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Microwave Assisted Synthesis and Biological Activity of Novel Bis{2-[2-(substituted benzylidene)hydrazinyl]thiazole} Derivatives[1]

N. H. Kumar Baba[a], D. Ashok[b]*, Boddu Ananda Rao[b], Madderla Sarasija[c], and N. Y. S. Murthy[d]

[a] *Department of Chemistry, Jawaharlal Nehru Technological University, Hyderabad, Telangana, 500085 India*

[b] *Green and Medicinal Chemistry Laboratory, Department of Chemistry, Osmania University, Hyderabad, Telangana, 500007 India*
**e-mail: ashokdou@gmail.com*

[c] *Department of Chemistry, Satavahana University, Karimnagar, Telangana, 505001 India*

[d] *Department of Chemistry, Anurag Group of Institutions, Hyderabad, Telangana, 501301 India*

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Abstract—New 4,4'-(4,6-dimethoxy-1,3-phenylene)bis{2-[2-(substituted benzylidene)hydrazinyl]thiazole} derivatives (**5a–5j**) have been synthesized from the corresponding 1,1'-(4,6-dimethoxy-1,3-phenylene)bis(2,2-dibromoethanone) and substituted thiosemicarbazones by the conventional method and under microwave irradiation. Structures of the synthesized compounds were characterized by FT-IR, ^{1}H, and ^{13}C NMR and Mass spectra. The products were evaluated for their *in vitro* antibacterial activity against Gram-positive and Gram-negative stains. Some of the compounds **5b, 5f, 5h** demonstrated high activity against *B. subtilis* (+ve), compound **5c** exhibited high activity against *E. coli* (–ve) and *P. aeruginosa* (–ve) stains. Among the titled compounds also evaluated for their *in vitro* antimycobacterial activity, the product **5b** demonstrated pronounced antimycobacterial activity against *M. bovis* stain.

Keywords: thiazole, microwave irradiation, anti-bacterial, antimycobacterial
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INTRODUCTION

