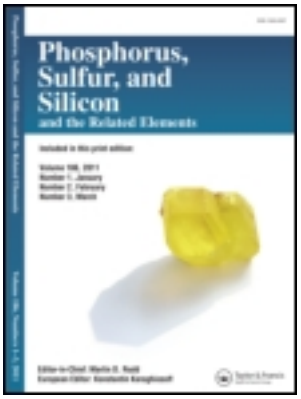

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Synthesis and Antimicrobial Evaluation of 1-{3-[(Furan-2-Ylmethyl)Sulfanyl] Propanoyl}-4-Substituted Thiosemicarbazides and their Products of Cyclization to 1,2,4-Triazole Ring

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SYNTHESIS AND ANTIMICROBIAL EVALUATION OF 1-{3-[(FURAN-2-YLMETHYL)SULFANYL] PROPANOYL}-4-SUBSTITUTED THIOSEMICARBAZIDES AND THEIR PRODUCTS OF CYCLIZATION TO 1,2,4-TRIAZOLE RING

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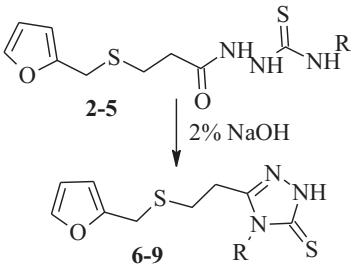
GRAPHICAL ABSTRACT



Abstract *By the reaction of 3-[(furan-2-ylmethyl)sulfanyl]propanoylhydrazide with various isothiocyanates, the corresponding 4-substituted 1-[(furan-2-ylmethyl)sulfanyl] propanoylthiosemicarbazide derivatives (**2–5**) were obtained. Thiosemicarbazide derivatives (**2–5**) by ring closure with 2% NaOH, provided 5-{2-[(furan-2-ylmethyl)sulfanyl]ethyl}-4-substituted-2,4-dihydro-3H-1,2,4-triazole-3-thiones (**6–9**). The new compounds were tested for their in vitro antimicrobial activity. Compounds **2, 3,** and **6** had in vitro activity against Gram-positive reference strains of bacteria with MIC values: 250–500 μg/mL (for compound 2), 125–250 μg/mL (for compound 3), 500–1000 μg/mL (for compound 6).*

[Supplementary materials are available for this article. Go to the publisher's online edition of Phosphorus, Sulfer, and Silicon and the Related Elements *for the following free supplemental files: Additional tables.]*

Keywords Furan derivatives; 1,2,4-triazole ring; antimicrobial activity

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INTRODUCTION

1,2,4-Triazoles are building blocks for many drugs such as Alprazolam, Estazolam, Fluconazole, and Vibunazole. Depending of the nature of substitutents, the 1,2,4-triazole derivatives can show various biological activities, such as analgesic,[1] anti-inflammatory,[2] anticancer,[3] antibacterial, [4,5] and antiviral properties.[6] In addition; 1,2,4-triazole-3-thiones derivatives with a furan ring have been reported as antibacterial,[7,8] antifungal,[9] antinociceptive, [10] and plant-growth regulative substances.[11] Besides, many drugs include a furan ring, such as Ranitidine (histamine H_2-receptor antagonist), and are used in the treatment of peptic ulcer disease;[12] Nitrofurazone, Nitrofurantoin, Furazolidone, Nifurtoinol, Nifurzide, and Nifuratel are used as antimicrobial drugs.[13] The design of new compounds contains the modification of molecules by the combinations of different pharmacophores in one frame, which may lead to the formation of new compounds with higher biological activity. In view of these facts and in continuation of our earlier research on antimicrobial activity of thiosemicarbazide and 1,2,4-triazole derivatives,[14] we connected a furan ring with 1,2,4-triazole heterocyclic systems that could help to increase the biological activity. The newly synthesized compounds were tested for their in vitro antimicrobial activity.

