Synthesis and Antimicrobial Activities of Novel Series of 3-(4-(2-substituted thiazol-4-yl)phenyl)-2-(4-methyl-2-substituted thiazol-5-yl)thiazolidin-4-one Derivatives

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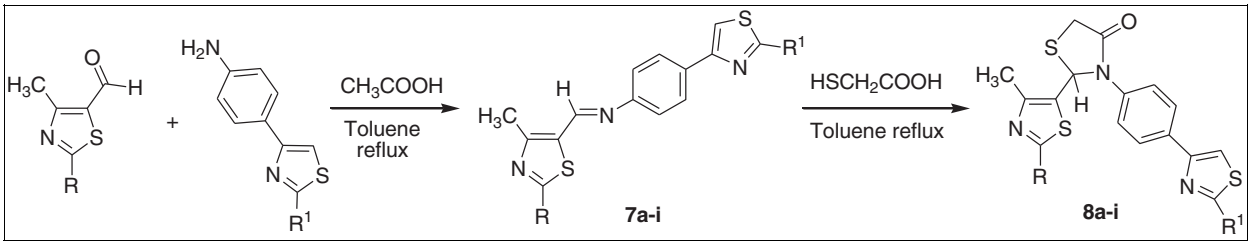

In the present investigation, a novel series of 3-(4-(2-substituted thiazol-4-yl)phenyl)-2-(4-methyl-2-substituted thiazol-5-yl)thiazolidin-4-one derivatives were synthesized by condensation of 2-substituted-4-methylthiazole-5-carbaldehyde with 4-(2-substituted thiazol-4-yl)benzenamine followed by cyclo-condensation with thioglycolic acid in toluene. All the newly synthesized compounds were characterized by spectral (IR, ^{1}H NMR, ^{13}C NMR, and Mass) methods. The title compounds were screened for quantitative antibacterial activity (minimal inhibitory concentration). All compounds **7a–h** and **8a–h** show moderate to good antimicrobial activity, whereas compounds (**7a–h**) also show moderate antifungal activity.

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INTRODUCTION

Thiazole and their derivatives have attracted continuing interest over the years because of their varied biological activities [1]. 1,3-Thiazole nucleus containing compounds have exhibited a broad range of biological activities [2–11]. Thiazolidinones have also received considerable attention because of their biological importance [12]. The thiazolidinone nucleus containing compounds show anti-inflammatory [13–20], anticonvulsant [21–24], hypnotic and anti-tubercular [25–27], and antimicrobial and anticancer [28–35] activities. In view of these observations and as a continuation of our previous work on thiazolidinone [36], it was thought to synthesize new thiazole based 1,3-thiazolidin-4-one by the condensation of 2-substituted-4-methylthiazole-5-carbaldehyde with 4-(2-substituted thiazol-4-yl)benzene-amine and thioglycolic acid.

RESULTS AND DISCUSSION

The synthesis of 3-(4-(2-methyl/aryl/benzylthiazol-4-yl) phenyl)-2-(4-methyl-2-aryl/benzylthiazol-5-yl)thiazolidin-4-one **8a–i** is illustrated in Figure 1. The starting material ethyl-2-aryl/benzyl-4-methylthiazole-5-carboxylate **1a–b** and 4-(2-aryl/benzyl/methylthiazol-4-yl)benzenamine were prepared according to earlier reported procedure [37]. Ester **1a–b** was reduced to corresponding alcohol **2a–b** using lithium aluminum hydride in dry diethyl ether. The alcohol **2a–b** was then oxidized to corresponding aldehyde **3a–b** using 2-iodoxy benzoic acid (IBX) [38–41].

Aldehydes **3a–b** were condensed with 4-(2-aryl/benzyl/methylthiazol-4-yl)benzenamine **6a–f** in toluene with azeotropic separation of water that gave corresponding Schiff's base **7a–i**. The infrared (IR) spectrum of Schiff's bases displayed the disappearance of absorption bands corresponding to C–H and C=O stretching frequency of aldehyde while appearance of the absorption band at 1600–1615 cm^{-1} and 3062–3150 cm^{-1} characteristic of C=N and N=CH confirmed the formation of imine functionality. The ^{1}H NMR spectrum of Schiff's base displayed the absence of singlet at δ 9.8–10.1 (CHO), whereas a new singlet that appeared between δ 7.94–8.66 was attributed to N=CH proton. Similarly, in the ^{13}C NMR spectrum disappearance of signal at δ 180–182 (C=O) and appearance of a new signal at δ 169.2–171.4 for N=CH carbon confirmed the structure of Schiff's base. Schiff's base on cyclo-condensation with thioglycolic acid afforded thiazolidinone derivative **8a–i**. The physical properties and yield of synthesized compounds **8a–i** are reported in Table 1.