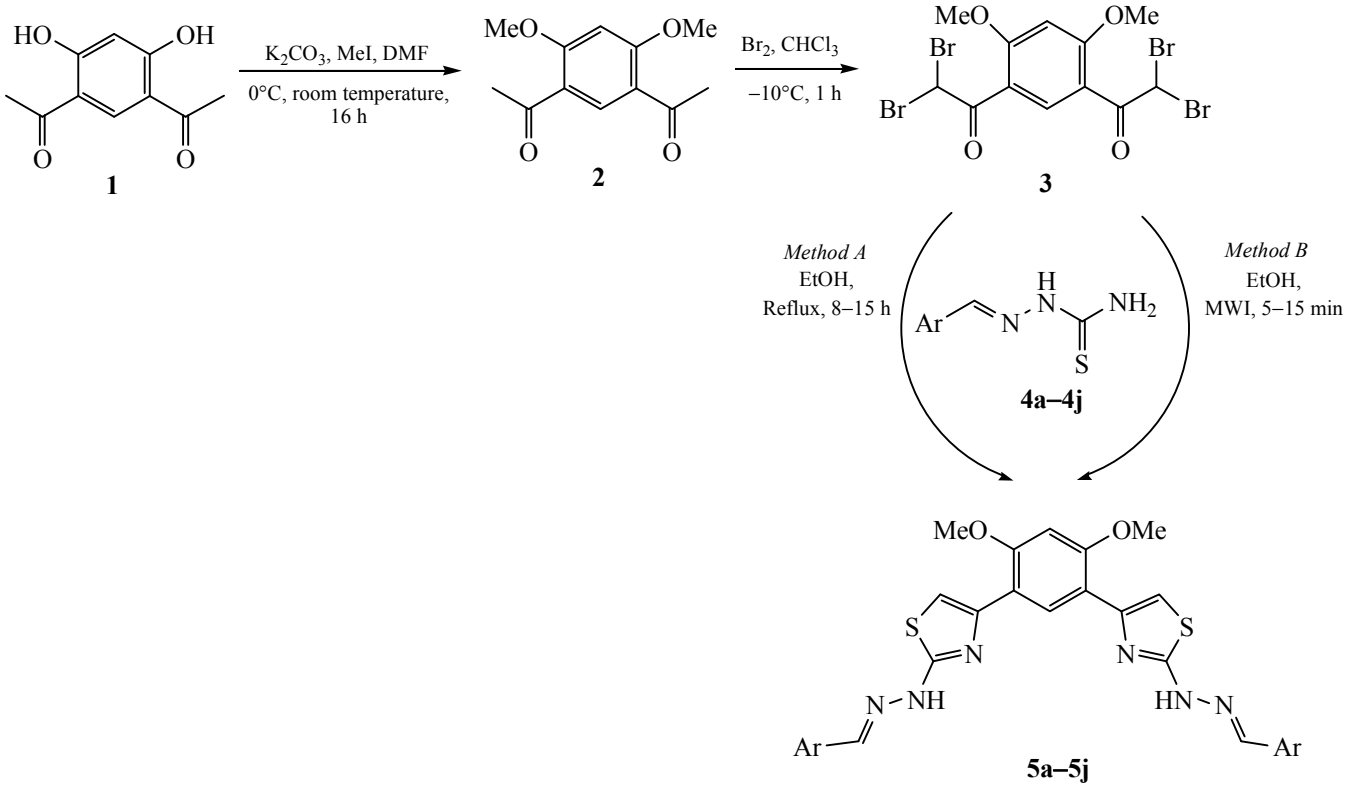
Synthesis of thiazole analogues is the hot topic due to their broad range of biological and pharmaceutical properties, such as antibacterial [1-3], hypertension [4], anti-HIV [5], antiviral [6, 7], anti-inflammatory [8], and anticancer [9, 10]. Thiosemicarbazones are of considerable importance in medicinal chemistry [11, 12], and synthesis of sulfur and nitrogen containing heterocyclic compounds such as thiazoles [13–16]. Bis-heterocyclic compounds have demonstrated higher biological activity than their monoheterocyclic analogues [17, 18]. The above information encouraged us to synthesize a symmetrical molecular system of bis {2-[2-(substituted benzylidene)hydrazinyl]thiazole} derivatives **5a–5j** starting with 2,4-diaceteylresorcinol (RDA) (Scheme 1). Such synthesis of new heterocyclic compounds from RDA became the development of our earlier studies [19–21]. Here we present two approaches to the target compounds: conventional and microwave assisted synthesis. The synthesized compounds were tested for their in vitro antibacterial and antimycobacterial activity.

RESULTS AND DISCUSSION

The synthetic pathway to the target compounds **5a–5j** (Scheme 1) started with accumulation of 2,4-diacteylresorcinol (RDA) (**1**) according to the developed earlier procedure [22]. Upon methylation by MeI the compound **1** in the presence of K_2CO_3 at room temperature gave the corresponding product **2** which was subjected to bromination in $CHCl_3$ at –10°C. Thus obtained 1,1'-(4,6-dimethoxy-1,3-phenylene)bis(2,2-dibromoethanone) (**3**) was treated with various thiosemicarbazones derivatives **4a–4j** in ethanol under microwave irradiation to accumulate 4,4'-(4,6-dimethoxy-1,3-phenylene)bis{2-[2-(substituted benzylidene)hydrazinyl]thiazole} derivatives **5a–5j**, accordingly. The alternative conventional method led to relatively low

[1] The text was submitted by the authors in English.

Scheme 1. Synthesis of 4,4'-(4,6-dimethoxy-1,3-phenylene)bis{2-[2-(substituted benzylidene)hydrazinyl]thiazole} derivatives **5a–5j**.