RESULT AND DISCUSSION

Chemistry

In the present study, 3-[(furan-2-ylmethyl)sulfanyl]propanoylhydrazide (**1**) was used as a starting material. This hydrazide was obtained by the reaction of ethyl ester of 3-[(furan-2-ylmethyl)sulfanyl]propanoic acid with hydrazine hydrate by the method described earlier.[15] The reaction of 3-[(furan-2-ylmethyl)sulfanyl]propanoylhydrazide with various isothiocyanates yield the corresponding 4-substituted 1-[(furan-2-ylmethyl) sulfanyl]propanoylthiosemicarbazide derivatives (**2–5**). Ring closure with 2% NaOH provided 5-{2-[(furan-2-ylmethyl)sulfanyl]ethyl}-4-substituted-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones (**6–9**). The reaction proceeded according to the Figure 1.

The structures of the newly synthesized compounds (**2–9**) were confirmed by elemental analysis, IR, ^{1}H NMR, and ^{13}C NMR methods.

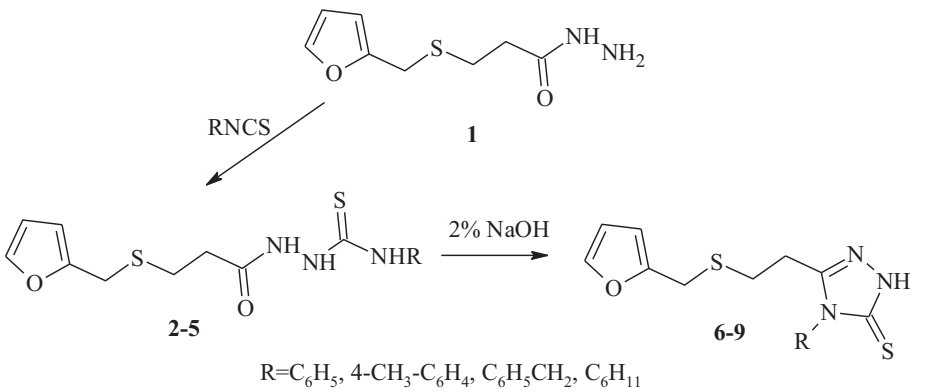

Figure 1 Synthesis of 1-[(furan-2-ylmethyl)sulfanyl]propanoyl-4-substituted thiosemicarbazide derivatives and reaction of their cyclization.

In the IR spectra, absorption bands characteristic for fragments: C=O for compounds (**2–5**) and C=S for compounds (**2–9**) are visible in the ranges of: 1675–1693 cm^{-1} and 1310–1340 cm^{-1}, respectively.

In the ^1H NMR spectra, all the compounds showed proton signals typical for furan ring in the range of 6.13–7.58 ppm. For the thiosemicarbazides (**2–5**), the signals of proton linked to nitrogens were shown at 7.26–9.99 ppm. Cyclic compounds (**6–9**) showed proton signals in the range 13.52–13.75 ppm, that is typical for the NH group of the 1,2,4-triazole ring.

The δ values of the carbons of the furan ring were in the range 107.6–107.7, 110.5–110.6, 142.4–142.5, and 151.2–151.6 ppm. In the thiosemicarbazide derivatives (2–5), the signals of C=S and C=O groups were observed in the range 170.1–170.3 and 180.7–180.8 ppm, respectively. All the 1,2,4-triazole derivatives (**6–9**) showed the carbon signals of C=S group in the range 166.1–167.7 ppm.

The detailed results of IR, ^1H NMR, and ^{13}C NMR spectra are presented in the experimental part.

Microbiology

The results of antibacterial in vitro activity of the newly synthesized compounds obtained using the agar dilution method did not show very significant effects against most of the examined microorganisms. It was found that the tested compounds were not active against Gram-negative bacteria and due majority of Gram-positive bacteria. Only compounds **2**, **3** with phenyl and 4-methylphenyl substituent respectively and **6** with phenyl substituent showed moderate activity against Gram-positive bacteria with MIC values from 125 to 1000 μg/mL (Table S1 Supplemental Materials). The most sensitive bacteria was *B. subtilis*. Three compounds had bactericidal effect toward this bacteria strain (MBC/MIC = 1 or 2).

