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Microwave-assisted synthesis and biological evaluation of thiazole-substituted dibenzofurans

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Abstract: New thiazole-substituted dibenzofurans **7a–j** were synthesized from dibenzofuran derivatives **5a–b** and substituted thiosemicarbazones **6a–h** under conventional and microwave irradiation conditions. The structures of all products were established on the basis of analytical and spectral data. The synthesized compounds were evaluated for their *in vitro* antibacterial activity against Gram-positive and Gram-negative strains. Compounds **7b, 7d** and **7h** are active against *Bacillus subtilis* (+ve), and compound **7i** displays good activity against *Pseudomonas aeruginosa* (–ve) strain. Compounds **7a–j** were also evaluated for their *in vitro* antimycobacterial activity, and compound **7b** shows antimycobacterial activity against *Mycobacterium bovis* strain.

Keywords: antibacterial; antimycobacterial; benzofuran; microwave irradiation; thiazole.

Introduction

During the past decades, the synthesis of thiazoles and analogs has gained interest due to their broad range of biological and pharmaceutical properties, such as antibacterial [1–4], anti-human immunodeficiency virus type 1 (HIV-1) [5], antihypertensive [6], anti-inflammatory [7], antiviral [8, 9] and anticancer activities [10]. Thiosemicarbazones have also gained importance in medicinal chemistry [11, 12] and are being extensively used in the synthesis of thiazoles [13]. In recent years, many thiazolyl hydrazone derivatives have been synthesized and screened for antimicrobial [14] and antimycobacterial [15] activities. Benzodifurans are also bioactive [16, 17]. In particular, benzo[*b*]furan derivatives substituted at the C-2 position show good biological activities [18, 19]. Microwave-assisted organic synthesis of heterocyclic compounds has become an effective technique for generating new heterocyclic scaffolds useful for drug discovery [20]. Currently, microwave irradiation methods, especially the synthesis of thiazolyl hydrazine derivatives via the condensation of α-bromoketones with thiosemicarbazones, have shown great promise as an attractive alternative to conventional methods. Inspired by the biological profile of thiazolyl hydrazine derivatives and in continuation of our previous work [21], we have focused our attention on the preparation of symmetrical thiazole and benzodifuran derivatives **7a–j**. These products were synthesized by conventional and microwave methods and investigated *in vitro* for antibacterial and antimycobacterial activities.

Results and discussion

Compounds **7a–j** were prepared from 2,4-diacetylresorcinol (**1**) which, in turn, was synthesized according to the literature procedure [22], as shown in Scheme 1. First, the starting material **1** was treated with two equivalents of a benzaldehyde in an aqueous solution of potassium hydroxide. The resulting bis-chalcones **2a–b** were then hydrogenated using 10% Pd/C in ethyl acetate. The products **3a–b** were treated with chloroacetone in acetone in the presence of potassium carbonate. Then, the products **4a–b** were brominated by pyridinium tribromide in acetic acid. The reaction of products **5a–b** with substituted thiosemicarbazones **6a–h** in ethanol under microwave irradiation afforded the desired final compounds **7a–j** in high yields (method B). The yields were lower for the same reactions conducted using the conventional heating method (method A). The structures of the synthesized compounds **3a,b, 4a,b, 5a,b** and **7a–j** were established by spectroscopic means [infrared (IR), proton nuclear magnetic resonance (^{1}H NMR), carbon-13 nuclear magnetic resonance (^{13}C NMR), mass spectrometry (MS)] and elemental analyses.