The IR spectrum of thiazolidin-4-one **8a–i** revealed characteristic absorption peak at 1685–1693 cm^{-1} (C=O) that indicated the formation of thiazolidin-4-one compound, which was further confirmed by its ^{1}H NMR spectrum which displayed an AB quartet between δ 3.88–4.00 integrated for two geminal protons of thiazolidine-4-one nucleus and singlet at δ 6.34–6.52 integrated for one proton of

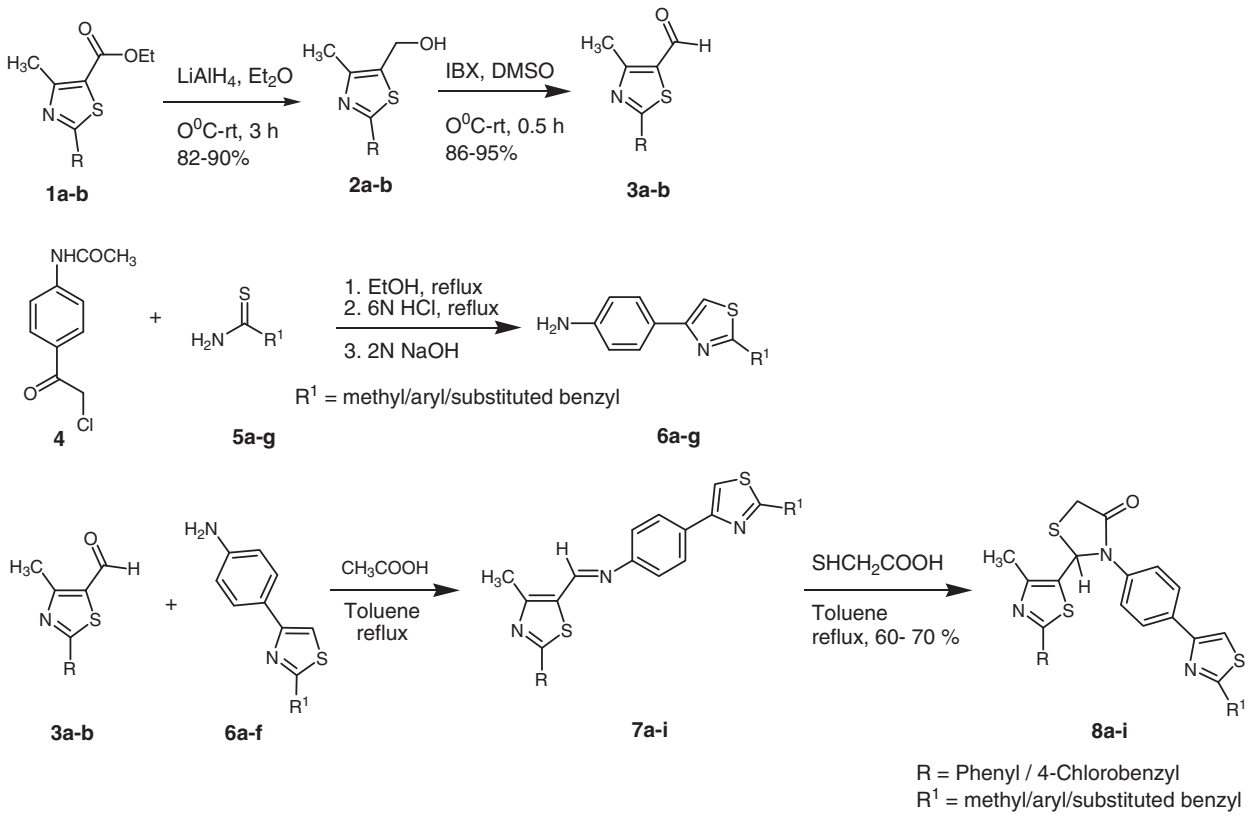

Figure 1. Synthetic pathway for formation of compounds **7a-i** and **8a-i**.

Table 1

The physical properties and yield of synthesized compounds **7a–i** and **8a–i**.

Compound	R	R^1	mp[a]	Yield[b]
7a	C_6H_5	CH_3	89–90	84
7b	C_6H_5	3-FC_6H_4	92–94	86
7c	C_6H_5	4-$ClC_6H_4CH_2$	139–140	89
7d	C_6H_5	2,4-$Cl_2C_6H_3CH_2$	94–96	80
7e	C_6H_5	3,4-$Cl_2C_6H_3CH_2$	78–80	86
7f	C_6H_5	4-$OMeC_6H_4CH_2$	93–94	76
7g	4-$ClC_6H_4CH_2$	CH_3	85–87	86
7h	4-$ClC_6H_4CH_2$	4-ClC_6H_4	86–88	72
7i	4-$ClC_6H_4CH_2$	4-$OMeC_6H_4CH_2$	79–80	70
8a	C_6H_5	CH_3	89–91	68
8b	C_6H_5	3-FC_6H_4	92–93	67
8c	C_6H_5	4-$ClC_6H_4CH_2$	138–140	70
8d	C_6H_5	2,4-$Cl_2C_6H_3CH_2$	95–96	70
8e	C_6H_5	3,4-$Cl_2C_6H_3CH_2$	78–80	69
8f	C_6H_5	4-$OMeC_6H_4CH_2$	93–94	65
8g	4-$ClC_6H_4CH_2$	CH_3	84–86	66
8h	4-$ClC_6H_4CH_2$	4-ClC_6H_4	86–88	66
8i	4-$ClC_6H_4CH_2$	4-$OMeC_6H_4CH_2$	78–80	60

mp, melting point.
[a]°C
[b]Isolated yield.

thiazolidin-4-one ring. The formation of the thiazolidin-4-one ring was further confirmed by its ^{13}C NMR spectra, which revealed peaks around 33, 58, and 171 due to CH_2, CH, and C═O of thizolidinone nucleus in each compound.

