DOI 10.1007/s10593-018-2323-x

Chemistry of Heterocyclic Compounds **2018**, *54*(6), 658–663

Microwave-assisted synthesis of novel benzodifuran-based bis(*N*-(het)arylthiazol-2-amine) derivatives and their antibacterial and antimycobacterial activities

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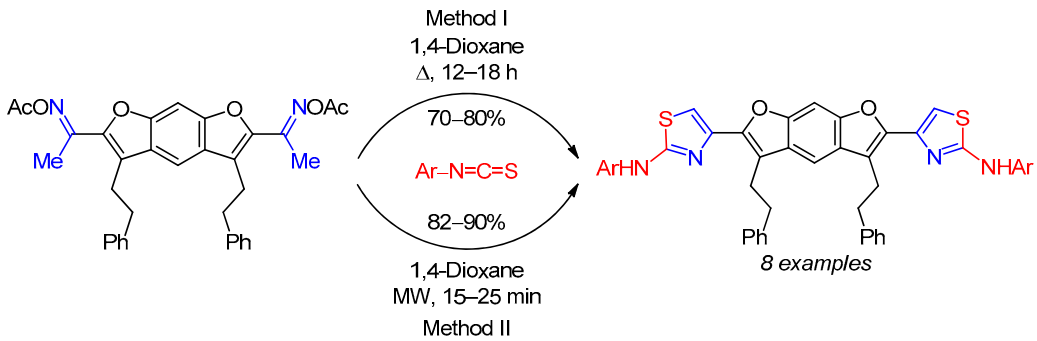
Published in Khimiya Geterotsiklicheskikh Soedinenii, 2018, *54*(6), 658–663