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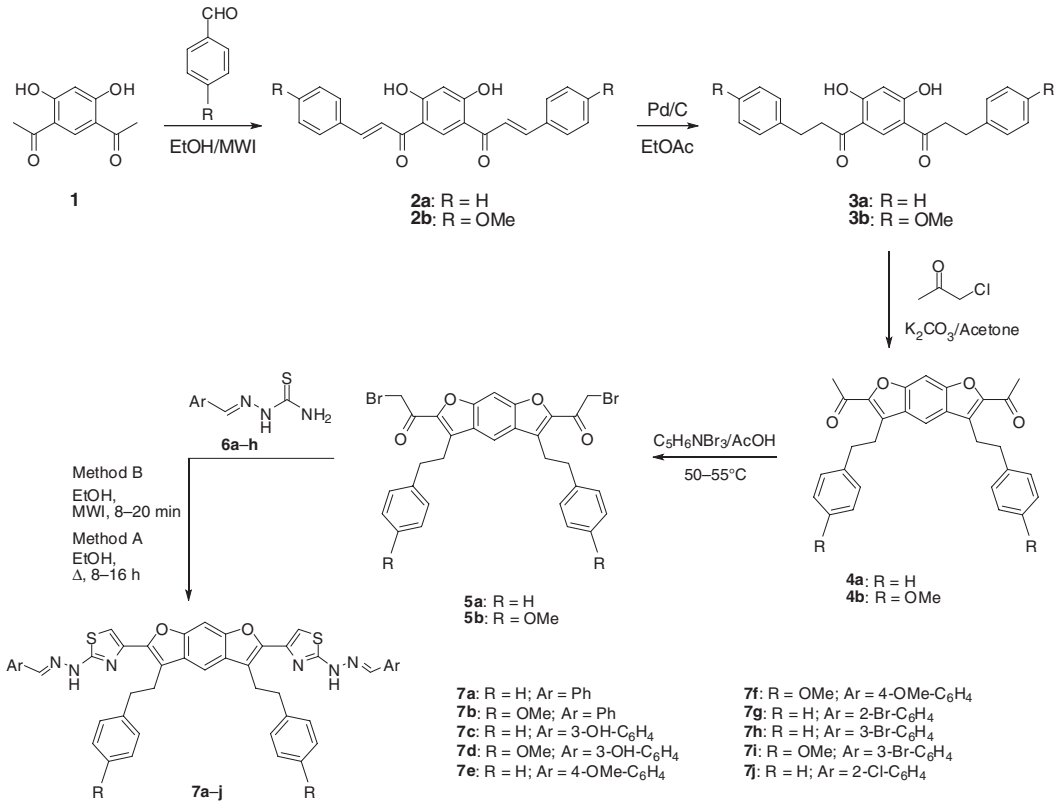

Scheme 1

Table 1 Antibacterial activity of compounds **7a–j.**

Compound	Zone of inhibition after 24 h (mm)			
	Gram-positive bacteria		Gram-negative bacteria	
	S. aureus (MTCC 737)	*B. subtilis* (MTCC 441)	*E. coli* (MTCC 443)	*P. aeruginosa* (MTCC 741)
7a	8.5	11	4.5	6
7b	14	25	5.5	7
7c	4	7	5.5	7
7d	11	21	4.5	6
7e	6.5	12	2.5	2.5
7f	4.5	6	5.5	5
7g	7.5	10	4	6.5
7h	9	21	6	8
7i	5.5	8	9	11
7j	5.5	9	5.5	6
Norfloxacin	16	20		
Ofloxacin			18	10

The *in vitro* antimicrobial activities of compounds **7a–j** were investigated against four pathogenic microorganisms, namely *Staphylococcus aureus* (MTCC 737), *Escherichia coli* (MTCC 443), *Bacillus subtilis* (MTCC 441) and *Pseudomonas aeruginosa* (MTCC 741) at a concentration of 100 μg/mL using norfloxacin and ofloxacin as standard drugs by the cup-plate agar diffusion method. The results are presented in Table 1. As can be seen, compounds **7b, 7d, 7h** (inhibition zone >20 mm) show excellent growth inhibition against *B. subtilis* as compared to norfloxacin (20 mm). Compound **7i** is more potent than the standard (oflaxin) against Gram-negative bacterial strain *P. aeruginosa*. The investigation of *in vitro* antimycobacterial activity (Table 2) revealed that compounds

Table 2 Antimycobacterial activity of compounds **7a–j**.

Compound	Zone of inhibition (mm)
	M. bovis
7a	15.1
7b	42.2
7c	19.5
7d	26.9
7e	27.8
7f	32.5
7g	16.9
7h	36.6
7i	10.9
7j	21.5
Isoniazid + rifampicin	40.0

7b and **7h** are active compared to the standard mixture of isoniazid and rifampicin (Scheme 1).

Conclusions

New antibacterial and antimycobacterial inhibitors **7a–j** were synthesized via symmetrical construction of a thiazole ring at each C-2 position of benzodifuran using both conventional and microwave irradiation methods. Compounds **7b, 7d, 7h** show excellent growth inhibition against *B. subtilis* as compared to norfloxacin. In comparison to oflaxin, compound **7i** is highly effective against Gram-negative bacterial strain *P. aeruginosa*. Compound **7b** shows excellent *in vitro* antimycobacterial activity.