Antimicrobial and antifungal testing. All the synthesized compounds were quantitatively evaluated for antimicrobial activity using the minimum inhibitory concentration (MIC) assay [42]. These compounds were tested against a number of reference test organisms including Gram-negative (*Escherichia coli* American Type Culture Collection (ATCC) 25922, *Pseudomonas aeruginosa* ATCC 27853) and Gram-positive (*Staphylococcus aureus* ATCC 25923, *Staphylococcus fecalis* ATCC 29212, *Bacillus subtilis* ATCC 6633) and fungi (*Candida albicans* ATCC 10231, *Aspergillus niger* ATCC 9029). The *in vitro* antimicrobial MIC screening results of synthesized compounds **7a–i** and **8a–i** are given in Table 2.

Most of the synthesized compounds (except **7i** and **8i)** exhibited moderate to good antimicrobial activities. The compounds **7h**, **8a**, **8b**, and **8 h** showed good activity (MIC values are twofold as compared with the standard) against Gram-positive bacteria strain *S. fecalis*. Compounds **7h** and **8h** (R = 4-Cl-C_6H_4-CH_2 and R^1 = 4-Cl-C_6H_4-) in Schiff's base as well as thiazolidin-4-one, compound **8a** (R = Ph and $R^1 = CH_3$) and **8b** (R = Ph and R^1 = 3-F-C_6H_4-) were found to be more active for *S. fecalis* strain as compared with other antibacterial strains. Compounds **7b**, **7c**, **7d**, **7e**, **7g**, **8c**, **8d**, **8f**, and **8g** showed moderate antibacterial activities (MIC values are fourfold or more as compared with the standard) against Gram-negative and/or Gram-positive species.

The result of antifungal activities revealed that Schiff's base (**7a–i**) did not show any significant activity, whereas their corresponding thiazolidin-4-one derivatives showed good activities. This result can be attributed because of the presence of thiazolidin-4-one ring in compounds **8a–h**. Compounds **8b** (R = Ph, R^1 = 3-F-C_6H_4), **8g** and **8h** (R = 4-Cl-C_6H_4-CH_2- and $R^1 = CH_3$ or 4-Cl-C_6H_4) exhibited good activities against yeast species with MIC value 12.5 μg/mL, whereas compounds **8a**, **8c**, **8d**, **8e**, and **8f** (R^1 = methyl or substituted benzyl) are moderately active with MIC values 25–50 μg/mL. Thus, it is concluded that compounds with R^1 = substituted phenyl group show good antifungal activity whereas compounds with substituted benzyl group show moderate activity.

CONCLUSION

In summary, we have synthesized a series of novel 4-(2-(substituted thiazol-4-yl)-N-((4-methyl-2-phenyl/benzylthiazol-5-yl)methylene)benzenamine (**7a–i**) and 3-(4-(2-substituted thiazol-4-yl)phenyl)-2-(4-methyl-2-aryl/benzylthiazol-5-yl)thiazolidin-4-one (**8a–i**). The *in vitro* antimicrobial results revealed that synthesized Schiff's bases (**7a–h**) shows only moderate to good antibacterial activity, whereas thiazolidin-4-one (**8a–h**) shows good to significant antibacterial as well as antifungal activities. The antimicrobial activity results make them interesting lead molecules for further synthetic and biological evaluation. Further studies are in progress to acquire more information regarding structure activity relationship.

Table 2

Antimicrobial activity of novel 4-(2-(methyl/phenyl/benzyl)thiazol-4-yl)-*N*-((4-methyl-2-phenyl/benzylthiazol-5-yl)methylene)benzenamine **7a–i** and 3-(4-(2-methyl/aryl/benzylthiazol-4-yl)phenyl)-2-(4-methyl-2-aryl/benzylthiazol-5-yl)thiazolidin-4-one **8a–i**.

Compound	Pathogen MIC μg/mL (μM)						
	Ec	Pa	Sa	Sf	Bs	Ca	An
7a	25 (66.66)	50 (133.33)	50 (133.33)	50 (133.33)	>100	>100	>100
7b	12.5 (27.47)	50 (109.88)	25 (54.94)	25 (54.94)	50 (109.88)	100 (219.78)	>100
7c	25 (51.49)	50 (102.98)	50 (102.98)	25 (51.49)	50 (102.98)	100 (205.96)	100 (205.96)
7d	50 (96.15)	25(48.07)	25 (48.07)	25 (48.07)	25 (48.07)	>100	>100
7e	25 (48.07)	50 (96.15)	25 (48.07)	25 (48.07)	25 (48.07)	>100	>100
7f	50 (103.95)	50 (103.95)	50 (103.95)	25 (51.97)	50 (103.95)	>100	>100
7g	12.5 (30.52)	12.5 (30.52	12.5 (30.52)	25 (61.04)	25 (61.04)	>100	>100
7h	12.5 (24.70)	25 (49.40)	25 (49.40)	12.5 (24.70)	25 (49.40)	>100	>100
7i	100 (193.98)	>100	>100	100 (193.98)	>100	>100	>100
8a	12.5 (27.83)	12.5 (27.83)	12.5 (27.83)	12.5 (27.83)	25 (55.67)	25 (55.67)	25 (55.67)
8b	12.5 (23.62)	12.5 (23.62)	25 (47.25)	12.5 (23.62)	25 (47.25)	12.5 (23.62)	12.5 (23.62)
8c	12.5 (22.34)	25 (44.68)	25 (44.68)	25 (44.68)	25 (44.68)	25 (44.68)	25 (44.68)
8d	25 (42.08)	50 (84.16)	50 (84.16)	50 (84.16)	50 (84.16)	50 (84.17)	50 (84.17)
8e	25 (42.08)	50 (84.16)	50 (84.16)	50 (84.16)	100 (168.3)	50 (84.16)	50 (84.16)
8f	25 (45.20)	50 (90.41)	50 (90.41)	25 (45.20)	50 (90.41)	50 (90.41)	50 (90.41)
8g	12.5 (21.42)	12.5 (21.42)	50 (85.68)	25 (42.84)	50 (85.68)	12.5 (21.42)	25 (42.84)
8h	25 (43.10)	50 (86.20)	25 (43.10)	12.5 (21.55)	50 (86.20)	12.5 (21.55)	12.5 (21.55)
8i	>100	>100	>100	50	50	>100	>100
Ciproflox.	0.78 (2.35)	0.78 (2.35)	1.56 (4.70)	6.25 (18.8)	6.25 (18.8)	—	—
Fluconazole	—	—	—	—	—	0.78 (2.54)	1.56 (5.09)

