, 7.28.

[4-(4-Chlorophenyl)-5-phenyl-thiazol-2-yl]-(3-*p*-tolyl-isoxazole-5-ylmethyl)-amine (**6b**). Oil; IR ν (cm^{−1}): 3278, 3132, 2923, 2853, 2337, 1736, 1672, 1531, 1333, 1268, 1023, 844, 778, 672; ¹H NMR (400 MHz, CDCl₃): δ 7.02–7.84 (m, 13H), 6.92 (s, 1H), 4.68 (s, 2H), 4.09 (br s, 1H), 2.37 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) 175.03, 164.95, 161.09, 155.28, 152.30, 147.11, 146.72, 138.11, 133.71, 130.35, 129.80, 129.54, 129.36, 128.59, 128.07, 127.93, 104.83, 53.43, 21.96; MS (EI) *m/z*: (M⁺ + 1) 458; Anal. Calcd. for C₂₆H₂₀ClN₃OS: C, 68.19; H, 4.40; Cl, 7.74; N, 9.18; S, 7.00. Found: C, 68.22; H, 4.39; Cl, 7.71; N, 9.25; S, 7.08.

[4-(4-Chlorophenyl)-5-phenyl-thiazol-2-yl]-(3-*o*-tolyl-isoxazole-5-ylmethyl)-amine (**6c**). Oil; IR ν (cm^{−1}): 3287, 3136, 2923, 2365, 1677, 1534, 1476, 1349, 1276, 1175, 848, 779; ¹H NMR (400 MHz, CDCl₃): δ 7.12–7.91 (m, 13H), 6.98 (s, 1H), 4.69 (s, 2H), 4.14 (br s, 1H), 2.42 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) 175.13, 165.01, 161.29, 155.23, 151.99, 148.12, 146.77, 138.12, 133.78, 130.31, 128.99, 129.44, 128.97, 128.19, 128.01, 127.93, 105.83, 53.42, 21.98; MS (EI) *m/z*: (M⁺ + 1) 458; Anal. Calcd. for C₂₆H₂₀ClN₃OS: C, 68.19; H, 4.40; Cl, 7.74; N, 9.18; S, 7.00. Found: C, 68.29; H, 4.38; Cl, 7.74; N, 9.24; S, 7.18.