Compounds **2** and **3** showed promising activity against *Micrococcus luteus* with MIC 250 and 125, respectively. But, on the basis of MBC/MIC ratio, it was found that these compounds have bacteriostatic effect (MBC/MIC = 4 or 8).

EXPERIMENTAL

Chemistry

Melting points were determined in a Fischer-Johns block (Sanyo, Japan) and are not corrected. The IR spectra were recorded in KBr using a Thermo Nicolet 6700 FT-IR spectrometer. The ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance DPX 250, in DMSO-d_6, using tetramethylsilane as internal standard. The purity of all compounds was checked by TLC on aluminium oxide 60 F_{254} plates (Merck), in a $CHCl_3/C_2H_5OH$ (10:1, v/v) solvent system with UV visualization ($\lambda = 254$ nm). Elemental microanalysis for C, H, N was performed on AMZ 851 CHX analyzer and the results were within $\pm$ 0.4% of theoretical values.

Synthesis of 1-{3-[(furan-2-ylmethyl)sulfanyl]propanoyl}-4-substituted Thiosemicarbazides (2–5)

General procedure. To 3-[(furan-2-ylmethyl)sulfanyl]propanoylhydrazide 0.005 mol, corresponding isothiocyanate (phenyl isothiocyanate, 4-methylphenyl isothiocyanate, benzyl isothiocyanate and cyclohexyl isothiocyanate) 0.005 mol was added. Then the

mixture was heated in an oil bath at 60°C for 12 h. The obtained products were washed with diethyl ether, dried, and recrystallized from ethanol.

1-{3-[(furan-2-ylmethyl)sulfanyl]propanoyl}-4-phenylthiosemicarbazide (2)

Yield 60%, mp 104–106°C. IR (KBr) ν(cm^{-1}): 3229 (NH); 3136 ($CH_{ar.}$); 2958 ($CH_{al.}$); 1689 (C=O); 1327 (C=S). ^{1}H NMR (DMSO-d$_6$) δ (ppm): 2.44, 2.69 (2m, 4H, CH_2CH_2S); 3.82 (s, 2H, CH_2S); 6.29, 6.39 (2d, 2H, furan ring, $J = 2.5$ Hz); 7.29 (m, 5H, C_6H_5); 7.58 (m, 1H, furan ring); 9.61, 9.91, 9.99 (3s, 3H, 3NH). ^{13}C NMR (DMSO-d$_6$) δ (ppm): 26.2, 27.1, 33.2 ($3CH_2$), 107.4, 110.4 (2C, furan ring), 127.8, 129.4, 129.7, 131.3 ($4C_{ar.}$), 142.4, 151.3 (2C, furan ring), 170.1 (C=S), 180.7 (C=O). Elemental anal. (%), Calcd for $C_{15}H_{17}N_3O_2S_2$ (335.44): C 53.71, H 5.11, N 12.53; Found: C 53.64, H 5.13, N 12.60

1-{3-[(furan-2-ylmethyl)sulfanyl]propanoyl}-4-(4-methylphenyl) thiosemicarbazide (3)