Ec, *Escherichia coli* (ATCC 25922); Pa, *Pseudomonas aeruginosa (*ATCC 27853); Sa, *Staphylococcus aureus* (ATCC 25923); Sf, *Staphylococcus fecalis* (ATCC 29212); Bc, *Bacillus subtilis* (ATCC 6633); Ca, *Candida albican* (ATCC 10231); An, *Aspergillus niger* (ATCC 9029).

EXPERIMENTAL

Melting points were determined in an open capillary on Veego melting point apparatus (Mumbai, India) and are uncorrected. All reactions were monitored by thin layer chromatography on 0.25 mm E. Merck silica gel plates (F-254) using UV light or iodine vapors as the visualizing methods. IR spectra (cm^{-1}) were recorded in KBr on a Shimadzu Model FTIR-435 spectrophotometer (Kyoto, Japan). ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 solution on a Varian Mercury YH-300 spectrometer (Darmstadt, Germany) operating at 300 MHz for ^1H and 75 MHz for ^{13}C, respectively. Chemical shifts are expressed relative to tetramethylsilane and were reported as δ (ppm). Liquid Cromatography Mass Spectrometry (LCMS) measurements were made on a Jeol-JMS-DX 303 mass spectrometer (Tokyo, Japan). The elemental analysis was performed on FLASH EA 1112 analyzer (Thermo Scientific, Cambridge, UK) and results were found within the ±0.4% of theoretical values.

General procedure for compounds (7a–i). To a solution of 4-methyl-2-phenylthiazole-5-carbaldehyde **3a** (0.005 mol) in dry toluene (30 mL), 4-(2-(3-fluorophenyl)thiazol-4-yl)benzenamine, **6b** (0.006 mol), and glacial acetic acid (0.2 mL) was added. The reaction mixture was refluxed for 5–6 h with azeotropic separation of water. After the completion of the reaction (TLC) solvent was removed under reduced pressure. The product was recrystalized from dry ethanol.

N-((4-methyl-2-phenylthiazol-5-yl)methylene)-4-(2-methylthiazol-4-yl)benzenamine 7a. IR: 3051, 1612, 1583, 1500, 1460, 1429, 1373, 1325, 1201, 1172 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.69 (s, 3H), 2.78 (s, 3H), 7.18 (s, 1H), 7.27–7.31 (m, 2H), 7.45–7.48 (m, 3H), 7.92 (d, J = 8.4Hz, 2H), 7.98–8.01 (m, 2H), 8.66 (s, 1H); ^{13} C NMR (75 MHz, $CDCl_3$): δ 15.8, 21.1, 117.4, 121.8, 126.9, 127.8, 128.9, 129.2, 129.6, 132.6, 133.5, 142.9, 151.5, 159.3, 162.2, 169.1, 169.6; ms: *m/z* 375 (M^+), 377.1 (M + 2). *Anal*. Calcd. for $C_{21}H_{17}N_3S_2$: C, 67.17; H, 4.56; N, 11.19. Found: C, 67.19; H, 4.55; N, 11.15.

4-(2-(3-fluorophenyl)thiazol-4-yl)-N-((4-methyl-2-phenylthiazol-5-yl)methylene)benzenamine 7b. IR: 3074, 2964, 1612, 1581, 1479, 1375, 1319, 1261, 1174 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.67 (s, 3H), 7.10–7.23 (m, 4H), 7.26–7.45 (m, 4H), 7.72–7.79 (m, 2H), 7.96–8.01 (m, 4H), 8.62 (s, 1H); ^{13} C NMR (75 MHz, $CDCl_3$): δ 15.2, 114.5, 114.9, 117.5, 123.2, 126.6, 126.9, 127.7, 128.4, 128.9, 129.3, 130.9, 131.7, 133.5, 135.2, 139.5, 152.2, 155.1, 161.0, 162.1, 167.9, 170.0; ms: *m/z* 455 (M^+), 457.1 (M + 2). *Anal*. Calcd. for $C_{26}H_{18}FN_3S_2$: C, 68.55; H, 3.98; N, 9.22. Found: C, 68.50; H, 4.00; N, 9.25.