Submitted January 18, 2018
Accepted March 17, 2018

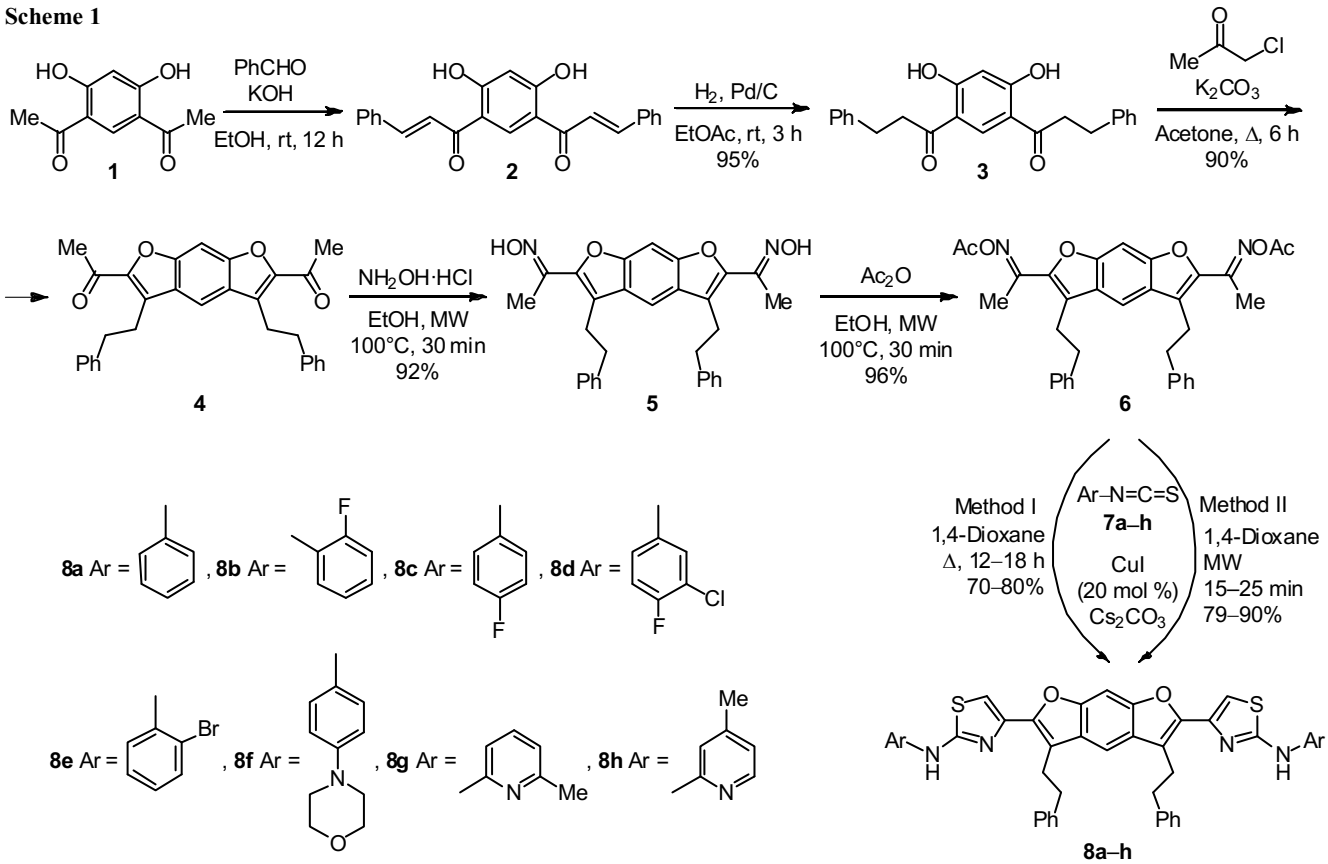


A new series of 4,4'-(3,5-diphenethylbenzo[1,2-*b*:5,4-*b*']difuran-2,6-diyl)bis(*N*-(het)arylthiazol-2-amine) derivatives have been synthesized from 1,1'-(3,5-diphenethylbenzo[1,2-*b*:5,4-*b*']difuran-2,6-diyl)diethanone *O*,*O*'-diacetyl dioxime and substituted isothiocyanates under conventional and microwave irradiation conditions. The obtained products were subjected to *in vitro* antibacterial and antimycobacterial activity tests. Some of the compounds exhibited noteworthy antibacterial activity against *Bacillus subtilis* (+ve) and *Pseudomonas aeruginosa* (-ve) strains and antimycobacterial activity against *Mycobacterium bovis* strain.

Keywords: benzodifuran, thiazole, antibacterial, antimycobacterial, microwave irradiation.

Benzofurans are a significant class of oxygen-containing heterocyclic compounds that have potential biological activities, such as antibacterial,[1] antimicrobial,[2] antitumor,[3] antiproliferative,[4] and antimalarial[5] activity. In addition, benzofurans with variously substituted heterocyclic rings connected directly at the C-2 position demonstrate substantial biological activities.[6] Heterocyclic compounds having nitrogen and sulfur atoms play an important role in medicinal chemistry, for example, derivatives of such five-membered heterocycles have shown an appreciable range of biological activities.[7] Additional studies on thiazole molecule have been conducted in organic and pharmaceutical chemistry.[8] Particularly, compounds based on thiazol-2-amine structure exhibit significant antimycobacterial[9] and antibacterial[10] activities. *Mycobacterium tuberculosis* complexes (MTC) include a set of mycobacterial strains like *M. tuberculosis*, *M. bovis*, *M. africanum*, etc. Drug-resistant *M. tuberculosis* has become a matter of concern for the public health due to the lack of newer antibacterial agents for the treatment of tuberculosis. Therefore, it is indispensable to discover a new lead compound against these drug-resistant strains. Research on antimicrobial agents is a herculean task, as the microorganisms continuously develop resistance to

Scheme 1



antimicrobial compounds and infections caused by *M. tuberculosis* strains are rare and often incurable. Investigation of the interaction of biologically active molecules with DNA is a critical step in the development of new medicines,[11] and various DNA-targeting compounds are presently available as approved antimicrobial drugs.[12] However, major unpleasant effects and high clinical expenditure associated with these drugs have encouraged investigations of new antimicrobial agents.[13] As a part of green chemistry, microwave-assisted organic synthesis (MAOS) has gained attention in organic and medicinal chemistry. Furthermore, advantages of the synthesis of thiazol-2-amine derivatives *via* copper-catalyzed oxidative coupling of oxime acetates and variously substituted isothiocyanates have been demonstrated in comparison to conventional synthetic methods.[14]

In view of the pharmacological importance of thiazol-2-amine derivatives and in continuation of our previous efforts,[15] we planned to perform a symmetrical construction of thiazole ring at each C-2 position of benzodifuran using 4,6-diacetylresorcinol (DAR) (**1**) as the starting material (Scheme 1). Herein, we present the synthesis of novel 4,4'-(3,5-diphenethylbenzo[1,2-*b*:5,4-*b*']difuran-2,6-diyl)bis-(*N*-(het)arylthiazol-2-amine) derivatives **8a**–**h** by both conventional and microwave-assisted methods and investigation of their *in vitro* antibacterial and antimycobacterial activities.

Compounds **8a**–**h** were prepared from DAR (**1**) which, in turn, was synthesized according to a previously described procedure[16] (Scheme 1). First, the starting material **1** was treated with two equivalents of benzaldehyde in 50% aq KOH solution. Furthermore, the resulting bis(chalcone) **2** was hydrogenated using 10% Pd/C in EtOAc to obtain product **3** which was then treated with chloroacetone in acetone in the presence of K_2CO_3. The resulting compound **4** was used in reaction with $NH_2OH·HCl$ in EtOH under microwave irradiation (MW) to afford dioxime **5**, which was subsequently treated with Ac_2O in EtOH under MW. Reaction of the respective *O*,*O*-diacetyl dioxime **6** and substituted isothiocyanates **7a**–**h** in the presence of Cs_2CO_3 and 20 mol % CuI in 1,4-dioxane under MW ensured the formation of the

Table 1. Yields of the synthesized compounds **8a**–**h***

Compound	Method I**		Method II***	
	Time, h	Yield, %	Time, min	Yield, %
8a	15	78	15	86
8b	18	76	20	82
8c	16	74	20	84
8d	16	72	20	79
8e	12	80	15	90
8f	18	70	25	85
8g	16	75	20	86
8h	16	77	20	89