Experimental

IR spectra were recorded on a Shimadzu FTIR-8400S spectrometer using KBr pellets. ^{1}H NMR spectra (300 MHz) and ^{13}C NMR spectra (75 MHz) were acquired on a Bruker Avance 300 spectrometer in $CDCl_3$ or dimethyl sulfoxide-d6 (DMSO-d_6) using tetramethylsilane (TMS) as the internal standard. Mass spectra were recorded using electrospray ionization (ESI) 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 instrument (850 W maximum power, 2.45 GHz). Analytical thin-layer chromatography (TLC) was performed on precoated Merck 60 F_{254} silica gel plates with visualization under ultraviolet (UV) light. Substituted thiosemicarbazones **6a–h** were synthesized as previously described [23–25].

Compounds 3a,b

A solution of bis-chalcone **2a** or **2b** (5.34 mmol) in ethyl acetate (20 mL) in a Parr hydrogenation bottle was treated with Pd/C (20%, 400 mg), and the mixture was hydrogenated under a pressure of 3 atm for 3 h at room temperature. The catalyst was removed by filtration using a celite pad. The filtrate was concentrated and the residue was purified by silica gel chromatography eluting with a gradient of 10–20% of ethyl acetate in hexanes [26].

1,1′-(4,6-Dihydroxy-1,3-phenylene)bis(3-phenylpropan-1-one) (3a) White solid; yield 95%; mp 88–90°C; IR: 3023, 1653 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 12.97 (s, 2H, OH), 8.04 (s, 1H, Ar), 7.34–7.20 (m, 10H, Ar), 6.42 (s, 1H, Ar), 3.19 (t, 4H, J = 7.3 Hz, CH_2), 3.04 (t, 4H, J = 7.3 Hz, CH_2); ^{13}C NMR ($CDCl_3$): δ 203.5, 168.7, 140.4, 134.6, 128.7, 128.4, 126.5, 113.1, 105.1, 39.6, 30.2; MS: m/z 374.9 [(M + H)$^+$, 100%]. Anal. Calcd for $C_{24}H_{22}O_4$: C, 76.99; H, 5.92. Found: C, 76.94; H, 5.89.

1,1′-(4,6-Dihydroxy-1,3-phenylene)bis(3-(4-methoxyphenyl) propan-1-one) (3b) White solid; yield 90%; mp 120–122°C; IR: 2910, 1634 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 12.98 (s, 2H, N-H), 8.07 (s, 1H, Ar), 7.13 (d, 4H, J = 7.1 Hz, Ar), 6.83 (d, 4H, J = 7.1 Hz, Ar), 6.41 (s, 1H, Ar-H), 3.77 (s, 6H, OCH_3), 3.16 (t, 4H, J = 7.5 Hz, CH_2), 2.98 (t, 4H, J = 7.5 Hz, CH_2); ^{13}C NMR ($CDCl_3$): δ 203.6, 168.7, 158.2, 134.6, 132.4, 129.4, 114.1, 113.1, 105, 55.2, 39.9, 29.4; MS: m/z 435.1 [(M + H)$^+$, 100%]. Anal. Calcd for $C_{26}H_{26}O_6$: C, 71.87; H, 6.03. Found: C, 71.82; H, 5.98.

Compounds 4a,b

A mixture of 1,1′-(4,6-dihydroxy-1,3-phenylene)bis(3-substituted propan-1-one) **3a** or **3b** (10 mmol), chloroacetone (22 mmol) and potassium carbonate (30 mmol) in dried acetone (10 mL) was heated under reflux for 6 h. Then the mixture was quenched with crushed ice and extracted with ethyl acetate (2×10 mL). The combined organic layers were dried over anhydrous sodium sulfate, concentrated and purified by silica gel (60–120 mesh) column chromatography eluting with a gradient of 20–30% of ethyl acetate in hexanes.

