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Microwave-assisted synthesis of bis(*N*-substituted thiazol-2-amine) derivatives and their biological activities

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Abstract: New 4,4′-(4,6-dimethoxy-1,3-phenylene)-bis-(*N*-substituted thiazol-2-amine) derivatives **5a–j** were synthesized from 1,1′-(4,6-dimethoxy-1,3-phenylene)-bis(2-bromoethanone) **3** and substituted thioureas **4a–j** under conventional and microwave irradiation conditions. All products were subjected to *in vitro* antibacterial and anti-TB evaluation. Some of the compounds exhibit good activities against *Bacillus subtilis* (+ve), *Escherichia coli* (–ve) strains and *Mycobacterium tuberculosis* H37Rv.

Keywords: anti-TB; antibacterial; microwave irradiation; thiazole.

Introduction

Thiazoles are an important class of heterocyclic compounds that are potent anticancer [1], antitumor [2], antimalarial [3], antimicrobial [4] and anti-inflammatory [5] agents. In particular, 2-aminothiazoles (Figure 1) exhibit a wide range of activities [6–17]. Many such compounds can be obtained using microwave assisted organic synthesis (MAOS) [15, 16]. In continuation of our previous efforts [18, 19], in this work, we synthesized novel bis(*N*-substituted thiazol-2-amine) derivatives **5a–j** by both conventional and microwave methods and investigated their *in vitro* antibacterial and anti-tuberculosis (TB) activities.

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Results and discussion

Synthesis

Compounds **5a–j** were prepared from 2,4-diacteylresorcinol (RDA) **1** which, in turn, was synthesized according to the literature procedure [20], as shown in Scheme 1. First, the starting material **1** was subjected to methylation with methyl iodide in *N*,*N*-dimethylformamide in the presence of potassium carbonate. Then, the resultant product **2** was brominated by the reaction with bromine in acetic acid. Product **3** was treated with various substituted thioureas **4a–j** in ethanol under microwave irradiation (MWI), which afforded the desired final compounds **5a–j** in high yields (method B). The yields were lower for the same reactions conducted using the conventional heating method (method A).

Solvent screening under conventional and MWI conditions indicated that the use of ethanol as a solvent resulted in the highest yields for both methods. Reactions conducted in other solvents including dimethyl sulfoxide, *N*,*N*-dimethylformamide and tetrahydrofuran furnished products in much lower yields. The optimization studies are presented in Table S1 of the online supplementary material.

Biological activity

The *in vitro* antimicrobial activities of compounds **5a–j** were investigated against four pathogenic microorganisms *Staphylococcus aureus* (MTCC 737), *Escherichia coli* (MTCC 443), *Bacillus subtilis* (MTCC 441) and *Pseudomonas aeruginosa* (MTCC 741) at the concentration of 100 μg/mL using streptomycin as a standard drug in the cup-plate agar diffusion method. As shown in Figure 2 and

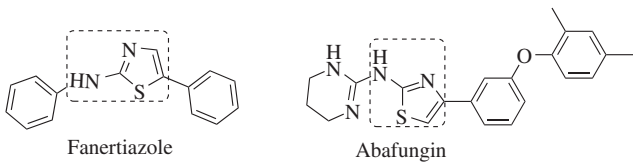


Figure 1 Examples of commercially available drugs containing a 2-aminothiazole moiety.

Table S2, compounds **5d**, **5f**, **5h** (inhibition zone >5 mm) show greater growth inhibition against *B. subtilis* then the reference drug streptomycin (5 mm). Activity of **5g** against Gram-negative bacteria *E. coli* equals the activity of the reference drug.

The investigation of *in vitro* anti-TB activity revealed that compounds **5d**, **5f** and **5h** are strongly antitubercular, and **5h** is much more active than the standard drug rifampicin (Figure 3). The results are also tabulated in Table S3.