Ar = phenyl (**5a**), 2-hydroxyphenyl (**5b**), 3-hydroxyphenyl (**5c**), 4-methoxyphenyl (**5d**), 2-bromophenyl (**5e**), 3-bromophenyl (**5f**), 2-chlorophenyl (**5g**), 4-chlorophenyl (**5h**), 2-nitrophenyl (**5i**), 3-nitrophenyl (**5j**).

yields (65–80%) upon lengthy procedure. The following optimization of the process was evaluated for the compound **5a** (Table 1). The optimized conditions allowed to synthesize the derivatives **5a–5j** in 80–92% yields within 5–15 min (Table 2). Chemical structures of the newly synthesized compounds **3** and **5a–5j** were elucidated from FT-IR, ^{1}H, and ^{13}C NMR, and Mass spectra. The FTIR spectrum of compound **5a** revealed three bands for the NH, C=N and C=C bonds at 3462, 1618, and 1495 cm^{-1}, respectively. The ^{1}H NMR spectrum of compound **5a** demonstrated characteristic signals of the thiazole ring proton at 7.26 ppm, CH=N proton at 8.09 ppm, and the signal at 4.02 ppm was assigned to the methoxy protons. Signals of carbon atoms of same groups were recorded at 106.07, 143.49 and 56 ppm in ^{13}C spectra, respectively. The mass spectrum of compound **5a** exhibited the peak at 541.4, which corresponded to the $[M + H]^+$ ion.

Biological activity. *Antibacterial activity.* The in vitro antimicrobial activity of all synthesized compounds **5a–5j** (Table 3) was studied against Gram-negative bacterial strains of *Escherichia coli* and *Pseudomonas aeruginosa*, and Gram-positive bacterial strains of *Bacillus subtilis* and *Staphylococcus aureus* at concentrations of 50 and 100 μg/mL using agar well diffusion method according to the literature protocol [23].

Compounds **5b**, **5f**, **5h** demonstrated activity against *Bacillus subtilis* higher than the standard drug

Table 1. Variety of conditions tested in the synthesis of compound **5a**

Solvent	Conventional method		MWI method	
	time, h	yield, %[a]	time, min	yield, %[a]
DMSO	16	65	20	82
DMF	18	63	30	78
THF	24	45	40	55
Ethanol	8	80	10	92
1,4-Dioxane	24	55	50	65

[a] Isolated yield.

Table 2. Yields of the synthesized compounds **5a–5j** under optimized conditions

Compound	mp, °C	Conventional method		MWI method	
		time, h	yield, %[a]	time, min	yield, %[a]
5a	248–250	8	80	5	92
5b	186–188	12	70	15	86
5c	193–195	12	69	15	85
5d	260–262	12	72	10	90
5e	180–182	12	76	10	88
5f	184–186	12	75	10	86
5g	220–222	10	71	10	82
5h	255–257	10	73	10	84
5i	250–252	15	65	15	80
5j	244–246	15	68	15	82

[a] Isolated yield.

Norfloxacin at both concentrations. In case of Gram-negative bacterial strains, **5c** was more active against *Escherichia coli* and *Pseudomonas aeruginosa* strains than Ofloxacin at both concentrations.

Antimycobacterial activity. The in vitro antimycobacterial activity of the synthesized compounds **5a–5j** (Table 4) was studied against *Mycobacterium bovis* stain. Only compound **5b** demonstrated higher activity against *M. bovis* stain than the standard Isoniazid + Rifampicin.

EXPERIMENTAL

All reagents and solvents were purchased from commercial sources. IR spectra were recorded on a Shimadzu FTIR-8400S spectrophotometer. ^{1}H and ^{13}C NMR spectra were measured on a Bruker Avance 300 spectrometer using DMSO-d_6 and $CDCl_3$ solvents and TMS as internal standard. Mass spectra were measured 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. All reactions were carried out under the atmosphere of Ar. Microwave assisted reactions were carried out in an Anton Paar Monowave 300 microwave (850 W, 2.45 GHz) with a maximum delivered power of 850 W in 10 W increments (pulsed irradiation). Analytical TLC was performed on pre-