4-(2-(4-chlorobenzyl)thiazol-4-yl)-N-((4-methyl-2-phenylthiazol-5-yl)methylene)benzenamine 7c. IR: 3062, 1610, 1575, 1491, 1419, 1375,1317, 1205, 1176 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.71 (s, 3H), 4.37 (s, 2H), 7.25–7.45 (m, 10H), 7.95–8.02 (m, 4H), 8.67 (s, 1H); ^{13} C NMR (75 MHz, $CDCl_3$): 16.1, 39.1, 112.7, 117.5, 121.5, 126.8, 127.2, 128.9, 129.0, 129.6, 130.4, 130.8, 132.6, 133.2, 136.2, 150.5, 151.1, 157.4, 162.2, 169.1, 169.6; ms: *m/z* 485.5 (M^+), 487.6 (M + 2). *Anal*. Calcd. for $C_{27}H_{20}ClN_3S_2$: C, 66.72; H, 4.15; N, 8.65. Found: C, 66.76; H, 4.11; N, 8.69.

4-(2-(2,4-dichlorobenzyl)thiazol-4-yl)-N-((4-methyl-2-phenylthiazol-5-yl)methylene)benzenamine 7d. IR: 3070, 1600, 1584, 1480, 1319, 1199 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.68 (s, 3H); 4.26 (s, 2H); 6.94–7.29 (m, 6H); 7.35–7.44 (m, 3H); 7.49–7.53 (m, 2H); 7.88–7.94 (m, 3H); ^{13} C NMR (75 MHz, $CDCl_3$): 16.0, 36.2, 112.9, 116.8, 122.0, 126.8, 127.3, 128.7, 129.0, 129.3, 130.4, 130.8, 131.8, 132.6, 133.2, 135.9, 136.2, 151.1, 151.8, 155.0, 162.0, 169.0, 169.8; ms: *m/z* 520 (M^+), 522.1 (M + 2), 524.1 (M + 4). *Anal*. Calcd. for $C_{27}H_{19}Cl_2N_3S_2$: C, 62.30; H, 3.68; N, 8.07. Found: C, 62.26; H, 3.70; N, 8.10.

4-(2-(3,4-dichlorobenzyl)thiazol-4-yl)-N-((4-methyl-2-phenylthiazol-5-yl)methylene)benzenamine 7e. IR: 3071, 1600, 1583, 1484, 1320, 1200 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.65 (s, 3H); 4.25 (s, 2H); 6.90–7.23 (m, 7H); 7.41–7.43 (m, 3H); 7.90–7.94 (m, 4H); ^{13} C NMR (75 MHz, $CDCl_3$): 16.1, 39.3, 113.2, 116.5, 122.8, 127.3, 128.6, 128.8, 129.0, 129.6, 130.1, 130.4, 130.8, 131.9, 132.9, 133.5, 135.8, 137.5, 151.3, 152.1, 162.0, 169.1, 169.6; ms: *m/z* 520 (M^+), 522.1 (M + 2), 524.1 (M + 4). *Anal*. Calcd. for $C_{27}H_{19}Cl_2N_3S_2$: C, 62.30; H, 3.68; N, 8.07. Found: C, 62.27; H, 3.70; N, 8.11.

4-(2-(4-methoxybenzyl)thiazol-4-yl)-N-((4-methyl-2-phenylthiazol-5-yl)methylene)benzenamine 7f. IR: 3070, 3047, 1612, 1575, 1518, 1460, 1315, 1248, 1178 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.65 (s, 3H), 3.76 (s, 3H), 4.29 (s, 2H), 6.85 (d, 2H, J = 8.6 Hz), 7.21–7.29 (m, 5H), 7.40–7.42 (m, 3H), 7.89 (d, 2H, J = 8.6 Hz); 7.94–7.97 (m, 2H), 8.61 (s, 1H); ^{13} C NMR (75 MHz, $CDCl_3$): δ 16.1, 39.0, 55.2, 112.6, 114.1, 121.4, 126.8, 127.2, 129.0, 129.9, 130.2, 130.8, 131.7, 132.8, 133.2, 150.4, 150.9, 154.7, 157.3, 158.7, 169.9, 171.4; ms: *m/z* 481.1 (M^+), 483.1 (M + 2). *Anal*. Calcd. for $C_{28}H_{23}N_3OS_2$: C, 69.83; H, 4.81; N, 8.72. Found: C, 69.85; H, 4.77; N, 8.75.

((2-(4-chlorobenzyl)-4-methylthiazol-5-yl)methylene)-4-(2-methylthiazol-4-yl)benzenamine 7g. IR: 3064, 1611, 1585, 1488, 1323, 1235, 1182 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.49 (s, 3H), 2.66 (s, 3H), 4.37 (s, 2H), 6.88–7.38 (m, 5H), 7.90–7.94 (m, 4H), 8.55 (s, 1H); ^{13} C NMR (75 MHz, $CDCl_3$): δ 15.5, 19.4, 39.0, 112.8, 122.5, 127.9, 128.8, 130.5, 131.5, 131.9, 133.9, 135.0, 137.3, 151.2, 153.7, 161.0, 168.8, 169.2; ms: *m/z* 423.6 (M^+), 425.6 (M + 2). *Anal*. Calcd. for $C_{22}H_{18}ClN_3S_2$: C, 62.32; H, 4.28; N, 9.91. Found: C, 62.30; H, 4.26; N, 9.83.