1,1′-(3,5-Diphenethylbenzo[1,2-*b*:5,4-*b*′]difuran-2,6-diyl)diethanone (4a) White solid; yield 90%; mp 138–140°C; IR: 3087, 2923, 1670, 1558 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.56 (s, 1H, Ar), 7.22 (m, 11H, Ar), 3.36 (t, 4H, J = 8 Hz, CH_2), 2.95 (t, 4H, J = 8 Hz, CH_2), 2.62 (s, 6H, CH_3); ^{13}C NMR ($CDCl_3$): δ 190.8, 154.3, 148.8, 141.3, 128.6, 128.3, 127.8, 126.4, 126.2, 113.6, 94.9, 35.6, 27.8, 26.4; MS: m/z 451 [(M + H)$^+$, 100%]. Anal. Calcd for $C_{30}H_{26}O_4$: C, 79.98; H, 5.82. Found: C, 79.94; H, 5.78.

1,1′-(3,5-Bis(4-methoxyphenethyl)benzo[1,2-*b*:5,4-*b*′]difuran-2,6-diyl)diethanone (4b) White solid; yield 90%; mp 136–138°C; IR: 3059, 2934, 1685, 1571 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.56 (s, 1H, Ar), 7.25 (s, 1H, Ar), 7.12 (d, 4H, J = 8 Hz, Ar), 6.77 (d, 4H, J = 8 Hz, Ar), 3.70 (s, 6H, OCH_3), 3.33 (t, 4H, J = 8 Hz, CH_2), 2.89 (t, 4H, J = 7.7 Hz, CH_2), 2.62 (s, 6H, CH_3); ^{13}C NMR ($CDCl_3$): δ 190.7, 158, 154.3, 148.9, 133.4, 127.9, 128, 126.5, 113.7, 113.7, 94.9, 55.1, 34.8, 27.8, 26.6; MS: m/z 511 [(M + H)$^+$, 100%]. Anal. Calcd for $C_{32}H_{30}O_6$: C, 75.28; H, 5.92. Found: C, 75.23; H, 5.89.

Compounds 5a,b

Pyridinium tribromide (70 mmol) was added in portions to a stirred solution of compound **4a** or **4b** (28 mmol) in acetic acid (100 mL) at 50–55°C and stirring was continued for 4 h. Then the mixture was quenched with crushed ice and extracted with ethyl acetate (2×10 mL). The combined organic layers were dried over anhydrous sodium sulfate, concentrated and purified by silica gel chromatography eluting with a gradient from 20% to 30% of ethyl acetate in hexanes.

1,1′-(3,5-Diphenethylbenzo[1,2-*b*:5,4-*b′*]difuran-2,6-diyl)-bis(2-bromoethanone) (5a) Off-white solid; yield 85%; mp 138–140°C; IR: 2924, 1682, 1571, 818 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.59 (s, 1H, Ar), 7.22 (m, 11H, Ar), 4.53 (s, 4H, CH_2), 3.38 (t, 4H, J=8 Hz, CH_2), 2.96 (t, 4H, J=8 Hz, CH_2); ^{13}C NMR ($CDCl_3$): δ 183.3, 154.8, 146.8, 141, 130.9, 128.7, 128.4, 126.5, 126.3, 114.2, 95.4, 35.6, 32.1, 26.5; MS: m/z 609.3 [(M+2H)$^+$, 100%]. Anal. Calcd for $C_{30}H_{24}Br_2O_4$: C, 59.23; H, 3.98. Found: C, 59.19; H, 3.94.

1,1′-(3,5-Bis(4-methoxyphenethyl)benzo[1,2-*b*:5,4-*b′*]difuran-2,6-diyl)-bis(2-bromoethanone) (5b) Off-white solid; yield 82%; mp 134–136°C; IR: 2931, 1678, 1577, 819 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.59 (s, 1H, Ar), 7.27 (s, 1H, Ar), 7.10 (d, 4H, J=8 Hz, Ar-H), 6.77 (d, 4H, J=8 Hz, Ar), 4.53 (s, 4H, CH_2), 3.70 (s, 6H, OCH_3), 3.36 (t, 4H, J=8 Hz, CH_2), 2.90 (t, 4H, J=8 Hz, CH_2); ^{13}C NMR ($CDCl_3$): δ 183.5, 158.1, 154.9, 146.7, 133.1, 131.2, 129.6, 126.5, 114.4, 113.8, 95.4, 55.2, 34.7, 32.1, 26.7; MS: m/z 669.2 [(M+2H)$^+$, 100%]. Anal. Calcd for $C_{32}H_{28}Br_2O_6$: C, 57.50; H, 4.22. Found: C, 57.45; H, 4.18.