Table 3. Antibacterial activity of the synthesized compounds **5a–5j**

Compound	Zone of inhibition after 24 h, mm							
	gram-positive bacteria				gram-negative bacteria			
	Staphylococcus aureus		*Bacillus subtilis*		*Escherichia coli*		*Pseudomonas aeruginosa*	
	concentration, μg/mL							
	50	100	50	100	50	100	50	100
5a	3.0	6.0	2.0	3.0	2.5	4.0	2.5	4.0
5b	3.0	4.0	4.5	6.5	5.0	6.0	4.0	8.0
5c	2.0	3.0	3.0	5.0	7.0	9.0	5.5	9.0
5d	2.5	4.0	2.0	3.0	2.5	4.0	3.0	4.0
5e	2.0	3.0	3.0	4.5	3.0	4.0	3.0	5.0
5f	3.0	5.0	5.0	6.0	3.0	4.0	2.5	4.0
5g	3.0	5.0	2.0	3.0	2.5	4.0	3.0	4.0
5h	2.5	4.0	4.5	6.0	2.5	3.0	2.5	4.0
5i	2.0	3.0	2.5	4.0	4.0	5.0	2.5	5.0
5j	2.0	3.0	2.0	3.0	4.0	5.0	3.5	5.0
Norfloxacin	5.0	8.0	4.0	6.0	–	–	–	–
Ofloxacin	–	–	–	–	7.0	8.0	5.0	9.0

coated Merck $^{60}F_{254}$ silica gel plates, and visualized by exposing to iodine vapour and under UV light.

Synthesis of 1,1'-(4,6-dimethoxy-1,3-phenylene)-diethanone (2) [24]. To a stirred solution of 1,1'-(4,6-dihydroxy-1,3-phenylene)diethanone (**1**) (1.0 g, 5.15 mmol) in *N,N*-dimethylformamide (20 mL) was added potassium carbonate (3.5 g, 25.75 mmol). The mixture was cooled down to 0°C and MeI (0.97 mL, 15.45 mmol) was added dropwise. The reaction mixture was stirred slowly at room temperature for 16 h. Ice water was added to the reaction mixture and the resulting solid was filtered off, washed with diethyl ether and dried under vacuum to affords 1,1'-(4,6-dimethoxy-1,3-phenylene)diethanone (**2**) [24] as white solid. Yield 87%, mp 164–166°C.

Synthesis of 1,1'-(4,6-dimethoxy-1,3-phenylene) bis(2,2-dibromoethanone) (3). To a stirred solution of 1,1'-(4,6-dimethoxy-1,3-phenylene)diethanone (**2**) (1.0 g, 0.0045 moles) in $CHCl_3$ (10 mL) was added Br_2 (0.92 mL, 0.018 mol) in $CHCl_3$ solution (5 mL) at –10°C, and the following stirring was continued for 1 h. The reaction mixture was quenched with crushed ice and extracted with CH_2Cl_2 (2×20 mL). The combined organic layers were dried over anhydrous sodium sulfate, concentrated and purified by silica gel (60–120 mesh) column chromatography (gradient elution with 10 to 15% EtOAc/Hexane) to afford compound **3** as off-white solid. Yield 90%, mp 160–165°C. IR spectrum, ν, cm^{-1}: 3016 (Ar-CH), 2954 (C–H), 1672 (C=O), 1558 (C=C). ^{1}H NMR spectrum, δ, ppm: 4.06 s (6H, $2OCH_3$), 6.89 s (1H, Ar-H), 7.38 s (2H, Ar-H), 8.20 s (1H, Ar-H). ^{13}C NMR spectrum, δ_C, ppm: 56.9, 68.9, 96.6, 117.2, 133.9, 164.2, 189.5. Found, %: C 26.74; H 1.83. $C_{12}H_{10}Br_4O_4$. Calculated, %: C 26.80; H 1.87. *M* 539.0 $[M + H]^+$.

General procedure for synthesis of compounds 4a–4j [25–27]. The appropriate thiosemicarbazide (1.0 g, 10.97 mmol) and aldehyde (12.07 mmol) were dissolved in ethanol (10 mL) and acetic acid (0.2 mmol) was added to the solution. The reaction mixture was refluxed for 5–6 h and then cooled down to room temperature. The resulting precipitate was filtered off, washed with ether and recrystallized from ethanol to obtain the corresponding thiosemicarbazones.