Conclusions

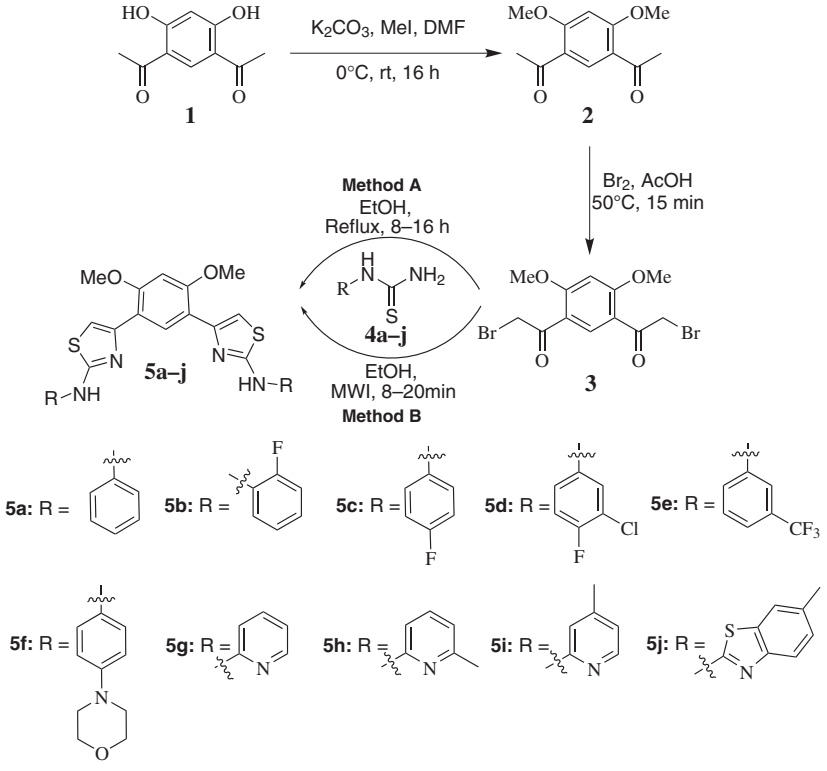
Symmetrical bis(*N*-substituted thiazol-2-amine) derivatives **5a–j** were synthesized. Some compounds show excellent *in vitro* anti-TB and antibacterial activity.

Experimental

Infra red (IR) spectra were recorded on a Shimadzu FTIR-8400S spectrometer. ^{1}H nuclear magnetic resonance (NMR) spectra (300 MHz) and ^{13}C NMR spectra (75 MHz) were acquired on a Bruker Avance 300 spectrometer in DMSO-d_6 using tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on a Shimadzu LCMS2020 spectrometer. Elemental analyses were performed on a Carlo Erba EA1106 elemental analyzer. Melting points were determined in open capillary tubes on a Stuart SMP3 melting point apparatus and are uncorrected. Microwave reactions were carried out in an Anton Paar Monowave 300 microwave (2.45 GHz) with a maximum delivered power of 850 W in 10 W increments (pulsed irradiation). A thin layer chromatography (TLC) analysis was performed on precoated Merck 60F_{254} silica gel plates with visualization by exposing to iodine vapor and under ultra violet (UV) light. Substituted thioureas **4a–j** were synthesized as previously described [21–23].

1,1′-(4,6-Dimethoxy-1,3-phenylene)diethanone (2)

A mixture of 1,1′-(4,6-dihydroxy-1,3-phenylene)diethanone (**1**, 1.0 g, 5.15 mmol) and potassium carbonate (3.5 g, 25.75 mmol) in *N*,*N*-dimethylformamide (20 mL) was stirred at 0°C, treated dropwise with methyl iodide (0.97 mL, 15.45 mmol) and then stirred at room temperature for 16 h. Ice water was added and the resulting solid was filtered, washed with diethyl ether and dried under reduced pressure [24]: white solid; yield 87%; mp 164–166°C (dec); ^{1}H NMR: δ 8.33 (s, 1H,



Scheme 1 Synthesis of compounds **5a–j**.