General procedures for the preparation of compounds 7a–j

Conventional heating method A To a stirred solution of **5a** or **5b** (0.001 mol) in ethanol (10 mL), was added substituted thiosemicarbazone **6a–h** (0.002 mol) in ethanol (10 mL). The mixture was heated under reflux for a period of time indicated below and then concentrated under reduced pressure, and the residue was subjected to column chromatography on basic alumina eluting with a gradient from 30 to 40% of ethyl acetate in hexanes.

Microwave irradiation method B A mixture of **5a** or **5b** (0.001 mol), substituted thiosemicarbazone **6a–h** (0.002 mol) and ethanol (10 mL) in a microwave tube was subjected to microwave irradiation at 180 W for 8–20 min. Work-up and purification were conducted as described above.

4,4′-(3,5-Diphenethylbenzo[1,2-*b*:5,4-*b′*]difuran-2,6-diyl)bis(2-(2-benzylidenehydrazino)thiazole) (7a) Reaction time 8 h, yield 85%, method A; reaction time 10 min, yield 92%, method B; off-white solid; mp 170–172°C (dec); IR: 3464, 1563, 1491, 1359, 753 cm^{-1}; ^1H NMR (DMSO-d_6): δ 12.16 (s, 2H, NH), 8.13 (s, 2H, CH=N), 7.71 (s, 1H, Ar), 7.69 (d, 4H, J=7 Hz, Ar), 7.40 (m, 11H, Ar), 7.27 (m, 6H, Ar, thiazole), 7.17 (t, 2H, J=7 Hz, Ar), 3.47 (t, 4H, J=7 Hz, CH_2), 2.98 (t, 4H, J=7 Hz, CH_2); ^{13}C NMR (DMSO-d_6): δ 168.7, 151.8, 146.8, 142.9, 142.5, 141.7, 134.3, 129.3, 128.8, 128.6, 128.1, 127.6, 126.3, 125.8, 115.6, 109.3, 106, 93.5, 35.5, 25.1; MS: m/z 769.1 [(M+H)$^+$, 100%]. Anal. Calcd for $C_{46}H_{36}N_6O_2S_2$: C, 71.85; H, 4.72; N, 10.93. Found: C, 71.80; H, 4.69; N, 10.94.

4,4′-(3,5-Bis(4-methoxyphenethyl)benzo[1,2-*b*:5,4-*b′*]difuran-2,6-diyl)-bis(2-(2-benzylidenehydrazino)thiazole) (7b) Reaction time 10 h, yield 80%, method A; reaction time 15 min, yield 86%; method B; off-white solid; mp 114–116°C (dec); IR: 3463, 1564, 1509, 1364, 754 cm^{-1}; ^1H NMR (DMSO-d_6 + D_2O): δ 8.12 (s, 2H, CH=N), 7.68 (d, 4H, J=7 Hz, Ar), 7.55 (s, 1H, Ar), 7.52–7.36 (m, 7H, Ar), 7.18 (s, 2H, thiazole), 7.14 (d, 4H, J=8 Hz, Ar), 6.77 (d, 4H, J=8 Hz, Ar), 3.61 (s, 6H, OCH_3), 3.44–3.25 (m, 4H, CH_2), 2.87 (t, 4H, J=7 Hz, CH_2); ^{13}C NMR (DMSO-d_6): δ 168.6, 157.4, 151.8, 146.8, 142.9, 141.6, 134.3, 133.6, 129.6, 129.3, 128.8, 128.6, 126.3, 115.6, 113.5, 109.4, 106, 93.4, 54.8, 34.7, 25.5; MS: m/z 829.2 [(M+H]$^+$, 100%]. Anal. Calcd for $C_{48}H_{40}N_6O_4S_2$: C, 69.54; H, 4.86; N, 10.14. Found: C, 69.50; H, 4.81; N, 10.15.