((2-(4-chlorobenzyl)-4-methylthiazol-5-yl)methylene)-4-(2-(4-chlorophenyl)thiazol-4-yl)benzenamine 7h. IR: 3065, 1613, 1588, 1486, 1322, 1208, 1189 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.62 (s, 3H), 4.28 (s, 2H), 6.92 (d, J = 8.4 Hz, 2H,), 7.10–7.35 (m, 9H), 7.80 (d, J = 8.4 Hz, 2H), 8.56 (s, 1H); ^{13} C NMR (75 MHz, $CDCl_3$): δ 15.6, 39.5, 112.4, 123.5, 126.0, 127.9, 128.6, 129.0, 129.5, 130.5, 130.9, 131.2, 131.7, 133.5, 134.0, 137.0, 151.2, 152.9, 160.8, 168.0, 169.8; ms: *m/z* 520.0 (M^+), 522.1 (M + 2), 524.1 (M + 4). *Anal*. Calcd. for $C_{27}H_{19}Cl_2N_3S_2$: C, 62.30; H, 3.68; N, 8.07. Found: C, 62.34; H, 3.62; N, 8.11.

((2-(4-chlorobenzyl)-4-methylthiazol-5-yl)methylene)-4-(2-(4-methoxybenzyl)thiazol-4-yl)benzenamine 7i. IR: 3059, 1612, 1594, 1484, 1377, 1318, 1242, 1178 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.60 (s, 3H), 3.79 (s, 3H), 4.25 (s, 2H), 4.32 (s, 2H), 6.88 (d, 2H, J = 8.4 Hz), 7.10–7.35 (m, 9H), 7.88 (d, 2H, J = 8.4 Hz), 8.56 (s, 1H); ^{13} C NMR (75 MHz, $CDCl_3$): δ 15.2, 38.8, 39.2, 55.2, 113.9, 114.5, 120.3, 126.5, 127.2, 129.1, 129.7, 130.3, 130.5, 132.2, 133.0, 134.0, 136.8, 150.9, 152.2 156.8, 158.7, 168.7, 169.5; ms: *m/z* 529.5 (M^+), 531.6 (M + 2). *Anal*. Calcd. for $C_{29}H_{24}ClN_3OS_2$: C, 65.71; H, 4.56; N, 7.93. Found: C, 65.67; H, 4.59; N, 7.96.

General procedure for compounds (8a–i). To a solution of 4-(2-(3-fluorophenyl) thiazol-4-yl)-N-((4-methyl-2-phenylthiazol-5-yl) methylene) benzenamine **7b** (0.5 mmol) in dry toluene (20 mL), thioglycolic acid (0.6 mmol) was added and the reaction mixture was refluxed for 8–10 h (TLC). The solvent was removed under reduced pressure and the residue was treated with saturated solution of $NaHCO_3$, the aqueous layer was extracted with ethyl

acetate (25 mL × 3). The organic layer was washed with water, brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure. The crude product was purified by column chromatography to afford 3-(4-(2-(3-fluorophenyl)thiazol-4-yl)phenyl)-2-(4-methyl-2-phenylthiazol-5-yl)thiazolidin-4-one **8b** 1.30 g (67%).

2-(4-methyl-2-phenylthiazol-5-yl)-3-(4-(2-methylthiazol-4-yl) phenyl)thiazolidin-4-one 8a. IR: 1689, 1602, 1533, 1500, 1373, 1317, 1242, 1174, 999, 848, 763, 692 cm^{-1}; 2.24 (s, 3H); 2.29 (s, 3H); 4.09 (AB quartet, 2H); 6.52 (s,1H); 7.00 (t, 1H); 7.19 (m, 2H); 7.35–7.43 (m, 5H); 7.67 (m, 2H); ^{13} C NMR (75 MHz, $CDCl_3$): δ 14.8, 19.5, 33.3, 58.1, 115.5, 126.5, 127.3, 127.9, 128.4, 128.8, 129.0, 129.6, 133.3, 137.8, 151.0, 151.8, 166.8, 169.0, 170.1; ms: *m/z* 449.0 (M^+), 451.0 (M + 2). *Anal*. Calcd. for $C_{23}H_{19}N_3OS_3$ C, 61.44; H, 4.26; N, 9.35. Found: C, 61.40; H, 4.22; N, 9.39.