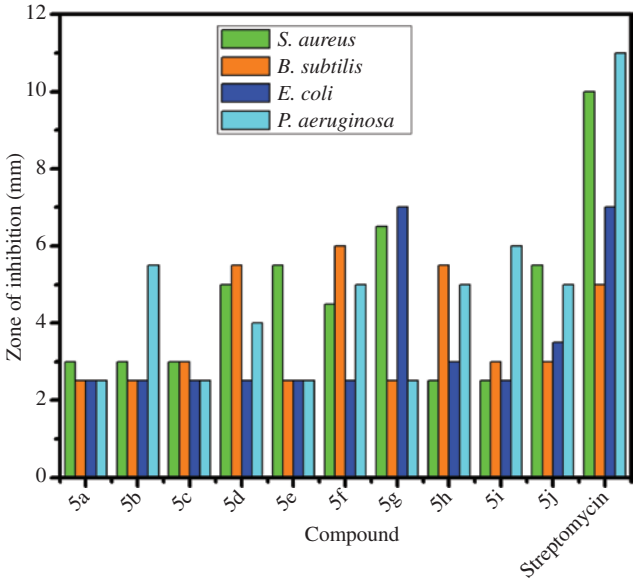


Figure 2 A graphical comparison of antibacterial activity of compounds **5a–j** and standard drug streptomycin against test microorganisms.

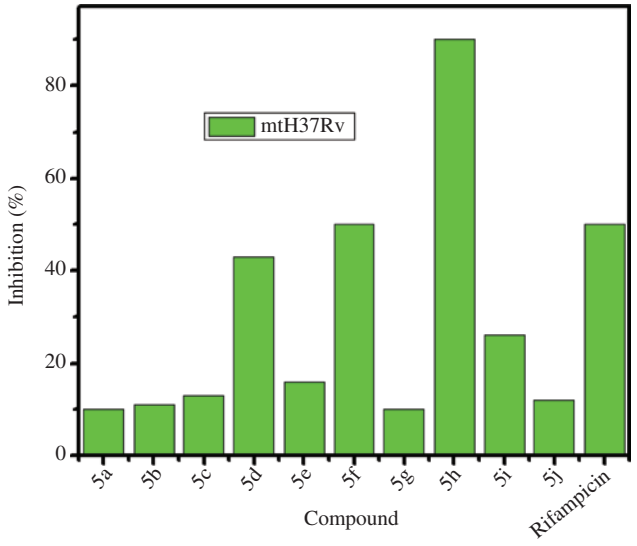


Figure 3 A graphical comparison of anti-TB activity of compounds **5a–j** and standard drug rifampicin.

Ar-H), 6.44 (s, 1H, Ar-H), 3.99 (s, 6H, OCH_3), 2.57 (s, 6H, CH_3); ^{13}C NMR: δ 195.7, 163.4, 132.8, 119.5, 96.2, 56.1, 31.2; MS: *m/z* 223, $[M+H]^+$ (100%).

1,1′-(4,6-Dimethoxy-1,3-phenylene)-bis(2-bromoethanone) (3)

A solution of **2** (1.0 g, 0.0045 mol) in acetic acid (10 mL) was heated to 50°C and treated with bromine (0.46 mL, 0.009 mol) in acetic acid (5 mL). The mixture was stirred at 50°C for 15 min, quenched with crushed ice and extracted with dichloromethane (2×10 mL). The combined organic layers were dried over anhydrous sodium sulfate, concentrated and the residue was subjected to silica gel (60–120 mesh) column chromatography eluting with 10%–20% EtOAc/hexane: white solid; yield 71%; mp 182–185°C (dec); IR: 3016 (Ar-CH), 2954 (C-H), 1672 (C=O), 1558 (C=C) cm^{-1}; ^1H NMR: δ 8.46 (s, 1H, Ar-H), 6.48 (s, 1H, Ar-H), 4.48 (s, 4H, CH_2), 4.05 (s, 6H, O-CH_3); ^{13}C NMR: δ 189.7, 163.9, 136.9, 118.2, 94.7, 56.3, 36.8; MS: *m/z* 381, $[M+H]^+$ (100%). Anal. Calcd for $C_{12}H_{12}Br_2O_4$: C, 37.93; H, 3.18. Found: C, 37.89; H, 3.16.