* Reaction conditions: *O*,*O*-diacetyl dioxime **6** (560 mg, 1 mmol), isothiocyanate **7a**–**h** (2 mmol), CuI (39 mg, 20 mol %), Cs_2CO_3 (163 mg, 0.5 mmol), 1,4-dioxane (10 ml).
** Reflux.
*** Microwave irradiation, 100°C.

desired final compounds **8a**–**h** in high yields (method II). The use of conventional heating for the same reaction (method I) resulted in lower yields of the products (Table 1). The structures of the newly synthesized compounds **3**–**6** and **8a**–**h** were established by spectroscopic (FTIR, ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry) and elemental analysis. The FTIR spectrum of compound **8a** revealed three bands at 3380 (N–H), 1600 (C=N), and 1535 cm^{-1} (C=C). The ^{1}H and ^{13}C NMR spectra of the representative compound **8a** contained characteristic signals of thiazole ring proton at 7.24 ppm and the respective carbon at 105.1 ppm. Finally, the mass spectrum of product **8a** exhibited a peak at 715, which corresponded to its $[M+H]^+$ ion.

The *in vitro* antimicrobial activities of the synthesized novel products **8a**–**h** at the concentration of 50 μg/ml were investigated by the cup-plate agar diffusion method against four pathogenic representative microorganisms: *Staphylococcus aureus* (MTCC 737), *Escherichia coli* (MTCC 443), *Bacillus subtilis* (MTCC 441), and *Pseudomonas aeruginosa* (MTCC 741) using norfloxacin and ofloxacin as the standard drugs. It was found that difuran derivatives **8b**,**e**,**g** (inhibition zone >10 mm) showed excellent growth inhibition against Gram-positive *B. subtilis* strain compared to norfloxacin (10 mm) (Fig. 1). Compounds **8b**,**e** contain *ortho*-substituted aromatic rings with electronegative F and Br atoms, respectively. Thereby, electron-withdrawing groups at *ortho* position increased the activity of the investigated compounds. In the case of compound **8g**, which also exhibited high activity, pyridine was substituted at the C-2 position with a methyl group. Among other difuran derivatives **8a**–**g** and standard ofloxacin, compound **8h** with electron-donating methyl group at the C-4 position of the pyridine ring was exceedingly potent against Gram-negative bacteria strain *P. aeruginosa*. Furthermore, the antibacterial effects of the remaining compounds **8a**,**c**,**d**,**f** on the growth inhibition of the tested bacterial strains were moderate to low. Product **8e** also exhibited excellent *in vitro* antimycobacterial activity against *M. bovis* strain, while compound **8g** showed a moderate zone of inhibition in comparison with the standard drugs (isoniazid + rifampicin) (Fig. 2).

In conclusion, novel symmetrical benzodifuran-based bis(*N*-(het)arylthiazol-2-amine) derivatives have been synthesized in copper-catalyzed oxidative coupling of 1,1'-(3,5-diphenethylbenzo[1,2-*b*:5,4-*b*']difuran-2,6-diyl)diethanone *O*,*O*-diacetyl dioxime and variously substituted isothiocyanates under both conventional and microwave irradiation conditions. The application of microwave irradiation allowed to reduce the reaction time and increase the yield of products, as well as promoted the two-step synthesis of the starting material *O*,*O*-diacetyl dioxime. The obtained benzodifuran-based bis(*N*-(het)arylthiazol-2-amine) derivatives were evaluated for their antibacterial and antimycobacterial activities. Some of these compounds showed noteworthy activity against *B. subtilis* (+ve) and *P. aeruginosa* (–ve) strains and antimycobacterial activity against *M. bovis* strain. The presence of F and Br atoms at *ortho* position of aromatic rings increased the antimycobacterial and antibacterial activity of the investigated compounds against *M. bovis* and *B. subtilis* strains, respectively, and the compound with a methyl group at the C-4 position of the pyridine ring was exceedingly potent against *P. aeruginosa* strain. The results of these studies will likely provide a basis for the design of a new series of promising benzodifuran-based thiazole derivatives. Further development of novel benzodifuran-based bis(*N*-(het)-arylthiazol-2-amine) analogs and investigation of their biological activities are in progress.

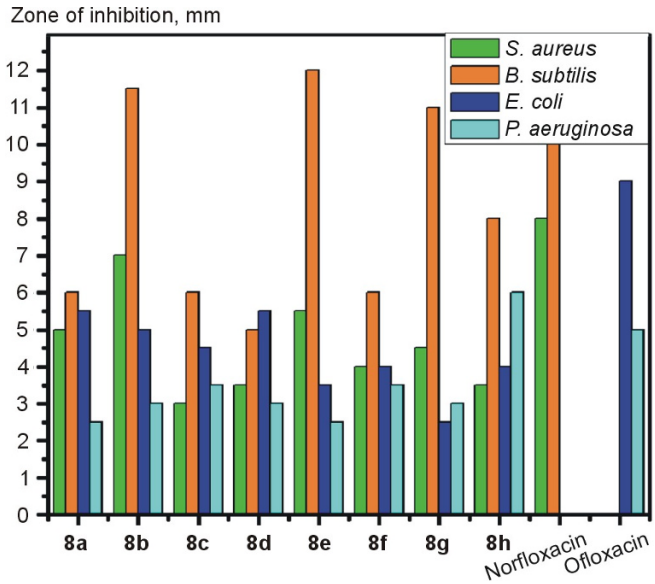


Figure 1. A graphical comparison of the antibacterial activity of the newly synthesized compounds **8a**–**h** and standard drugs nor-