4,4′-(3,5-Bis(phenethyl)benzo[1,2-*b*:5,4-*b′*]difuran-2,6-diyl)-bis((2-(3-hydroxybenzylidene)hydrazino)thiazole) (7c) Reaction time 12 h, yield 75%, method A; reaction time 20 min, yield 86%, method B; off-white solid; mp 138–140°C (dec); IR: 3463, 1560, 1491, 1364, 748 cm^{-1}; ^1H NMR (DMSO-d_6): δ 12.09 (s, 2H, N-H), 9.66 (s, 2H, OH), 8.03 (s, 2H, CH=N), 7.71 (s, 1H, Ar), 7.43 (s, 1H, Ar), 7.41–7.04 (m, 18H, Ar, thiazole), 6.80 (d, 2H, J=7 Hz, Ar), 3.49 (m, 4H, CH_2), 2.94 (m, 4H, CH_2); ^{13}C NMR (DMSO-d_6): δ 168.7, 157.6, 151.9, 146.9, 142.9, 142, 141.7, 135.6, 129.9, 128.7, 128.2, 126.3, 125.9, 118, 116.8, 115.6, 112.1, 109.3, 106.1, 93.5, 35.6, 25.2; MS: m/z 801.3 [(M+H)$^+$, 100%]. Anal. Calcd for $C_{46}H_{36}N_6O_4S_2$: C, 68.98; H, 4.53; N, 10.49. Found: C, 68.93; H, 4.49; N, 10.50.

4,4′-(3,5-Bis(4-methoxyphenethyl)benzo[1,2-*b*:5,4-*b′*]difuran-2,6-diyl)-bis(2-(2-(3-hydroxybenzylidene)hydrazino)thiazole) (7d) Reaction time 16 h, yield 70%, method A; reaction time 20 min, yield 85%; method B; brown solid; mp 124–126°C (dec); IR: 3465, 1562, 1508, 1365, 730 cm^{-1}; ^1H NMR (DMSO-d_6): δ 12.09 (s, 2H, N-H), 9.65 (s, 2H, O-H), 8.03 (s, 2H, CH=N), 7.70 (s, 1H, Ar), 7.33 (s, 1H, Ar), 7.29–7.19 (m, 8H, Ar, thiazole), 7.13 (s, 2H, Ar), 7.06 (d, 2H, J=7 Hz, Ar), 6.81 (m, 6H, Ar), 3.66 (s, 6H, OCH_3), 3.53 (m, 4H, CH_2), 2.91 (t, 4H, J=7Hz, CH_2); ^{13}C NMR (DMSO-d_6): δ 168.7, 157.6, 157.5, 151.8, 146.8, 142.9, 141.9, 135.6, 133.6, 129.9, 129.6, 126.4, 118, 116.8, 115.7, 113.5, 112.1, 109.4, 106, 93.5, 54.9, 34.7, 25.5; MS: m/z 861.2 [(M+H)$^+$, 100%]. Anal. Calcd for $C_{48}H_{40}N_6O_6S_2$: C, 66.96; H, 4.68; N, 9.76. Found: C, 66.91; H, 4.63; N, 9.78.

4,4′-(3,5-Diphenethylbenzo[1,2-*b*:5,4-*b′*]difuran-2,6-diyl)-bis(2-(2-(4-methoxybenzylidene)hydrazino)thiazole) (7e) Reaction time 12 h, yield 85%, method A; reaction time 8 min, yield 91%, method B; off-white solid; mp 112–114°C (dec); IR: 3465, 1557, 1506, 1362, 742 cm^{-1}; ^1H NMR (DMSO-d_6): δ 11.99 (s, 2H, N-H), 8.07 (s, 2H, CH=N), 7.69 (s, 1H, Ar), 7.62 (d, 4H, J=8 Hz, Ar), 7.43 (s, 1H, Ar), 7.36 (d, 4H, J=7 Hz, Ar), 7.29 (m, 4H, Ar, thiazole), 7.18 (d, 4H, J=7 Hz, Ar), 7.01 (d, J=8 Hz, 4H, Ar), 3.80 (s, 6H, OCH_3), 3.55–3.44 (m, 4H, CH_2), 3.04–2.89 (m, 4H, CH_2); ^{13}C NMR (DMSO-d_6): δ 168.8, 160.2, 151.8, 146.9, 142.9, 141.7, 141.2, 128.6, 128.1, 127.8, 126.9, 126.3, 125.8, 115.5, 114.3, 109.2, 105.7, 93.4, 55.2, 35.5, 25.1; MS: m/z 829.2 [(M+H])$^+$, 100%]. Anal. Calcd for $C_{48}H_{40}N_6O_4S_2$: C, 69.54; H, 4.86; N, 10.14. Found: C, 69.50; H, 4.81; N, 10.16.