3-(4-(2-(3-fluorophenyl)thiazol-4-yl)phenyl)-2-(4-methyl-2-phenylthiazol-5-yl)thiazolidin-4-one 8b. IR: 1690, 1603, 1591, 1531, 1479, 1375, 1263, 1178, 1066, 790, 686 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ : 2.23 (s, 3H); 4.00 (AB quartet, 2H); 6.43 (s, 1H); 7.12 (t, *J* = 6.8 Hz, 1H); 7.24 (d, *J* = 8.1 Hz, 2H); 7.39–7.41 (m, 4H); 7.76 (s, 1H); 7.73 (d, *J* = 7.8 Hz, 2H); 7.83–7.86 (m, 2H); 7.95 (d, *J* = 8.1 Hz, 2H) ^{13} C NMR (75 MHz, $CDCl_3$): δ 15.2, 33.4, 58.5, 113.4, 113.8, 116.9, 122.2, 126.4, 126.7, 127.1, 127.4, 128.9, 130.4, 130.5, 132.0, 133.0, 133.8, 136.5, 152.1, 155.1, 163.0, 166.1, 167.9, 170.0; ms: *m/z* 529.0 (M^+), 531.0 (M + 2). *Anal*. Calcd. for $C_{28}H_{20}FN_3OS_3$: C, 63.49; H, 3.81; N, 7.93. Found: C, 63.44; H, 3.85; N, 7.97.

3-(4-(2-(4-chlorobenzyl)thiazol-4-yl)phenyl)-2-(4-methyl-2-phenylthiazol-5-yl)thiazolidin-4-one 8c. IR: 1685, 1601, 1537, 1494, 1410, 1377, 1323, 1242, 1178, 842, 756, 688 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.24 (s, 3H); 4.00 (AB quartet, 2H); 4.33 (s, 2H); 6.44 (s, 1H); 67.21–7.70 (m, 10H); 7.85–7.88 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.0, 33.6, 39.5, 58.0, 113.5, 117.2, 122.7, 127.3, 127.5, 128.5, 128.9, 129.2, 129.6, 130.5, 131.2, 133.2, 134.1, 137.0, 151.1, 152.3, 168.0, 169.2, 171.0; ms: *m/z* 559.6 (M^+), 561.6 (M + 2). *Anal*. Calcd. for $C_{29}H_{22}ClN_3OS_3$: C, 62.18; H, 3.96; N, 7.50. Found: C, 62.15; H, 4.00; N, 7.53.

3-(4-(2-(2,4-dichlorobenzyl)thiazol-4-yl)phenyl)-2-(4-methyl-2-phenylthiazol-5-yl)thiazolidin-4-one 8d. IR: 1693, 1601, 1535, 1496, 1465, 1373, 1242, 1030,819, 761, 688 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.22 (s, 3H); 3.98 (AB quartet, 2H); 4.29 (s, 2H); 6.42 (s, 1H); 7.15 - 7.22 (m, 3H); 7.33 – 7.41 (m, 6H); 7.85 (d, *J* = 7.9 Hz 4H); ^{13} C NMR (75 MHz, $CDCl_3$): δ 14.9, 33.5, 39.6, 58.1, 113.6, 122.9, 127.0, 127.4, 127.6, 128.5, 128.8, 129.2, 129.9, 130.2, 131.8, 132.7, 133.2, 135.6, 136.0, 137.0, 151.1, 152.3, 168.0, 169.2, 170.8; ms: *m/z* 594.1 (M^+), 596.1 (M + 2), 598.1 (M + 4). Anal. Calcd. for $C_{29}H_{21}Cl_2N_3OS_3$: C, 58.58; H, 3.56; N, 7.07. Found: C, 58.55; H, 3.60; N, 7.11.

3-(4-(2-(3,4-dichlorobenzyl)thiazol-4-yl)phenyl)-2-(4-methyl-2-phenylthiazol-5-yl)thiazolidin-4-one 8e. IR: 1687, 1597, 1535, 1494, 1377, 1321, 1242, 1182, 1053, 846, 760, 690 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.21(s, 3H);3.98 (AB quartet, 2H); 4.44 (s, 2H); 6.42 (s, 1H); 7.19–7.41 (m, 9H); 7.84 (m, 4H); ^{13} C NMR (75 MHz, $CDCl_3$): δ 15.0, 33.4, 39.5, 58.0, 113.5, 123.0, 127.4, 127.6, 128.0, 128.5, 128.8, 129.0, 129.3, 129.9, 130.2, 130.4, 133.1, 133.5, 135.8, 137.3, 151.2, 152.2, 168.2, 169.2, 171.1; ms: *m/z* 594.0 (M^+), 596.0 (M + 2), 598.0 (M + 4). Anal. Calcd. for $C_{29}H_{21}Cl_2N_3OS_3$: C, 58.58; H, 3.56; N, 7.07. Found: C, 58.54; H, 3.61; N, 7.10.

3-(4-(2-(4-methoxybenzyl)thiazol-4-yl)phenyl)-2-(4-methyl-2-phenylthiazol-5-yl)thiazolidin-4-one 8f. IR: 1692, 1601, 1536, 1489, 1477, 1326, 1241, 1055, 844, 761, 688 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.21 (s, 3H); 3.80 (s, 3H); 3.98 (AB quartet, 2H); 4.28 (s, 2H); 6.41 (s, 1H); 6.85–6.90(m, 2H); 7.18–7.29 (m, 5H); 7.38–7.43 (m, 3H); 7.83–7.87 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.0, 33.5, 39.6, 55.5, 58.1, 113.2, 114.6, 122.7, 127.3, 127.5, 128.2, 128.5, 128.9, 129.2, 129.5, 130.3, 133.5, 137.1, 158.2, 151.2, 152.0, 168.1, 169.2, 171.2; ms: *m/z* 555.0 (M^+), 557.0 (M + 2). *Anal*. Calcd. for $C_{30}H_{25}N_3O_2S_3$: C, 64.84; H, 4.53; N, 7.56. Found: C, 64.80; H, 4.49; N, 7.61.