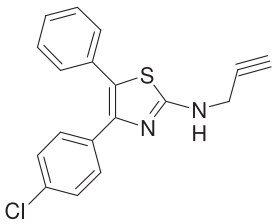
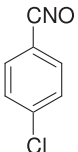
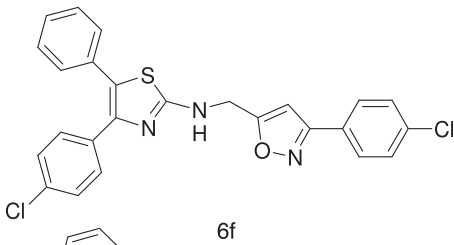
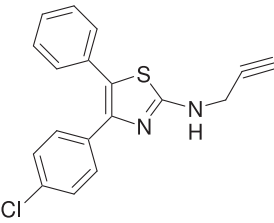
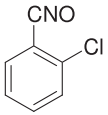
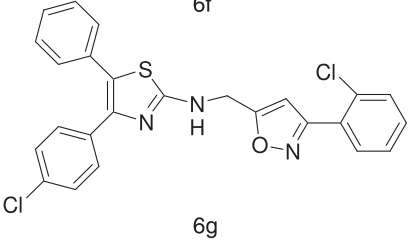
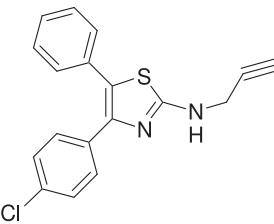
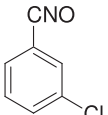
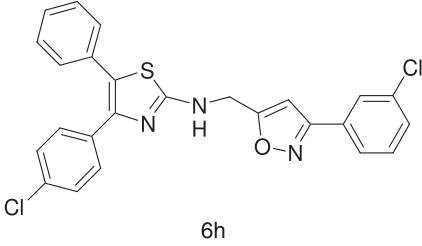
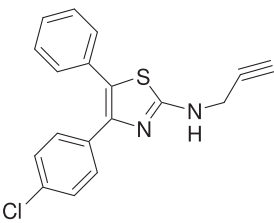
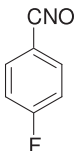
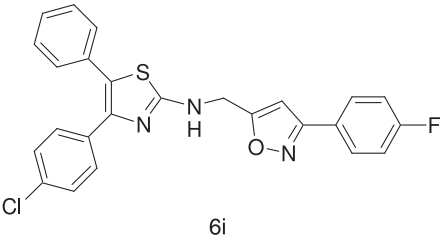
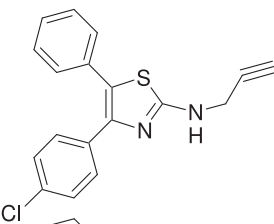
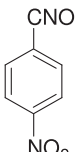
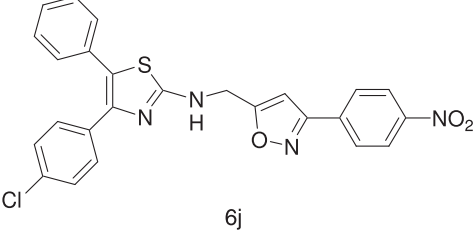
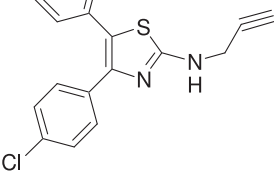
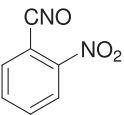
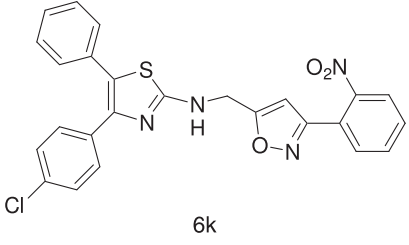
[4-(4-Chlorophenyl)-5-phenyl-thiazol-2-yl]-(3-*m*-tolyl-isoxazole-5-ylmethyl)-amine (**6d**). Oil; IR ν (cm^{−1}): 3285, 3134, 2925, 2361,

Table 1
Synthesis of isoxazole-based and thiazole-based novel unsymmetrical bis-heterocycles.

Entry	<i>N</i> -substituted propargylamine	Nitrile oxide	Bis-heterocycle ^a	Reaction yield ^b	
				Time (h)	%
1				17	94
2				25	91
3				28	86
4				22	79
5				25	91

(Continued)

Table 1
(Continued)

Entry	<i>N</i> -substituted propargylamine	Nitrile oxide	Bis-heterocycle ^a	Reaction yield ^b	
				Time (h)	%
6			 6f	31	87
7			 6g	27	84
8			 6h	22	79
9			 6i	32	83
10			 6j	34	82
11			 6k	29	81

(Continued)

Table 1
(Continued)

Entry	<i>N</i> -substituted propargylamine	Nitrile oxide	Bis-heterocycle ^a	Reaction yield ^b	
				Time (h)	%
12				22	79

^aAll products were characterized by IR, ¹H NMR, ¹³C NMR, and mass spectrometry.^bYields obtained after column chromatography.

1678, 1536, 1473, 1344, 1276, 1178, 846, 774; ¹H NMR (400 MHz, CDCl₃): δ 7.15–7.92 (m, 13H), 6.99 (s, 1H), 4.70 (s, 2H), 4.16 (br s, 1H), 2.34 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) 175.15, 164.91, 161.22, 155.24, 151.95, 148.92, 146.70, 138.16, 133.88, 130.91, 128.09, 129.45, 128.97, 128.19, 128.01, 127.93, 105.83, 53.42, 20.99; MS (EI) *m/z*: (*M*⁺ + 1) 458; *Anal.* Calcd. for C₂₆H₂₀ClN₃OS: C, 68.15; H, 4.40; Cl, 7.74; N, 9.18; S, 7.00. Found: C, 68.31; H, 4.15; Cl, 7.71; N, 9.26; S, 7.12.