General procedure for the synthesis of compounds 5a–5j. *Conventional heating method A.* To a stirred solution of 1,1'-(4,6-dimethoxy-1,3-phenylene)-bis(2,2-dibromoethanone) **3** (0.150 g, 0.279 mmol) in ethanol (5 mL), was added a substituted thiosemicarbazone **4a–4j** (0.782 mmol) in ethanol (5 mL). The reaction mixture was refluxed for 8–15 h. Upon completion of the reaction, the mixture was concentrated under *rota vacuo* and the crude product was purified by column chromatography using basic alumina (gradient elution with 30 to 40% EtOAc/Hexane) to yield the desired solid compounds **5a–5j** respectively.

Table 4. Antimycobacterial activity of the compounds **5a–5j**

Compound	Zone of inhibition, mm
	Mycobacterium bovis
5a	14.068
5b	41.120
5c	26.897
5d	19.459
5e	21.821
5f	34.496
5g	21.455
5h	30.848
5i	9.830
5j	5.597
Isoniazid + Rifampicin	40.000

Microwave irradiation method B. A microwave tube was filled with the mixture of 1,1'-(4,6-dimethoxy-1,3-phenylene)bis(2,2-dibromoethanone) **3** (0.150 g, 0.279 mmol), a substituted thiosemicarbazone **4a–4j** (0.782 mmol) and ethanol (10 mL), and subjected to MWI (Monowave-300 reactor) at 100 W for 5–15 min. Upon completion of the reaction, the mixture was concentrated under *rota vacuo* and the crude product was purified by column chromatography using basic alumina (gradient elution with 30 to 40% EtOAc/Hexane) to yield the desired solid compounds **5a–5j**, respectively.

4,4'-(4,6-Dimethoxy-1,3-phenylene)bis[2-(2-benzyl-idenehydrazinyl)thiazole] (5a). White solid. IR spectrum, ν, cm^{-1}: 3462 (NH), 1618 (HC=N, azomethine), 1495 (C=N, thiazole), 1367 (C–N), 754 (C–S). ^{1}H NMR spectrum, δ, ppm: 4.0 s (6H, $2OCH_3$), 6.83 s (1H, Ar-H), 7.26 s (2H, thiazole-H), 7.35–7.50 m (6H, Ar-H),7.68 d (4H, Ar-H, J = 6.9 Hz), 8.09 s (2H, NH=CH), 8.64 s (1H, Ar-H). ^{13}C NMR spectrum, δ_C, ppm: 56.0, 96.3, 106.1, 113.8, 126.6, 126.8, 128.9,

129.7, 130.1, 134.0, 143.5, 157.5, 166.8. Found, %: C 62.16; H 4.43; N 15.57. $C_{28}H_{24}N_6O_2S_2$. Calculated, %: C 62.20; H 4.47; N 15.54. *M* 541.4 $[M + H]^+$ (100%).

2,2'-{2,2'-[4,4'-(4,6-Dimethoxy-1,3-phenylene)bis-(thiazole-5,2-diyl)]bis(hydrazin-2-yl-1-ylidene)}bis-(methan-1-yl-1-ylidene)diphenol (5b). Off-white solid. IR spectrum, ν, cm^{-1}: 3400 (NH), 1611 (HC=N, azomethine), 1561 (C=N, thiazole), 1366 (C–N), 749 (C–S). ^{1}H NMR spectrum, δ, ppm: 3.99 s (6H, 2OMe), 6.81 s (1H, Ar-H), 6.89 t (4H, Ar-H, *J* = 7.9 Hz), 7.21 d (2H, Ar-H, *J* = 7.9 Hz), 7.24 s (2H, thiazole-H), 7.63 d (2H, Ar-H *J* = 7.9 Hz), 8.33 s (2H, NH=CH), 8.72 s (1H, Ar-H), 10.14 s (2H, OH), 12.05 s (2H, NH). ^{13}C NMR spectrum, δ_C, ppm: 55.7, 96.1, 105.3, 115.4, 116.1, 119.5, 120.1, 126.6, 130.0, 130.4, 139.6, 146.5, 155.9, 156.9, 166.2. Found, %: C 58.70; H 4.19; N14.70. $C_{28}H_{24}N_6O_4S_2$. Calculated, %: C 58.73; H 4.22; N 14.68. *M* 573.2 $[M + H]^+$.