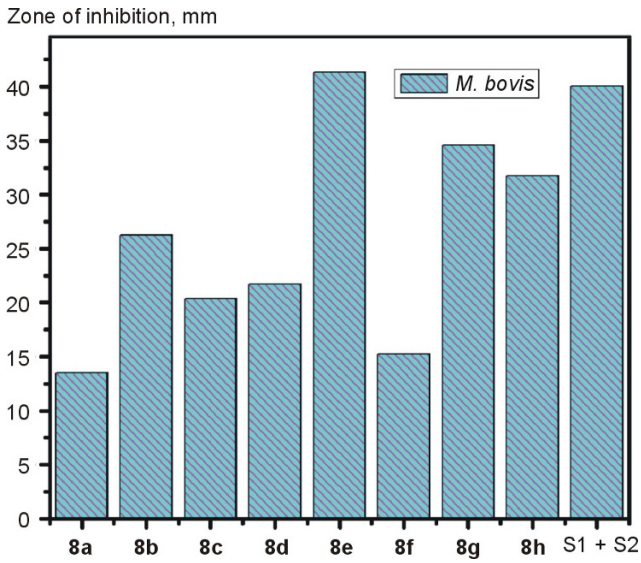


Figure 2. A graphical comparison of the antimycobacterial activity of the newly synthesized compounds **8a**–**h** and standard drugs

Experimental

IR spectra were recorded on a Shimadzu FTIR-8400S spectrometer. ^{1}H and ^{13}C NMR spectra (300 and 75 MHz, respectively) were acquired on a Bruker Avance 300 spectrometer in $CDCl_3$ (compounds **3** and **4**) or DMSO-d_6

(compounds **5**, **6**, and **8a**–**h**) using tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on a Shimadzu LCMS-2020 spectrometer/Agilent Technologies 6420 Triple Quad LC/MS (ESI). 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 reactor (2.45 GHz) with a maximum delivered power of 850 W in 10 W increments (pulsed irradiation). TLC was performed on silica gel-coated Merck $^{60}F_{254}$ plates, and visualization was achieved by exposure to I_2 vapor and UV light (254 nm).

All chemicals were purchased from Sigma-Aldrich, TCI, and Alfa Aesar. Substituted isothiocyanates **7a**–**h**[17] and compound **2**[18] were synthesized as described previously.

1,1'-(4,6-Dihydroxy-1,3-phenylene)bis(3-phenylpropan-1-one) (3). 10% Pd/C (400 mg, 20%) was added to a stirred solution of bis(chalcone) **2** (2.00 g, 5.40 mmol) in EtOAc (20 ml) in Parr hydrogenation bottle, and the bottle was charged with H_2 (30 psi). The reaction mixture was shaken at room temperature for 3 h. The catalyst was then filtered off using a Celite pad. The filtrate was concentrated, and the residue was purified by flash column chromatography (silica gel, gradient elution with EtOAc–hexane, 10–20%). Yield 1.92 g (95%), white solid, mp 88–90°C. IR spectrum, ν, cm^{-1}: 3023 (O–H), 1653 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.04 (4H, t, *J* = 7.4, $C\underline{H}_2CH_2CO$); 3.19 (4H, t, *J* = 7.4, $CH_2C\underline{H}_2CO$); 6.42 (1H, s, H-5); 7.20–7.34 (10H, m, H Ar); 8.04 (1H, s, H-2); 12.98 (2H, s, OH). ^{13}C NMR spectrum, δ, ppm: 30.2; 39.6; 105.0; 113.1; 126.5; 128.4; 128.7; 134.6; 140.4; 168.7; 203.5. Mass spectrum, *m*/*z* (I_{rel}, %): 375 $[M+H]^+$ (100), 130 (30). Found, %: C 76.94; H 5.89. $C_{24}H_{22}O_4$. Calculated, %: C 76.99; H 5.92.

1,1'-(3,5-Diphenethylbenzo[1,2-*b*:5,4-*b*']difuran-2,6-diyl)-diethanone (4). A mixture of 1,1'-(4,6-dihydroxy-1,3-phenylene)bis(3-phenylpropan-1-one) (**3**) (3.74 g, 10 mmol), chloroacetone (1.8 ml, 22 mmol), and K_2CO_3 (4.14 g, 30 mmol) in dry acetone (50 ml) was refluxed for 6 h. The reaction mixture was then quenched with crushed ice and extracted with EtOAc (2×50 ml). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated, and purified by column chromatography (silica gel, gradient elution with EtOAc–hexane, 20–30%). Yield 4.05 g (90%), white solid, mp 138–140°C. IR spectrum, ν, cm^{-1}: 3087 (C–H Ar), 2923 (CH_3), 1670 (C=O), 1571 (C=C). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.62 (6H, s, CH_3); 2.95 (4H, t, *J* = 7.9, $CH_2C\underline{H}_2Ph$); 3.36 (4H, t, *J* = 7.9, $C\underline{H}_2CH_2Ph$); 7.16–7.27 (11H, m, H Ar); 7.56 (1H, s, H-4). ^{13}C NMR spectrum, δ, ppm: 26.4; 27.8; 35.6; 94.9; 113.6; 126.2; 126.4; 127.8; 128.3; 128.6; 141.3; 148.8; 154.3; 190.8. Mass spectrum, *m*/*z* (I_{rel}, %): 451 $[M+H]^+$ (100). Found, %: C 79.94; H 5.78. $C_{30}H_{26}O_4$. Calculated, %: C 79.98; H 5.82.