2-(2-(4-chlorobenzyl)-4-methylthiazol-5-yl)-3-(4-(2-methylthiazol-4-yl)phenyl)thiazolidin-4-one 8g. **I**R: 1685, 1601, 1535, 1496, 1373, 1217, 1176, 1095, 1018, 977, 846, 752, 663 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.12 (s, 3H); 2.76 (s, 3H); 3.88 (AB quartet, 2H); 4.12 (s, 2H); 6.32 (s, 1H); 7.09–7.16 (m, 3H); 7.26–7.30 (m, 4H); 7.84 (d, *J* = 8.6 Hz 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.0, 19.3, 33.3, 39.1 58.2, 113.1, 126.7, 126.9, 127.2, 129.0, 130.3, 132.3, 134.1, 135.7, 136.1, 151.0, 153.8, 166.2, 169.8, 170.1; ms: *m/z* 497.6 (M^+), 499.6 (M + 2). *Anal*. Calcd. for $C_{24}H_{20}ClN_3OS_3$: C, 57.87; H, 4.05; N, 8.44. Found: C, 57.90; H, 4.01; N, 8.49.

2-(2-(4-chlorobenzyl)-4-methylthiazol-5-yl)-3-(4-(2-(4-chlorophenyl)thiazol-4-yl)phenyl)thiazolidin-4-one 8h. IR: 1693, 1599, 1529, 1481, 1352, 1240, 1095, 972, 840, 750 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.15 (s, 3H); 3.90 (AB quartet, 2H); 4.13 (s, 2H); 6.35 (s, 1H); 7.14–7.17 (m, 4H); 7.22–7.30 (m, 2H); 7.41–7.46 (m, 3H); 7.92–7.97 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.1, 33.4, 39.2, 58.2, 113.6, 126.7, 127.3, 127.8, 129.0, 129.2, 130.3, 132.0, 132.4, 133.2, 133.8, 135.7, 136.1, 136.5, 151.0, 155.1, 166.8, 169.8, 170.0; ms: *m/z* 594.0 (M^+), 596.1 (M + 2), 598.1 (M + 4). *Anal*. Calcd. for $C_{29}H_{21}Cl_2N_3OS_3$: C, 58.58; H, 3.56; N, 7.07. Found: C, 58.55; H, 3.51; N, 7.10.

2-(2-(4-chlorobenzyl)-4-methylthiazol-5-yl)-3-(4-(2-(4-methoxybenzyl)thiazol-4-yl)phenyl)thiazolidin-4-one 8i. IR: 1690, 1604, 1508, 1373, 1307, 1249, 1182, 1030, 844, 758, 646 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.15 (s, 3H); 3.90 (s, 3H); 3.96 (AB quartet, 2H); 4.15 (s, 2H); 4.32 (s, 2H); 6.34 (s, 1H); 6.91 (d, 2H); 7.17 (m, 4H); 7.21–7.31(m, 4H); 7.65 (s, 1H); 7.86 (d, 2H); ^{13} C NMR (75 MHz, $CDCl_3$): δ 14.9, 33.3, 38.8, 39.0, 55.2, 58.2, 113.8, 114.2, 120.2, 126.7, 127.0, 129.0, 129.7, 130.2, 130.3, 132.4, 133.2, 134.1, 135.6, 136.1, 150.9, 153.9, 158.8, 169.8, 171.9; ms: *m/z* 603.5 (M^+), 605.5 (M + 2). *Anal*. Calcd. for $C_{31}H_{26}ClN_3O_2S_3$: C, 61.62; H, 4.34; N, 6.95. Found: C, 61.59; H, 4.36; N, 6.99.

Antimicrobial activity. The MIC values of the synthesized compounds were determined in duplicate based on the micro dilution method in 96 multi-well microtiter plates as previously described [42]. The tested strains were obtained from the American type culture collection (ATCC). The following micro organisms were used in the present work: *E. coli* (ATCC 25922), *S. fecalis* (ATCC29212), *S. aureus* (ATCC 25923), *P. aeruginosa* (ATCC 27853) *B. subtilis* (ATCC6633) *C. albicans* (ATCC 10231), *A. Niger* (ATCC 9029). A total of 100 µL of Mueller Hilton broth or potato dextrose broth media was added into each well of the 96 well microtiter plates leaving the peripheral wells blank. The samples were dissolved in DMSO at 1.0 mg mL^{-1}. Approximately 100 µL test compound was added into the two wells B2 and C2 (for duplicate MIC readings) of a particular concentration and serially diluted (twofold dilutions) until B6 and C6 well. The final concentration of the test compounds adopted to evaluate antimicrobial activity was from 100 to 6.25 µg. A total of 100 µL of homogenized bacterial or fungal cell culture suspension (10^6 cells per well) was added to all the wells (wells with and without drug). Then, the plates were labeled and incubated at 37 °C for 48 h in an incubator.

Then, 50 μL of 0.02% resazurin solution was added and plates were observed after 24 and 48 h. Color change was assessed visually. Any color change from purple to pink or colorless was recorded as positive. The lowest concentration at which color change occurred was taken as MIC value. The MIC values reported are the average of two experiments (B and C).

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