[4-(4-Chlorophenyl)-5-phenylthiazol-2-yl]-[3-(4-methoxyphenyl)-isoxazol-5-ylmethyl]-amine (6e). Oil; IR *v* (cm⁻¹): 3348, 3072, 2994, 2360, 1654, 1578, 1438, 1367, 1281, 1105, 876, 745; ¹H NMR (400 MHz, CDCl₃): δ 6.98–7.83 (m, 13H), 6.84 (s, 1H), 4.76 (s, 2H), 4.11 (br s, 1H), 3.49 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) 176.19, 163.63, 161.56, 158.26, 155.03, 153.36, 146.78, 138.56, 135.74, 133.46, 132.05, 129.87, 129.49, 129.01, 128.42, 128.00, 119.67, 108.43, 101.73, 56.82, 53.81; MS (EI) *m/z*: (*M*⁺ + 1) 474; *Anal.* Calcd. for C₂₆H₂₀ClN₃O₂S: C, 65.88; H, 4.25; Cl, 7.48; N, 8.87; S, 6.77. Found: C, 67.93; H, 4.23; Cl, 7.42; N, 8.82; S, 6.82.

[4-(4-Chlorophenyl)-5-phenylthiazol-2-yl]-[3-(4-chlorophenyl)-isoxazol-5-ylmethyl]-amine (6f). Solid; mp 196–197.5°C; IR *v* (cm⁻¹): 3342 3072, 2923, 2853, 2337, 1771, 1598, 1457, 1343, 1258, 1105, 1021, 876, 750, 672; ¹H NMR (400 MHz, CDCl₃): δ 7.14–7.97 (m, 13H), 6.92 (s, 1H), 4.68 (s, 2H), 4.10 (br s, 1H); ¹³C NMR (75 MHz, CDCl₃) 175.19, 163.45, 161.41, 158.00, 155.43, 153.27, 146.91, 137.97, 135.24, 133.46, 132.05, 129.87, 129.49, 129.21, 127.09, 126.03, 119.04, 108.93, 102.86, 55.22, 52.81; MS (EI) *m/z*: (*M*⁺ + 1) 478; *Anal.* Calcd. for C₂₅H₁₇Cl₂N₃OS: C, 62.77; H, 3.58; Cl, 14.82; N, 8.78; S, 6.70. Found: C, 62.93; H, 3.34; Cl, 14.92; N, 8.82; S, 6.82.

[4-(4-Chlorophenyl)-5-phenylthiazol-2-yl]-[3-(2-chlorophenyl)-isoxazol-5-ylmethyl]-amine (6g). Solid; mp 142–144°C; IR *v* (cm⁻¹): 3345 3074, 2927, 2856, 2338, 1775, 1594, 1456, 1345, 1257, 1109, 1023, 875, 757, 674; ¹H NMR (400 MHz, CDCl₃): δ 7.11–7.95 (m, 13H), 6.98 (s, 1H), 4.71 (s, 2H), 4.15 (br s, 1H); ¹³C NMR (75 MHz, CDCl₃) 175.18, 163.55, 161.47, 158.01, 155.51, 153.17, 146.95, 137.98, 135.23, 133.46, 132.05, 129.87, 129.49, 129.25, 127.19, 126.08, 119.14, 108.92, 102.14, 55.54, 52.83; MS (EI) *m/z*: (*M*⁺ + 1) 478; *Anal.* Calcd. for C₂₅H₁₇Cl₂N₃OS: C, 62.77; H, 3.58; Cl, 14.82; N, 8.78; S, 6.70. Found: C, 62.82; H, 3.58; Cl, 14.76; N, 8.88; S, 6.71.