4,4′-(3,5-Bis(4-methoxyphenethyl)benzo[1,2-*b*:5,4-*b′*]difuran-2,6-diyl)-bis(2-(2-(4-methoxybenzylidene)hydrazino)thiazole) (7f) Reaction time 15 h, yield 72%, method A; reaction time 15 min, yield 86%, method B; off-white solid; mp 110–112°C (dec); IR: 3465, 1562, 1508, 1364, 731 cm^{-1}; ^1H NMR (DMSO-d_6 + D_2O): δ 8.02 (s, 2H,

CH=N), 7.63 (s, 1H, Ar), 7.57 (d, 4H, J = 8 Hz, Ar), 7.28 (s, 1H, Ar), 7.19 (d, 4H, J = 7 Hz, Ar), 7.12 (s, 2H, thiazole), 6.96 (d, 4H, J = 8 Hz, Ar), 6.75 (d, 4H, J = 7 Hz, Ar), 3.78 (s, 6H, OCH_3), 3.60 (s, 6H, OCH_3), 3.47–3.21 (m, 4H, CH_2), 2.88 (m, 4H, CH_2); ^{13}C NMR (DMSO-d_6): δ 168.7, 160.2, 157.4, 151.8, 146.8, 142.9, 141.7, 133.6, 129.6, 127.8, 126.9, 126.3, 115.6, 114.3, 113.5, 109.3, 105.6, 93.4, 55.2, 54.8, 34.7, 25.5; MS: m/z 889.2 [$(M+H)^+$, 100%]. Anal. Calcd for $C_{50}H_{44}N_6O_6S_2$: C, 67.55; H, 4.99; N, 9.45. Found: C, 67.50; H, 4.94; N, 9.47.

4,4′-(3,5-Diphenethylbenzo[1,2-*b*:5,4-*b*′]difuran-2,6-diyl)-bis(2-(2-(2-bromobenzylidene)hydrazino)thiazole) (7g) Reaction time 10 h, yield 75%, method A; reaction time 10 min, yield 89%, method B; brown solid; mp 206–208°C (dec); IR: 3463, 1560, 1508, 1348, 752 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 12.40 (s, 2H, N-H), 8.46 (s, 2H, CH=N), 8.02–7.86 (m, 2H, Ar), 7.84 (s, 1H, Ar), 7.68 (d, 2H, J = 7.5 Hz, Ar), 7.52–7.19 (m, 17H, Ar-H, thiazole), 3.47 (t, J = 7 Hz, 4H, CH_2), 2.98 (t, J = 7 Hz, 4H, CH_2); ^{13}C NMR (DMSO-d_6): δ 168.4, 152.1, 146.8, 142.4, 141.6, 139.8, 133.1, 133, 130.9, 128.5, 128.3, 128.1, 126.5, 125.8, 124.6, 122.7, 116.1, 109.2, 106.3, 93.7, 35.5, 25.6; MS: m/z 927.3 (M^+, 100%). Anal. Calcd for $C_{46}H_{34}Br_2N_6O_2S_2$: C, 59.62; H, 3.70; N, 9.07. Found: C, 59.58; H, 3.65; N, 9.10.

4,4′-(3,5-Diphenethylbenzo[1,2-*b*:5,4-*b*′]difuran-2,6-diyl)-bis(2-(2-(3-bromobenzylidene)hydrazino)thiazole) (7h) Reaction time 10 h, yield 78%, method A; reaction time 10 min, yield 87%, method B; brown solid; mp 216–218°C (dec); IR: 3463, 1558, 1479, 1359, 739 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 12.31 (s, 2H, N-H), 8.08 (s, 2H, CH=N), 7.86 (s, 2H, Ar), 7.71 (s, 1H, Ar), 7.68 (d, 2H, J = 8 Hz, Ar), 7.58 (d, 2H, J = 8 Hz Ar), 7.45 (s, 1H, Ar), 7.42 (d, 2H, J = 8 Hz, Ar), 7.41–7.24 (m, 10H, Ar, thiazole), 7.17 (t, 2H, J = 8 Hz, Ar), 3.47 (t, 4H, J = 8 Hz, CH_2), 2.98 (t, 4H, J = 8 Hz, CH_2); ^{13}C NMR (DMSO-d_6): δ 168.5, 151.8, 146.8, 142.9, 141.6, 139.8, 136.8, 131.8, 131, 128.6, 128.4, 128.1, 126.3, 125.8, 125.2, 122.2, 115.6, 109.3, 106.3, 93.5, 35.5, 25.1; MS: m/z 926.9 (M^+, 100%). Anal. Calcd for $C_{46}H_{34}Br_2N_6O_2S_2$: C, 59.62; H, 3.70; N, 9.07. Found: C, 59.57; H, 3.66; N, 9.09.