3,3'-{2,2'-[4,4'-(4,6-Dimethoxy-1,3-phenylene)bis-(thiazole-5,2-diyl)]bis(hydrazin-2-yl-1-ylidene)}bis-(methan-1-yl-1-ylidene)diphenol (5c). Off white solid. IR spectrum, ν, cm^{-1}: 3462 (NH), 1568 (HC=N, azomethine), 1499 (C=N, thiazole), 1367 (C–N), 745 (C–S). ^{1}H NMR spectrum, δ, ppm: 4.00 s (6H,2OMe), 6.77 d (2H, Ar-H, *J* = 7.7 Hz), 6.81 s (1H, Ar-H), 7.04 d (2H, Ar-H, *J* = 7.7 Hz), 7.12 s (2H, Ar-H), 7.17–7.28 m (4H, Ar-H, thiazole-H), 7.95 s (2H,NH=CH), 8.75 s (1H, Ar-H), 9.58 s (2H, OH), 12.01 s (2H, NH). ^{13}C NMR spectrum, δ_C, ppm: 55.7, 96.1, 105.6, 111.8, 115.6, 116.5, 117.9, 129.8, 129.9, 135.7, 141.0, 146.5, 156.8, 157.6, 166.4. Found %: C 58.69; H 4.18; N 14.71. $C_{28}H_{24}N_6O_4S_2$. Calculated, %: C58.73; H 4.22; N14.68. *M* 573.2 $[M + H]^+$.

4,4'-(4,6-Dimethoxy-1,3-phenylene)bis{2-{2-(4-methoxybenzylidene)hydrazinyl]thiazole} (5d). Off-white solid. IR spectrum, ν, cm^{-1}: 3463 (NH), 1571 (HC=N, azomethine), 1505 (C=N, thiazole), 1367 (C–N), 742 (C–S). ^{1}H NMR spectrum, δ, ppm: 3.79 s (6H, $2OCH_3$), 3.99 s (6H, OMe), 6.80 s (1H, Ar-H), 7.00 d (4H, Ar-H, *J* = 8.6 Hz), 7.22 s (2H, thiazole-H), 7.60 d (4H, Ar-H, *J* = 8.6 Hz), 8.00 s (2H, NH=CH), 8.75 s (1H, Ar-H), 11.89 s (2H, NH). ^{13}C NMR spectrum, δ_C, ppm: 55.2, 55.7, 96.1, 105.3, 114.3, 115.5, 127.7, 130.0, 131.3, 141.0, 146.5, 156.8, 160.1, 166.6. Found %: C 59.95; H 4.68; N 14.01. $C_{30}H_{28}N_6O_4S_2$. Calculated, %: C 59.98; H 4.70; N 13.99. *M* 601.3 $[M + H]^+$.

4,4'-(4,6-Dimethoxy-1,3-phenylene)bis{2-[2-(2-bromobenzylidene)hydrazinyl]thiazole} (5e). Brown solid. IR spectrum, ν, cm^{-1}: 3464 (NH), 1602 (HC=N, azomethine), 1558(C=N, thiazole), 1366 (C–N), 749 (C–S). ^{1}H NMR spectrum, δ, ppm: 4.00 s (6H, 2OMe), 6.82 s (1H, Ar-H), 7.28 s (2H, thiazole-H), 7.32 d (2H, Ar-H, *J* = 7.7 Hz), 7.46 t (2H, Ar-H, *J* = 7.7 Hz), 7.67 d (2H, Ar-H, *J* = 7.7 Hz), 7.92 d (2H, Ar-H, *J* = 7.7 Hz), 8.37 s (2H, NH=CH), 8.73 s (1H, Ar-H), 12.36 s (2H, Ar-H). ^{13}C NMR spectrum, δ_C, ppm: 55.7, 96.1, 106.0, 115.4, 122.4, 126.5, 127.8, 128.0, 129.9, 130.7, 133.1, 138.9, 146.6, 156.9, 166.1. Found %: C 48.11; H 3.13; N12.04. $C_{28}H_{22}Br_2N_6O_2S_2$. Calculated, %: C 48.15; H 3.17; N 12.03. *M* 699 $[M + H]^+$.