[4-(4-Chlorophenyl)-5-phenylthiazol-2-yl]-[3-(3-chlorophenyl)-isoxazol-5-ylmethyl]-amine (6h). Semi solid; IR *v* (cm⁻¹): 3352 3094, 2926, 2858, 2334, 1773, 1589, 1448, 1342, 1259, 1115, 1025, 872, 751, 673; ¹H NMR (400 MHz, CDCl₃): δ 7.12–7.90 (m, 13H), 7.00 (s, 1H), 4.72 (s, 2H), 4.18 (br s, 1H); ¹³C NMR (75 MHz, CDCl₃) 175.13, 163.47, 161.49, 158.07, 155.49, 153.29, 146.99, 137.97, 135.29, 133.45, 132.55, 129.88, 129.54, 129.31, 127.19, 126.08, 119.06, 108.95, 102.82, 55.41, 52.82; MS (EI) *m/z*: (*M*⁺ + 1) 478; *Anal.* Calcd. for C₂₅H₁₇Cl₂N₃OS: C, 62.77; H, 3.58; Cl, 14.82; N, 8.78; S, 6.70. Found: C, 62.77; H, 3.51; Cl, 14.90; N, 8.87; S, 6.62.

[4-(4-Chlorophenyl)-5-phenylthiazol-2-yl]-[3-(4-fluorophenyl)-isoxazol-5-ylmethyl]-amine (6i). Yellow solid; mp 212–213°C; IR *v* (cm⁻¹): 3342 3044, 2936, 2872, 1602, 1534, 1458, 1386, 1280, 1175, 1031, 816, 757, 678; ¹H NMR (400 MHz, CDCl₃): δ 7.14–7.97 (m, 13H), 6.99 (s, 1H), 4.67 (s, 2H), 4.08 (br s, 1H); ¹³C NMR (75 MHz, CDCl₃) 176.00, 163.09, 161.40, 159.00, 155.45, 153.76, 147.91, 138.97, 136.24, 134.66, 132.15, 129.97, 129.81, 129.23, 128.19, 126.43, 119.14, 108.86, 103.86, 55.28, 53.87; MS (EI) *m/z*: (*M*⁺ + 1) 462; *Anal.* Calcd. for C₂₅H₁₇ClFN₃OS: C, 65.00; H, 3.71; Cl, 7.67; F, 4.11; N, 9.10; S, 6.94. Found: C, 65.13; H, 3.78; Cl, 7.87; F, 4.16; N, 9.23; S, 6.88.

[4-(4-Chlorophenyl)-5-phenylthiazol-2-yl]-[3-(4-nitrophenyl)-isoxazol-5-ylmethyl]-amine (6j). Oil; IR *v* (cm⁻¹): 3342, 2936, 2853, 2361, 1764, 1599, 1532, 1458, 1402, 1343, 1258, 1125, 1021, 858, 801, 750, 672; ¹H NMR (400 MHz, CDCl₃): δ 7.21–7.96 (m, 13H), 7.01 (s, 1H), 4.72 (s, 2H), 4.14 (br s, 1H); ¹³C NMR (75 MHz, CDCl₃) 176.01, 163.19, 162.45, 159.06, 154.45, 153.71, 147.67, 137.92, 136.24, 133.76, 132.25, 129.91, 129.81, 129.23, 128.19, 126.43, 119.14, 109.86, 104.86, 54.84, 52.87; MS (EI) *m/z*: (*M*⁺ + 1) 489; *Anal.* Calcd. for C₂₅H₁₇ClN₄O₃S: C, 61.41; H, 3.50; Cl, 7.27; N, 11.46; S, 6.56. Found: C, 61.48; H, 3.58; Cl, 7.24; N, 11.53; S, 6.81.