4,4′-(3,5-Bis(4-methoxyphenethyl)benzo[1,2-*b*:5,4-*b*′]difuran-2,6-diyl)-bis(2-(2-(3-bromobenzylidene)hydrazino)thiazole) (7i) Reaction time 12 h, yield 75%, method A; reaction time 10 min, yield 86%, method B; brown solid; mp 118–120°C (dec); IR: 3462, 1565, 1511, 1366, 735 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 12.31 (s, 2H, N-H), 8.09 (s, 2H, CH=N), 7.86 (s, 2H, Ar), 7.70 (m, 3H, Ar), 7.58 (d, 2H, J = 8 Hz, Ar), 7.41 (t, 2H, J = 8 Hz, Ar), 7.34 (s, 1H, Ar), 7.25 (m, 6H, Ar, thiazole), 6.82 (d, 4H, J = 8 Hz, Ar), 3.66 (s, 6H, OCH_3), 3.41 (m, 4H, CH_2), 2.91 (t, 4H, J = 7 Hz, CH_2); ^{13}C NMR (DMSO-d_6): δ 168.4, 157.4, 151.8, 146.7, 143, 139.7, 136.8, 133.6, 131.7, 130.9, 129.6, 128.4, 126.3, 125.2, 122.2, 115.7, 113.5, 109.4, 106.2, 93.4, 54.8, 34.7, 25.5; MS: m/z 986.79 (M^+, 100%). Anal. Calcd for $C_{48}H_{38}Br_2N_6O_4S_2$: C, 58.42; H, 3.88; N, 8.52. Found: C, 58.38; H, 3.84; N, 8.54.

4,4′-(3,5-Diphenethylbenzo[1,2-*b*:5,4-*b*′]difuran-2,6-diyl)-bis(2-(2-(2-chlorobenzylidene) hydrazino)thiazole) (7j) Reaction time 8 h; off-white solid; yield 70%, method A; reaction time 10 min, yield 86%, method B; mp 150–152°C (dec); IR: 3463, 1559, 1508, 1362, 748 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 12.40 (s, 2H, N-H), 8.49 (s, 2H, CH=N), 7.95 (dd, 2H, J = 2.2, 6.7 Hz, Ar), 7.70 (s, 1H, Ar), 7.52 (dd, 2H, J = 2.2, 6.7 Hz, Ar), 7.48–7.40 (m, 5H, Ar), 7.36 (d, 4H, J = 7.1 Hz, Ar), 7.29 (d, 4H, J = 7.1 Hz, Ar), 7.25 (s, 2H, thiazole), 7.17 (t, 2H, J = 7.1 Hz, Ar), 3.46 (t, 4H, J = 7.3 Hz, CH_2), 2.98 (t, 4H, J = 7.3 Hz, CH_2); ^{13}C NMR (DMSO-d_6): δ 168.3, 151.8, 146.7, 143, 141.7, 141.2, 137.4, 132.2, 131.5, 130.6, 129.9, 128.6, 128.1, 127.6, 126.1, 125.8, 115.7, 109.2, 106.3, 93.5, 35.5, 25.2; MS: m/z 837.5 (M^+, 100%). Anal. Calcd for $C_{46}H_{34}Cl_2N_6O_2S_2$: C, 65.94; H, 4.09; N, 10.03. Found: C, 65.90; H, 4.04; N, 10.05.

Antibacterial assay

Gram-negative strains (*P. aeruginosa* and *E. coli*) and Gram-positive strains (*B. subtilis* and *S. aureus*) were obtained from the Microbial Type Culture Collection. The biological activities were assayed using the standard disc diffusion method [27] for 100 μg/mL solutions in DMSO. Inhibition zones were measured, compared with the standard positive control of norfloxacin (+ve stains) and ofloxacin (–ve stains) at 100 μg/mL.

Antimycobacterial assay

Isolated single colonies of *Mycobacterium bovis*, 7H10 agar plate and Middlebrook 7H9 medium were used. The activity was assayed by the turbidometry method [28] using a mixture of isoniazid and rifampicin as standard.

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