1,1'-(3,5-Diphenethylbenzo[1,2-*b*:5,4-*b*']difuran-2,6-diyl)-diethanone dioxime (5). A solution of 1,1'-(3,5-diphenethylbenzo[1,2-*b*:5,4-*b*']difuran-2,6-diyl)diethanone (**4**) (450 mg, 1 mmol) and $NH_2OH{\cdot}HCl$ (139 mg, 2 mmol) in EtOH (10 ml) was placed into a microwave tube and subjected to microwave irradiation at 100°C for 30 min. The reaction mixture was then quenched with crushed ice. The resulting solid was filtered off, washed with Et_2O (10 ml), and dried under reduced pressure. Yield 441 mg (92%), off-white solid, mp 216–218°C. IR spectrum, ν, cm^{-1}: 3095 (C–H Ar), 3027 (O–H), 2927 (CH_3), 1673 (C=N), 1579 (C=C). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.19 (6H, s, CH_3); 2.90 (4H, t, *J* = 7.6, $CH_2C\underline{H}_2Ph$); 3.20 (4H, t, *J* = 7.6, $C\underline{H}_2CH_2Ph$); 7.13–7.20 (2H, m, H Ar); 7.24–7.32 (8H, m, H Ar); 7.41 (1H, s, H-8); 7.74 (1H, s, H-4); 11.61 (2H, s, OH). ^{13}C NMR spectrum, δ, ppm: 11.5; 25.6; 34.9; 93.8; 109.5; 117.1; 125.8; 126.1; 128.0; 128.5; 141.6; 148.0; 148.2; 151.6. Mass spectrum, *m*/*z* (I_{rel}, %): 481 $[M+H]^+$ (100). Found, %: C 74.94; H 5.83; N 5.85. $C_{30}H_{28}N_2O_4$. Calculated, %: C 74.98; H 5.87; N 5.83.

1,1'-(3,5-Diphenethylbenzo[1,2-*b*:5,4-*b*']difuran-2,6-diyl)-diethanone *O*,*O*-diacetyl dioxime (6). A solution of 1,1'-(3,5-diphenethylbenzo[1,2-*b*:5,4-*b*']difuran-2,6-diyl)diethanone dioxime (**5**) (480 mg, 1 mmol) and Ac_2O (0.19 ml, 2 mmol) in EtOH (10 ml) was placed into a microwave tube and subjected to microwave irradiation at 100°C for 30 min. The reaction mixture was then quenched with crushed ice. The resulting solid was filtered off, triturated with MeOH (10 ml), repeatedly filtered off, and dried under reduced pressure. Yield 540 mg (96%), white solid, mp 192–194°C. IR spectrum, ν, cm^{-1}: 3018 (C–H Ar), 2920 (CH_3), 1767 (C=O), 1622 (C=N), 1579 (C=C). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.30 (6H, s, CH_3CO_2); 2.40 (6H, s, CH_3); 2.99 (4H, t, *J* = 7.6, $CH_2C\underline{H}_2Ph$); 3.33 (4H, t, *J* = 7.6, $C\underline{H}_2CH_2Ph$); 7.13–7.20 (2H, m, H Ar); 7.21 (1H, s, H-8); 7.23–7.31 (8H, m, H Ar); 7.50 (1H, s, H-4). ^{13}C NMR spectrum, δ, ppm: 13.4; 19.8; 26.8; 35.4; 94.1; 110.6; 122.0; 126.0; 126.6; 128.2; 128.8; 141.9; 146.0; 153.5; 156.5; 168.4. Mass spectrum, *m*/*z* (I_{rel}, %): 565 $[M+H]^+$ (25), 505 (100). Found, %: C 72.28; H 5.67; N 4.98. $C_{34}H_{32}N_2O_6$. Calculated, %: C 72.32; H 5.71; N 4.96.

Synthesis of benzodifuran derivatives 8a–h (General method). Substituted isothiocyanate **7a**–**h** (2 mmol), CuI (39 mg, 20 mol %), and Cs_2CO_3 (163 mg, 0.5 mmol) were added to a stirred solution of 1,1'-(3,5-diphenethylbenzo-[1,2-*b*:5,4-*b*']difuran-2,6-diyl)diethanone *O*,*O*-diacetyl dioxime (**6**) (560 mg, 1 mmol) in 1,4-dioxane (10 ml). The reaction was performed according to method I or II. After completion of the reaction, the reaction mixture was concentrated under reduced pressure, and the obtained residue was subjected to column chromatography (basic alumina, gradient elution with EtOAc–hexane, 30–40%).