General procedure for the preparation of 4,4′-(4,6-dimethoxy-1,3-phenylene)-bis(*N*-substituted thiazol-2-amine)s 5a–j

Conventional heating method (A) To a stirred solution of **3** (0.38 g, 0.001 mol) in ethanol (10 mL), was added substituted thiourea **4a–j** (0.002 mol) in ethanol (10 mL) and the mixture was heated under refluxed for a period of time indicated below. After completion of the reaction, the mixture was concentrated under reduced pressure and the residue was subjected to column chromatography on basic alumina eluting with 30%–40% EtOAc/hexane.

Microwave irradiation method (B) A mixture of **3** (0.38 g, 0.001 mol), substituted thiourea **4a–j** (0.002 mol) and ethanol (10 mL) was placed in a microwave tube and subjected to microwave irradiation at 180 W for 8–20 min. Workup and purification were conducted as described above.

4,4′-(4,6-Dimethoxy-1,3-phenylene)-bis(*N*-phenylthiazol-2-amine) (5a) Reaction time 5 h, yield 85%, method A; reaction time 8 min, yield 91%, method B; white solid; mp 158–160°C (dec); IR: 3403 (N-H), 1604 (C=N), 1539 (C=C), 1367 (C-N), 750 (C-S) cm^{-1}; ^1H NMR: δ 10.17 (s, 2H, N-H), 8.89 (s, 1H, Ar-H), 7.72 (d, 4H, *J*=7.5 Hz, Ar-H), 7.26 (s, 2H, thiazole-H), 7.07 (t, 4H, *J*=7.5 Hz, Ar-H), 6.84 (s, 1H, Ar-H), 6.76 (t, 2H, *J*=7.5 Hz, Ar-H), 4.01 (s, 6H, O-CH_3); ^{13}C NMR: δ 161.3, 156.8, 146.1, 141.3, 130.5, 129, 120.7, 116.5, 115.4, 104.9, 96.2, 55.7; MS: *m/z* 487.2, $[M+H]^+$ (100%). Anal. Calcd for $C_{26}H_{22}N_4O_2S_2$: C, 64.17; H, 4.56; N, 11.51. Found: C, 64.11; H, 4.54; N, 11.49.

4,4′-(4,6-Dimethoxy-1,3-phenylene)-bis(*N*-(2-fluorophenyl)thiazol-2-amine) (5b) Reaction time 8 h, yield 81%, method A; reaction time 10 min, yield 92%, method B; white solid; mp 160–162°C (dec); IR: 3399 (N-H), 1616 (C=N), 1548 (C=C), 1360 (C-N), 737 (C-S) cm^{-1}; ^1H NMR: δ 9.98 (s, 2H, N-H), 8.85 (s, 1H, Ar-H), 8.58 (t, 2H, *J*=9.2 Hz, Ar-H), 7.29 (s, 2H, thiazole-H), 7.20 (t, 2H, *J*=9.2 Hz, Ar-H), 6.84 (s, 1H, Ar-H), 6.82–6.72 (m, 2H, Ar-H), 6.64 (t, 2H, *J*=9.2 Hz, Ar-H), 4.01 (s, 6H, O-CH_3); ^{13}C NMR: δ 161.3, 156.8, 151.3 (d, $^1J_{CF}$=242.6 Hz, CF), 145.8, 130.3, 129.2 (d, $^3J_{CF}$=10.4 Hz, Ar-C), 124.7 (d, $^4J_{CF}$=2.7 Hz, Ar-C), 121.4 (d, $^3J_{CF}$=7.1 Hz, Ar-C), 119.1, 115.4, 114.8 (d, $^3J_{CF}$=18.6 Hz, Ar-C), 106.1, 96.2, 55.7; MS: *m/z* 523.5, $[M+H]^+$ (100%). Anal. Calcd for $C_{26}H_{20}F_2N_4O_2S_2$: C, 59.76; H, 3.86; N, 10.72. Found: C, 59.71; H, 3.82; N, 10.69.