4,4'-(4,6-Dimethoxy-1,3-phenylene)bis{2-[2-(3-bromobenzylidene)hydrazinyl]thiazole} (5f). Brown solid. IR spectrum, ν, cm^{-1}: 3460 (NH), 1602 (HC=N, azomethine), 1563 (C=N, thiazole), 1366 (C–N), 782 (C–S). ^{1}H NMR spectrum, δ, ppm: 4.00 s (6H, 2OMe), 6.82 s (1H, Ar-H), 7.27 s (2H, thiazole-H), 7.40 t (2H, Ar-H, *J* = 7.9 Hz), 7.56 d (2H, Ar-H, *J* = 7.9 Hz), 7.67 d (2H, Ar-H, *J* = 7.9 Hz), 7.85 s (2H, Ar-H), 8.02 s (2H, NH=CH), 8.76 s (1H, Ar-H), 12.25 s (2H, Ar-H). ^{13}C NMR spectrum, δ_C, ppm: 55.7, 96.1, 105.9, 115.4, 122.1, 125.2, 128.2, 129.9, 130.9, 131.5, 136.9, 139.0, 146.5, 156.9, 166.2. Found %: C 48.12; H 3.14; N 12.05. $C_{28}H_{22}Br_2N_6O_2S_2$. Calculated, %: C 48.15; H 3.17; N 12.03. *M* 699 $[M + H]^+$.

4,4'-(4,6-Dimethoxy-1,3-phenylene)bis{2-[2-(2-chlorobenzylidene)hydrazinyl]thiazole} (5g). Off-white solid. IR spectrum, ν, cm^{-1}: 3463 (NH), 1602 (HC=N, azomethine), 1560 (C=N, thiazole), 1366 (C–N), 749 (C–S). ^{1}H NMR spectrum, δ, ppm: 4.01 s (6H, 2OMe), 6.82 s (1H, Ar-H), 7.29 s (2H, thiazole-H), 7.41 t (4H, Ar-H, *J* = 7.3 Hz), 7.51 d (2H, Ar-H, *J* = 7.3 Hz), 7.94 d (2H, Ar-H, *J* = 7.3 Hz), 8.41 s (2H, NH=CH), 8.74 s (1H, Ar-H), 12.35 s (2H, NH). ^{13}C NMR spectrum, δ_C, ppm: 55.7, 96.1, 106.0, 115.7, 126.1, 127.5, 129.8, 129.9, 130.4, 131.6, 132.0, 136.5, 146.9, 156.9, 166.1. Found %: C 55.13; H 3.60; N 13.83. $C_{28}H_{22}Cl_2N_6O_2S_2$. Calculated, %: C 55.17; H 3.64; N 13.79. *M* 609.2 $[M]^+$.

4,4'-(4,6-Dimethoxy-1,3-phenylene)bis{2-[2-(4-chlorobenzylidene)hydrazinyl]thiazole} (5h). Off-white solid. IR spectrum, ν, cm^{-1}: 3462 (NH), 1616 (HC=N, azomethine), 1569 (C=N, thiazole), 1369 (C–N), 761 (C–S). ^{1}H NMR spectrum, δ, ppm: 3.99 s (6H, 2OMe), 6.82 s (1H, Ar-H), 7.26 s (2H, thiazole-H), 7.49 d (4H, Ar-H, *J* = 7.9 Hz), 7.69 d (4H, Ar-H, *J* = 7.9 Hz), 8.06 s (2H, NH=CH), 8.67 s (1H, Ar-H). ^{13}C NMR spectrum, δ_C, ppm: 55.9, 96.2, 106.0, 114.7, 128.0, 128.9, 130.1, 133.2, 133.8, 140.8, 145.2, 157.2,

166.5. Found %: C 55.12; H 3.61; N 13.81. $C_{28}H_{22}Cl_2N_6O_2S_2$. Calculated, %: C 55.17; H 3.64; N 13.79. *M* 609.2 $[M]^+$.