Method I. The reaction mixture was refluxed for 12–18 h (Table 1).

Method II. The reaction mixture was placed into a microwave tube and subjected to microwave irradiation at 100°C for 15–25 min (Table 1).

4,4'-(3,5-Diphenethylbenzo[1,2-*b*:5,4-*b*']difuran-2,6-diyl)bis(*N*-phenylthiazol-2-amine) (8a). Off-white solid, mp 170–172°C. IR spectrum, ν, cm^{-1}: 3380 (N–H), 1600 (C=N), 1535 (C=C), 1350 (C–N), 748 (C–S). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.96–3.10 (4H, m, $CH_2C\underline{H}_2Ph$); 3.48–3.64 (4H, m, $C\underline{H}_2CH_2Ph$); 6.90 (2H, t, *J* = 7.4, H Ar); 7.14 (4H, t, *J* = 7.4, H Ar); 7.18–7.37 (14H, m, H thiazole,

H Ar); 7.39 (1H, s, H-8); 7.67 (2H, d, J = 7.4, H Ar); 7.72 (1H, s, H-4); 10.38 (2H, s, NH). ^{13}C NMR spectrum, δ, ppm: 24.6; 35.5; 93.4; 105.1; 109.1; 115.6; 116.7; 121.1; 125.8; 126.3; 128.1; 128.4; 128.8; 140.8; 141.5; 142.3; 146.7; 151.8; 163.6. Mass spectrum, *m/z* (I_{rel}, %): 715 $[M+H]^+$ (100). Found, %: C 73.88; H 4.74; N 7.86. $C_{44}H_{34}N_4O_2S_2$. Calculated, %: C 73.92; H 4.79; N 7.84.

4,4'-(3,5-Diphenethylbenzo[1,2-*b*:5,4-*b*']difuran-2,6-diyl)bis[*N*-(2-fluorophenyl)thiazol-2-amine] (8b). Off-white solid, mp 108–110°C. IR spectrum, ν, cm^{-1}: 3434 (N–H), 1620 (C=N), 1542 (C=C), 1349 (C–N), 745 (C–S). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.94–3.06 (4H, m, $CH_2C\underline{H}_2Ph$); 3.44–3.56 (4H, m, $C\underline{H}_2CH_2Ph$); 6.76 (2H, t, J = 7.9, H Ar); 6.82–7.01 (2H, m, H Ar); 7.16–7.37 (15H, m, H thiazole, H Ar); 7.70 (1H, s, H-4); 8.42 (2H, t, J = 7.9, H Ar); 10.20 (2H, s, NH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 24.6; 35.5; 93.4; 106.3; 109.1; 115.0 (d, $^2J_{CF}$ = 18.6, C Ar); 115.5; 121.9 (d, $^3J_{CF}$ = 6.5, C Ar); 124.3; 125.7 (d, $^2J_{CF}$ = 18.6, C Ar); 125.8; 126.3; 128.0; 128.2 (d, $^3J_{CF}$ = 12.6, C Ar); 141.2; 141.5; 141.9; 146.6; 151.5 (d, $^1J_{CF}$ = 243.7, C Ar); 151.8; 163.6. Mass spectrum, *m/z* (I_{rel}, %): 751 $[M+H]^+$ (48), 102 (100). Found, %: C 70.33; H 4.27; N 7.48. $C_{44}H_{32}F_2N_4O_2S_2$. Calculated, %: C 70.38; H 4.30; N 7.46

4,4'-(3,5-Diphenethylbenzo[1,2-*b*:5,4-*b*']difuran-2,6-diyl)bis[*N*-(4-fluorophenyl)thiazol-2-amine] (8c). Off-white solid, mp 102–104°C. IR spectrum, ν, cm^{-1}: 3389 (N–H), 1614 (C=N), 1538 (C=C), 1349 (C–N), 753 (C–S). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.03 (4H, t, J = 7.2, $CH_2C\underline{H}_2Ph$); 3.54 (4H, t, J = 7.2, $C\underline{H}_2CH_2Ph$); 6.82 (4H, t, J = 8.5, H Ar); 7.22–7.32 (12H, m, H thiazole, H Ar); 7.43 (1H, s, H-8); 7.64 (4H, dd, J = 8.5, J = 4.7, H Ar); 7.71 (1H, s, H-4); 10.39 (2H, s, NH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 24.2; 35.3; 93.4; 105.0; 109.2; 115.3 (d, $^2J_{CF}$ = 9.9, C Ar); 115.7; 118.2 (d, $^3J_{CF}$ = 7.1, C Ar); 125.8; 126.3; 128.1; 128.3; 137.3 (d, $^4J_{CF}$ = 2.2, C Ar); 141.6; 142.2; 146.6; 151.8; 156.7 (d, $^1J_{CF}$ = 237.6, C Ar); 163.6. Mass spectrum, *m/z* (I_{rel}, %): 751 $[M+H]^+$ (100). Found, %: C 70.34; H 4.26; N 7.49. $C_{44}H_{32}F_2N_4O_2S_2$. Calculated, %: C 70.38; H 4.30; N 7.46.