4,4′-(4,6-Dimethoxy-1,3-phenylene)-bis(*N*-(4-fluorophenyl)thiazol-2-amine) (5c) Reaction time 8 h, yield 80%, method A; reaction time 10 min, yield 91%, method B; white solid; mp 195–197°C (dec); IR: 3403 (N-H), 1611 (C=N), 1540 (C=C), 1368 (C-N), 766 (C-S) cm^{-1}; ^1H NMR: δ 10.20 (s, 2H, N-H), 8.92 (s, 1H, Ar-H), 7.74 (dd, 4H, *J*=4.7, 8.6 Hz, Ar-H), 7.26 (s, 2H, thiazole-H), 6.83 (s, 1H, Ar-H), 6.80 (d, 4H, *J*=8.6 Hz, Ar-H), 4.01 (s, 6H, O-CH_3); ^{13}C NMR: δ 161.3, 158, 156.8, 156.4

(d, $^{1}J_{CF}$ = 237.1Hz, CF), 146, 130.5, 117.8 (d, $^{3}J_{CF}$ = 7.6 Hz, Ar-C), 115.5, 115.3 (d, $^{3}J_{CF}$ = 7.6 Hz, Ar-C), 104.8, 96.1, 55.7; MS: *m/z* 523.2, $[M+H]^+$ (100%). Anal. Calcd for $C_{26}H_{20}F_2N_4O_2S_2$: C, 59.76; H, 3.86; N, 10.72. Found: C, 59.73; H, 3.84; N, 10.67.

4,4′-(4,6-Dimethoxy-1,3-phenylene)-bis(*N*-(3-chloro-4-fluorophenyl)thiazol-2-amine) (5d) Reaction time 10 h, yield 79%, method A; reaction time 12 min, yield 88%, method B; white solid; mp 165–168°C (dec); IR: 3441 (N-H), 1606 (C=N), 1540 (C=C), 1393 (C-N), 739 (C-S) cm^{-1}; ^{1}H NMR: δ 10.36 (s, 2H, N-H), 8.95 (s, 1H, Ar-H), 8.05 (d, 2H, *J* = 6.2 Hz, Ar-H), 7.59 (d, 2H, *J* = 8.8 Hz, Ar-H), 7.29 (s, 2H, thiazole-H), 6.94 (t, 2H, *J* = 8.8 Hz, Ar-H), 6.85 (s, 1H, Ar-H), 4.02 (s, 6H, O-CH_3); ^{13}C NMR: δ 160.7, 156.9, 151.3 (d, $^{1}J_{CF}$ = 239.8 Hz, CF), 146.1, 138.5, 130.7, 119.3 (d, $^{3}J_{C}$ = 18.1 Hz, Ar-C), 117.5, 116.6, 116.4 (d, $^{4}J_{CF}$ = 4.9 Hz, Ar-C), 115.3, 105.2, 96.2, 55.8; MS: *m/z* 591.1, $[M]^+$. Anal. Calcd for $C_{26}H_{18}C_{12}F_2N_4O_2S_2$: C, 52.80; H, 3.07; N, 9.47. Found: C, 52.76; H, 3.03; N, 9.45.

4,4′-(4,6-Dimethoxy-1,3-phenylene)-bis(*N*-(3-(trifluoromethyl)phenyl)thiazol-2-amine) (5e) Reaction time 12 h, yield 78%, method A; reaction time 15 min, yield 90%, method B; white solid; mp 230–233°C (dec); IR: 3401 (N-H), 1606 (C=N), 1540 (C=C), 1393 (C-N), 739 (C-S) cm^{-1}; ^{1}H NMR: δ 10.50 (s, 2H, N-H), 8.86 (s, 1H, Ar-H), 8.12 (s, 2H, Ar-H), 7.95 (d, 2H, *J* = 6.9 Hz, Ar-H), 7.28 (s, 2H, thiazole-H), 7.16 (t, 2H, *J* = 6.9 Hz, Ar-H), 7.02 (d, 2H, *J* = 6.9 Hz, Ar-H), 6.86 (s, 1H, Ar-H), 4.02 (s, 6H, O-CH_3); ^{13}C NMR: δ 160.6, 157, 146.3, 141.8, 130.7, 129.7, 129.5 (q, $^{2}J_{CF}$ = 31.5 Hz, Ar-C), 124 (q, $^{1}J_{CF}$ = 272.1 Hz, C-F), 119.8, 116.6 (q, $^{4}J_{CF}$ = 4.4 Hz, Ar-C), 115.5, 112.5 (q, $^{4}J_{CF}$ = 4.4 Hz, Ar-C), 105.4, 96.3, 55.8; MS: *m/z* 623.2, $[M+H]^+$ (100%). Anal. Calcd for $C_{28}H_{20}F_6N_4O_2S_2$: C, 54.01; H, 3.24; N, 9.00. Found: C, 53.96; H, 3.22; N, 8.96.