[4-(4-Chlorophenyl)-5-phenylthiazol-2-yl]-[3-(2-nitrophenyl)-isoxazol-5-ylmethyl]-amine (6k). Oil; IR *v* (cm⁻¹): 3392, 3063, 2963, 2857, 2360, 1602, 1517, 1438, 1363, 1280, 1122, 1030, 841, 738, 644; ¹H NMR (400 MHz, CDCl₃): δ 7.02–7.79 (m, 14H), 6.89 (s, 1H), 4.78 (s, 2H), 4.11 (br s, 1H); ¹³C NMR (75 MHz, CDCl₃) 172.99, 163.65, 154.23, 153.60, 148.73, 147.82, 135.82, 134.81, 131.35, 129.84, 129.39, 129.00, 128.69,

Table 2
Antibacterial activity (minimum inhibition concentration; MIC) of **6a–l**.

Compound	Antibacterial activity (MIC, $\mu\text{g mL}^{-1}$)				
	<i>P. aeruginosa</i>	<i>S. aureus</i>	<i>E. coli</i>	<i>S. faecalis</i>	<i>P. acnes</i>
6a	85	90	85	80	90
6b	75	75	75	75	75
6c	55	40	38	75	75
6d	75	50	55	80	40
6e	20	20	18	20	23
6f	10	15	15	15	10
6g	14	14	14	15	14
6h	20	18	20	20	20
6i	—	50	80	75	75
6j	50	50	—	25	25
6k	50	—	80	90	75
6l	55	25	40	90	80
Ciprofloxacin	12	12	12	12	12

128.11, 127.03, 103.23, 106.06, 53.81, 51.04; MS (EI) m/z : ($M^+ + 1$) 489; *Anal.* Calcd. for $\text{C}_{25}\text{H}_{17}\text{ClN}_4\text{O}_3\text{S}$: C, 61.41; H, 3.50; Cl, 7.27; N, 11.46; S, 6.56. Found: C, 61.45; H, 3.54; Cl, 7.28; N, 11.52; S, 6.76

[4-(4-Chlorophenyl)-5-phenyl-thiazol-2-yl]-(3-(3-nitrophenyl)-isoxazol-5-ylmethyl)-amine (6l). Oil; IR ν (cm^{-1}): 3402, 3069, 2974, 2847, 2351, 1612, 1527, 1439, 1391, 1284, 1126, 1038, 843, 743, 649; ^1H NMR (400 MHz, CDCl_3): δ 7.00–7.79 (m, 13H), 6.89 (s, 1H), 4.65 (s, 2H), 4.03 (br s, 1H); ^{13}C NMR (75 MHz, CDCl_3) 174.39, 164.81, 161.23, 155.87, 151.93, 147.76, 146.37, 138.91, 134.93, 129.99, 129.82, 129.64, 129.26, 128.79, 128.27, 127.43, 104.93, 53.13, 22.01; MS (EI) m/z : ($M^+ + 1$) 489; *Anal.* Calcd. for $\text{C}_{25}\text{H}_{17}\text{ClN}_4\text{O}_3\text{S}$: C, 61.41; H, 3.50; Cl, 7.27; N, 11.46; S, 6.56. Found: C, 61.41; H, 3.49; Cl, 7.16; N, 11.38; S, 6.42.

Antibacterial activity. The compounds **6a–l** were 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 tube

dilution method [30]. 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 $90 \mu\text{g mL}^{-1}$. The compounds **6e–h** were highly active against all the five organisms employed. Compound **6l** was highly active against *P. aeruginosa*, *E. coli*, and *S. aureus* and the compound **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. The activity, however, was the maximum for a compound with two chloro groups.

Antifungal activity. The compounds **6a–l** were screened also for their antifungal activity (Table 3) against *Candida albicans* and *Aspergillus niger* using fungicide clotrimazole in DMF as the standard [31]. 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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Table 3
Antifungal activity of **6a–l**.

Compound	Zone of inhibition (in mm)	
	<i>C. albicans</i>	<i>A. niger</i>
6a	10	15
6b	16	19
6c	20	19
6d	14	12
6e	12	10
6f	20	17
6g	15	15
6h	14	10
6i	09	12
6j	13	14
6k	18	14
6l	12	10
Clotrimazole ($10 \mu\text{g cup}^{-1}$)	27	19

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