4,4'-(3,5-Diphenethylbenzo[1,2-*b*:5,4-*b*']difuran-2,6-diyl)bis[*N*-(3-chloro-4-fluorophenyl)thiazol-2-amine] (8d). Off-white solid, mp 140–142°C. IR spectrum, ν, cm^{-1}: 3384 (N–H), 1604 (C=N), 1535 (C=C), 1349 (C–N), 745 (C–S). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.98 (4H, t, J = 7.2, $CH_2C\underline{H}_2Ph$); 3.44–3.53 (4H, m, $C\underline{H}_2CH_2Ph$); 6.99 (2H, t, J = 9.1, H Ar); 7.13–7.22 (10H, m, H Ar); 7.24 (2H, s, H thiazole); 7.46–7.58 (3H, m, H Ar); 7.61 (1H, s, H-4); 7.94 (2H, t, J = 6.4, H Ar); 10.54 (2H, s, NH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 24.5; 35.5; 93.1; 105.3; 109.0; 115.6; 116.6 (d, $^2J_{CF}$ = 21.4, C Ar); 117.9 (d, $^3J_{CF}$ = 6.7, C Ar); 119.1 (d, $^3J_{CF}$ = 7.7, C Ar); 124.4 (d, $^2J_{CF}$ = 18.7, C Ar); 125.7; 127.9; 128.3; 137.9; 141.4; 141.7; 142.2; 146.4; 151.7; 151.8 (d, $^1J_{CF}$ = 239.8, C Ar); 163.1. Mass spectrum, *m/z* (I_{rel}, %): 819 $[M]^+$ (30), 232 (100). Found, %: C 64.43; H 3.67; N 6.85. $C_{44}H_{30}Cl_2F_2N_4O_2S_2$. Calculated, %: C 64.47; H 3.69; N 6.83.

4,4'-(3,5-Diphenethylbenzo[1,2-*b*:5,4-*b*']difuran-2,6-diyl)-bis[*N*-(2-bromophenyl)thiazol-2-amine] (8e). Off-white solid, mp 206–208°C. IR spectrum, ν, cm^{-1}: 3379 (N–H), 1590 (C=N), 1535 (C=C), 1353 (C–N), 744 (C–S). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.91 (4H, t, J = 7.4, $CH_2C\underline{H}_2Ph$); 3.37–3.48 (4H, m, $C\underline{H}_2CH_2Ph$); 6.97 (2H, t, J = 7.6, H Ar); 7.08 (2H, t, J = 7.6, H Ar); 7.18–7.23 (10H, m, H Ar); 7.28 (2H, s, H thiazole); 7.34 (1H, s, H-8); 7.65 (2H, t, J = 7.6, H Ar); 7.70 (1H, s, H-4); 8.18 (2H, d, J = 7.6, H Ar); 9.69 (2H, s, NH). ^{13}C NMR spectrum, δ, ppm: 24.9; 35.5; 93.4; 106.5; 109.1; 113.7; 115.6; 122.3; 124.4; 125.7; 126.3; 128.0; 128.2; 128.4; 132.8; 138.6; 141.6; 141.8; 146.6; 151.8; 164.5. Mass spectrum, *m/z* (I_{rel}, %): 873 $[M]^+$ (100). Found, %: C 60.51; H 3.66; N 6.44. $C_{44}H_{32}Br_2N_4O_2S_2$. Calculated, %: C 60.56; H 3.70; N 6.42.

4,4'-(3,5-Diphenethylbenzo[1,2-*b*:5,4-*b*']difuran-2,6-diyl)bis[*N*-(morpholin-4-ylphenyl)thiazol-2-amine] (8f). Off-white solid, mp 218–220°C. IR spectrum, ν, cm^{-1}: 3293 (N–H), 1601 (C=N), 1537 (C=C), 1350 (C–N), 746 (C–S). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.85–2.99 (4H, m, $CH_2C\underline{H}_2Ph$); 3.05–3.11 (8H, m, $NC\underline{H}_2CH_2O$); 3.48–3.63 (4H, m, $C\underline{H}_2CH_2Ph$); 3.68–3.79 (8H, m, $NCH_2C\underline{H}_2O$); 6.59 (4H, d, J = 7.7, H Ar); 7.13–7.38 (12H, m, H thiazole, H Ar); 7.43 (1H, s, H-8); 7.51 (4H, d, J = 7.7, H Ar); 7.70 (1H, s, H-4); 10.13 (2H, s, NH). ^{13}C NMR spectrum, δ, ppm: 24.0; 35.3; 49.2; 66.0; 93.4; 105.1; 109.1; 115.2; 115.8; 117.9; 124.8; 125.7; 128.1; 128.3; 130.4; 133.6; 141.6; 142.3; 145.8; 151.8; 163.9. Mass spectrum, *m/z* (I_{rel}, %): 885 $[M+H]^+$ (30), 668 (100). Found, %: C 70.52; H 5.42; N 9.50. $C_{52}H_{48}N_6O_4S_2$. Calculated, %: C 70.56; H 5.47; N 9.49.