4,4′-(4,6-Dimethoxy-1,3-phenylene)-bis(*N*-(4-morpholinophenyl)thiazol-2-amine) (5f) Reaction time 10 h, yield 75%, method A; reaction time 15 min, yield 88%, method B; white solid; mp 265–267°C; IR: 3461 (N-H), 1602 (C=N), 1547 (C=C), 1369 (C-N), 746 (C-S) cm^{-1}; ^{1}H NMR: δ 9.92 (s, 2H, N-H), 8.91 (s, 1H, Ar-H), 7.64 (d, 4H, *J* = 8.3 Hz, Ar-H), 7.17 (s, 2H, thiazole-H), 6.81 (s, 1H, Ar-H), 6.69 (d, 4H, *J* = 8.3 Hz, Ar-H), 4.00 (s, 6H, O-CH_3), 3.70–3.56 (m, 8H, morpholine-H), 2.86–2.73 (m, 8H, morpholine-H); ^{13}C NMR: δ 161.5, 156.7, 146, 134.2, 130.6, 124.8, 117.5, 116.2, 115.5, 104.1, 96, 66, 55.7, 49; MS: *m/z* 657.3, $[M+H]^+$ (100%). Anal. Calcd for $C_{34}H_{36}N_6O_4S_2$: C, 62.17; H, 5.52; N, 12.80. Found: C, 62.12; H, 5.50; N, 12.78.

4,4′-(4,6-Dimethoxy-1,3-phenylene)-bis(*N*-(pyridin-2-yl)thiazol-2-amine) (5g) Reaction time 6 h, yield 72%, method A; reaction time 10 min, yield 86%, method B; yellow solid; yield 72%; IR: 3465 (N-H), 1599 (C=N), 1542 (C=C), 1372 (C-N), 771 (C-S) cm^{-1}; ^{1}H NMR: δ 11.43 (s, 2H, N-H), 8.64 (s, 1H, Ar-H), 8.34–8.31 (m, 2H, pyridine-H), 7.71 (t, 2H, *J* = 6.7 Hz, Ar-H), 7.35 (s, 2H, thiazole-H), 7.07 (d, 2H, *J* = 6.7 Hz, Ar-H), 6.92 (t, 2H, *J* = 6.7 Hz, Ar-H), 6.85 (s, 1H, Ar-H), 4.05 (s, 6H, O-CH_3); ^{13}C NMR: δ 162.4, 159.3, 157.5, 149.7, 145.3, 137.8, 128.9, 117.4, 116.6, 108.7, 107.7, 95.7, 55.9; MS: *m/z* 489.2, $[M+H]^+$ (100%). Anal. Calcd for $C_{24}H_{20}N_6O_2S_2$: C, 59.00; H, 4.13; N, 17.20. Found: C, 58.96; H, 4.10; N, 17.17.

4,4′-(4,6-Dimethoxy-1,3-phenylene)-bis(*N*-(6-methylpyridin-2-yl)thiazol-2-amine) (5h) Reaction time 12 h, yield 77%, method A; reaction time 15 min, yield 89%, method B; brown solid; mp 270–273°C (dec); IR: 3461 (N-H), 1623 (C=N), 1565 (C=C), 1369 (C-N), 783 (C-S) cm^{-1}; ^{1}H NMR: δ 11.27 (s, 2H, N-H), 8.88 (s, 1H, Ar-H), 7.58 (d, 2H, *J* = 7.5 Hz, pyridine-H), 7.32 (s, 2H, thiazole-H), 6.90 (d, 2H, *J* = 7.5 Hz, pyridine-H), 6.82 (s, 1H, Ar-H), 6.77 (d, 2H, *J* = 7.5 Hz, pyridine-H), 4.00 (s, 6H, O-CH_3), 2.47 (s, 6H, CH_3); ^{13}C NMR: δ 157.6, 156.8, 155.1, 151.3, 144.5, 138.1, 130.1, 115.7, 114.6, 107.8, 107.4, 96.1, 55.7, 23.5; MS: *m/z* 517.2, $[M+H]^+$ (100%). Anal. Calcd for $C_{26}H_{24}N_6O_2S_2$: C, 60.44; H, 4.68; N, 16.27. Found: C, 60.40; H, 4.65; N, 16.24.