4,4'-(4,6-Dimethoxy-1,3-phenylene)bis{2-[2-(2-nitrobenzylidene)hydrazinyl]thiazole} (5i). Brown solid. IR spectrum, ν, cm^{-1}: 3461 (NH), 1620 (HC=N, azomethine), 1518 (C=N, thiazole), 1352 (C–N), 746 (C–S). ^{1}H NMR spectrum, δ, ppm: 4.00 s (6H, 2OMe), 6.83 s (1H, Ar-H), 7.30 s (2H, thiazole-H), 7.61 t (2H, Ar-H, *J* = 7.3 Hz), 7.79 t (2H, Ar-H, *J* = 7.3 Hz), 8.03–8.09 m (4H, Ar-H), 8.45 s (2H, NH=CH), 8.68 s (1H, Ar-H). ^{13}C NMR spectrum, δ_C, ppm: 55.9, 96.3, 106.6, 114.6, 124.7, 127.6, 128.5, 129.9, 130.0, 133.6, 137.2, 145.2, 147.4, 157.3, 166.4. Found %: C 53.30; H 3.48; N 17.80. $C_{28}H_{22}N_8O_6S_2$. Calculated, %: C 53.33; H 3.52; N 17.7. *M* 631.2 $[M + H]^+$.

4,4'-(4,6-Dimethoxy-1,3-phenylene)bis{2-[2-(3-nitrobenzylidene)hydrazinyl]thiazole} (5j). Brown solid. IR spectrum, ν, cm^{-1}: 3312 (NH), 1562 (HC=N, azomethine), 1524 (C=N, thiazole), 1352 (C–N), 728 (C–S). ^{1}H NMR spectrum, δ, ppm: 4.01 s (6H, 2OMe), 6.82 s (1H, Ar-H), 7.30 s (2H, thiazole-H), 7.73 t (2H, Ar-H, *J* = 7.9 Hz, Ar-H), 8.10 d (2H, Ar-H, *J* = 7.9 Hz), 8.18 s (2H, Ar-H), 8.20 d (2H, Ar-H, *J* = 7.9 Hz), 8.48 s (2H, NH=CH), 8.77 s (1H, Ar-H), 12.38 s (2H, NH). ^{13}C NMR spectrum, δ_C, ppm: 55.7, 96.1, 106.1, 115.3, 120.1, 123.2, 129.9, 130.4, 132.2, 136.3, 138.4, 146.6, 148.2, 156.9, 166.1. Found, %: C 53.29; H 3.49; N 17.79. $C_{28}H_{22}N_8O_6S_2$. Calculated, %: C 53.33; H 3.52; N 17.77. *M* 631.3 $[M + H]^+$.

Antibacterial activity. *Pseudomonas aeruginosa* (Gram-negative), *Escherichia coli* (Gram-negative), *Bacillus subtilis* (Gram-positive), and *Staphylococcus aureus* (Gram-positive) microbes were obtained from the Microbial Type Culture Collection–MTCC in auto calved LB broth media and incubate overnight at 37°C in a shaker for bacterial growth. From that 0.3 mL of bacterial culture was inoculated by using spreader on freshly prepared auto calved agar plates, Petri dishes. The following common manipulations were carried out. DMSO solutions of samples had concentrations 50 and 100 μg/mL. Norfloxacin was used as a positive control.

Antimycobacterial activity. Isolated single colonies of *Mycobacterium* on 7H10 agar plate was grown overnight in Middlebrook 7H9 medium (0.47% Middlebrook 7H9 broth base, 10% ADS, 0.2% glycerol, and 0.1% Tween-80) to mid-exponential phase at 37°C. The following procedure was carried out according to the conventional method. Isoniazid and Rifampicin were used for positive control. DMSO was used as a solvent.

CONCLUSIONS

New symmetrical derivatives of bis{2-[2-(substituted benzylidene)hydrazinyl]thiazole} **5a–5j** were synthesized via condensation of corresponding 1,1'-(4,6-dimethoxy-1,3-phenylene)bis(2,2-dibromoethanone) with thiosemicarbazones by the conventional method and under microwave irradiation. Compound **5c** demonstrated high activity against all Gram negative strains (*E. coli* and *P. aeruginosa*). The compounds **5b**, **5f**, **5h** showed high activity against Gram positive stain (*B. substilis*) and compound **5b** demonstrated high antimycobacterial activity against *M. bovis*.

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