4,4'-(3,5-Diphenethylbenzo[1,2-*b*:5,4-*b*']difuran-2,6-diyl)bis[*N*-(6-methylpyridin-2-yl)thiazol-2-amine] (8g). Off-white solid, mp 160–162°C. IR spectrum, ν, cm^{-1}: 3259 (N–H), 1608 (C=N), 1537 (C=C), 1328 (C–N), 734 (C–S). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.56 (6H, s, CH_3); 3.01 (4H, t, J = 7.2, $CH_2C\underline{H}_2Ph$); 3.54 (4H, t, J = 7.2, $C\underline{H}_2CH_2Ph$); 6.82 (2H, d, J = 7.7, H pyridine); 6.99 (2H, d, J = 7.7, H pyridine); 7.15 (2H, t, J = 7.4, H Ar); 7.26 (4H, d, J = 7.4, H Ar); 7.31 (2H, s, H thiazole); 7.35 (4H, d, J = 7.4, H Ar); 7.42 (1H, s, H-8); 7.61 (2H, t, J = 7.7, H pyridine); 7.73 (1H, s, H-4); 11.31 (2H, s, NH). ^{13}C NMR spectrum, δ, ppm: 23.4; 25.0; 35.4; 93.7; 107.6; 108.3; 109.2; 115.1; 115.3; 125.8; 126.3; 128.1; 128.6; 138.2; 140.9; 141.6; 147.1; 151.3; 153.3; 155.1; 159.9. Mass spectrum, *m/z* (I_{rel}, %): 745 $[M+H]^+$ (100). Found, %: C 70.90; H 4.83; N 11.30. $C_{44}H_{36}N_6O_2S_2$. Calculated, %: C 70.94; H 4.87; N 11.28.

4,4'-(3,5-Diphenethylbenzo[1,2-*b*:5,4-*b*']difuran-2,6-diyl)bis[*N*-(4-methylpyridin-2-yl)thiazol-2-amine] (8h). Brown solid, mp 184–186°C. IR spectrum, ν, cm^{-1}: 3200 (N–H), 1616 (C=N), 1536 (C=C), 1303 (C–N), 744 (C–S). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.30 (6H, s, CH_3); 3.01 (4H, t, J = 7.6, $CH_2C\underline{H}_2Ph$); 3.53 (4H, t, J = 7.6, $C\underline{H}_2CH_2Ph$); 6.81 (2H, d, J = 5.1, H pyridine); 7.01 (2H, s, H pyridine); 7.15 (2H, t, J = 7.4, H Ar); 7.24 (4H, d, J = 7.4, H Ar); 7.28 (2H, s, H thiazole); 7.35 (4H, d, J = 7.4, H Ar); 7.42 (1H, s, H-8); 7.72 (1H, s, H-4); 8.19 (2H, t, J = 5.1, H pyridine); 11.30 (2H, s, NH). ^{13}C NMR spectrum, δ, ppm: 20.7; 25.1; 35.4; 93.4; 108.2; 109.1; 110.7; 115.3; 117.6; 125.8; 126.3; 128.1; 128.6; 140.9;

141.6; 146.0; 147.1; 148.5; 151.7; 151.8; 160.0. Mass spectrum, *m*/*z* (I_{rel}, %): 745 $[M+H]^+$ (80), 373 (100). Found, %: C 70.89; H 4.82; N 11.29. $C_{44}H_{36}N_6O_2S_2$. Calculated, %: C 70.94; H 4.87; N 11.28.

Antibacterial activity assay.[19] *P. aeruginosa* (Gram-negative), *E. coli* (Gram-negative), *B. subtilis* (Gram-positive), and *S. aureus* (Gram-positive) were obtained from the Microbial Type Culture Collection. The microbes were inoculated in an autoclaved Lysogeny broth media and incubated overnight at 37°C in a shaker for bacterial growth. An aliquot (0.2 ml) of the bacterial culture was taken and inoculated on freshly prepared autoclaved agar plates (Petri dishes) using spreader. After drying of the plates, 5 mm sample discs, dissolved in DMSO (50 μg/ml), were put on the microbial plate along with the standard drugs – norfloxacin and ofloxacin. The samples were incubated overnight at 37°C in Biochemical Oxygen Demand incubator and zone of inhibition was then measured by a measuring scale.

Antimycobacterial activity assay. Isolated single colonies of *M. bovis*, Middlebrook 7H10 agar plates, and 7H9 medium were used. The activity was assayed by the turbidimetry method[20] using isoniazid + rifampicin as the standard.

The Supplementary information file, containing IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data of compounds **3**–**6** and **8a**–**h**, is available at the journal website at http://link.springer.com/journal/10593.

The authors are grateful to the Head of Department of Chemistry, Osmania University, Hyderabad and IICT, Hyderabad for providing analytical and biological facilities. D. Ashok is also thankful to DST, PURSE-II programme, Osmania University for the financial assistance. Ananda Rao thanks CSIR, New Delhi, India for the research associate fellowship.

The authors are thankful to Chemveda Life Sciences Pvt. Ltd., IDA, Uppal, and Hyderabad for providing laboratory facilities.

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