4,4′-(4,6-Dimethoxy-1,3-phenylene)-bis(*N*-(4-methylpyridin-2-yl)thiazol-2-amine) (5i) Reaction time 12 h, yield 73%, method A; reaction time 15 min, yield 89%, method B; brown solid; mp 272–275°C (dec); IR: 3460 (N-H), 1615 (C=N), 1539 (C=C), 1372 (C-N) cm^{-1}; ^{1}H NMR: δ 11.71 (s, 2H, N-H), 8.69 (s, 1H, Ar-H), 8.30–8.13 (m, 2H, pyridine-H), 7.40 (s, 2H, thiazole-H), 7.03 (s, 2H, pyridine-H), 6.95–6.81 (m, 3H, Ar-H, pyridine-H), 4.03 (s, 6H, O-CH_3), 2.34 (s, 6H, CH_3); ^{13}C NMR: δ 158.5, 157.2, 151, 150.2, 144.7, 143.6, 130.1, 118, 114.5, 111.3, 108.1, 96.3, 55.9, 20.9; MS: *m/z* 517.2, $[M+H]^+$ (100%). Anal. Calcd for $C_{26}H_{24}N_6O_2S_2$: C, 60.44; H, 4.68; N, 16.27. Found: C, 60.39; H, 4.64; N, 16.25.

***N,N′*-(4,4′-(4,6-Dimethoxy-1,3-phenylene)-bis(thiazole-4,2-diyl))-bis(6-methylbenzo[*d*] thiazol-2-amine) (5j)** Reaction time 16 h, yield 74%, method A; reaction time 20 min, yield 90%, method B; green solid; mp 180–182°C (dec); IR: 3460 (N-H), 1598 (C=N), 1541 (C=C), 1381 (C-N), 750 (C-S) cm^{-1}; ^{1}H NMR: δ 12.49 (s, 2H, N-H), 8.71 (s, 1H, Ar-H), 7.67 (s, 2H, Ar-H), 7.54–7.47 (m, 2H, Ar-H), 7.39 (s, 2H, thiazole-H), 7.22 (d, 2H, *J* = 8.1 Hz, Ar-H), 6.88 (s, 1H, Ar-H), 4.04 (s, 6H, O-CH_3), 2.40 (s, 6H, CH_3); ^{13}C NMR: δ 185.8, 162.6, 160, 157.1, 145.7, 132.2, 131.5, 130.4, 128.2, 127, 121.1, 113.1, 108.7, 96.2, 55.8, 20.7; MS: *m/z* 629.2, $[M+H]^+$ (100%). Anal. Calcd for $C_{30}H_{24}N_6O_2S_4$: C, 57.30; H, 3.85; N, 13.36. Found: C, 57.27; H, 3.82; N, 13.33.

Antibacterial activity assay

Gram-negative strains (*P. aeruginosa* and *E. coli*) and Gram-positive strains (*B. subtilis* and *S. aureus*) were obtained from Microbial Type Culture Collection MTCC. The biological activities of the compounds were assayed using the standard disc diffusion method [25] for 100 μg/mL solutions in DMSO. Inhibition zones were measured and compared with the standard positive control (streptomycin) at 100 μg/mL.

Antimycobacterial activity assay

Mycobacterium tuberculosis H37Rv (ATCC 27294) and Middlebrook 7H9 medium were used. The activity was assayed by the turbidometry method [26] using rifampicin as standard.

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Online-only supplementary material: Optimization of synthesis and biological activity (three Tables).

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