Yield 62%, mp 127–130°C. IR (KBr) ν(cm^{-1}): 3237 (NH); 3134 ($CH_{ar.}$); 2960 ($CH_{al.}$); 1693 (C=O); 1325 (C=S). ^{1}H NMR (DMSO-d$_6$) δ (ppm): 2.27 (s, 3H, CH_3); 2.42, 2.65 (2m 4H, CH_2CH_2S); 3.78 (s, 2H, CH_2S); 6.28, 6.39 (2d, 2H, furan ring, $J = 2.5$ Hz); 7.12 (d, 2H, 4-$CH_3C_6H_4$, $J = 7.5$ Hz); 7.27 (d, 2H, 4-$CH_3C_6H_4$, $J = 7.5$ Hz); 7.57 (s, 1H, furan ring); 9.40, 9.53, 9.96 (3s, 3H, 3NH). ^{13}C NMR (DMSO-d$_6$) δ (ppm): 20.5 (CH_3), 26.4, 27.2, 33.5 ($3CH_2$), 107.6, 110.6 (2C, furan ring), 125.3, 128.6, 134.3, 136.4 ($4C_{ar.}$), 142.5, 151.5 (2C, furan ring), 170.3 (C=S), 180.8 (C=O). Elemental anal. (%), Calcd for $C_{16}H_{19}N_3O_2S_2$ (349.47): C 54.99, H 5.48, N 12.02; Found: C 54.82, H 5.45, N 12.00

4-benzyl-1-{3-[(furan-2-ylmethyl)sulfanyl]propanoyl}thiosemicarbazide (4)

Yield 58%, mp 90–93°C. IR (KBr) ν(cm^{-1}): 3236 (NH); 3133 ($CH_{ar.}$); 2949 ($CH_{al.}$); 1690 (C=O); 1322 (C=S). ^{1}H NMR (DMSO-d$_6$) δ (ppm): 2.40, 2.64 (2m, 4H, CH_2CH_2S); 3.73 (s, 2H, CH_2S); 4.27 (s, 2H, $CH_2C_6H_5$); 6.26 (d,1H, furan ring, $J = 3.1$ Hz); 6.37 (m, 1H, furan ring); 7.21 (m, 5H, C_6H_5); 7.56 (m, 1H, furan ring); 8.32, 9.23, 9.83 (3s, 3H, 3NH). ^{13}C NMR (DMSO-d$_6$) δ (ppm): 25.3, 26.4, 27.0, 46.2 ($4CH_2$), 107.6, 110.5 (2C, furan ring), 126.3, 127.6, 128.5, 135.1 ($4C_{ar.}$), 142.5 (C, furan ring), 151.4 (C, furan ring), 170.2 (C=S) 180.6 (C=O). Elemental anal. (%), Calcd for $C_{16}H_{19}N_3O_2S_2$ (349.47): C 54.99, H 5.48, N 12.02; Found: C 54.87, H 5.51, N 11.98

4-cyclohexyl-1-{3-[(furan-2-ylmethyl)sulfanyl]propanoyl} thiosemicarbazide (5)

Yield 52%, mp 116–118°C. IR (KBr) ν(cm^{-1}): 3240 (NH); 3136 ($CH_{ar.}$); 2929, 2852 ($CH_{al.}$); 1675 (C=O); 1333 (C=S). ^{1}H NMR (DMSO-d$_6$) δ (ppm): 1.20, 1.67 (2m, 10H, cyclohexyl); 2.41, 2.68 (2m, 4H, CH_2CH_2S); 3.81 (s, 2H, CH_2S); 4.02 (s, 1H, cyclohexyl); 6.28 (d, 1H, furan ring, $J = 3.2$ Hz); 6.38, 7.58 (2m, 2H, furan ring); 7.26, 9.16, 9.76 (3s, 3H, 3NH). ^{13}C NMR (DMSO-d$_6$) δ (ppm): 24.6, 24.8 ($2CH_2$, cyclohexyl), 25.0, 26.7, 27.0 ($3CH_2$), 31.6, 52.6 ($2CH_2$, cyclohexyl), 107.7, 110.6, 142.5, 151.3 (4C, furan ring), 170.0

(C=S), 180.7 (C=O). Elemental anal. (%), Calcd for $C_{15}H_{23}N_3O_2S_2$ (341.49): C 52.76, H 6.79, N 12.31; Found: C 52.82, H 6.71, N 12.27

Synthesis of 5-{2-[(furan-2-ylmethyl)sulfanyl]ethyl}-4-substituted-2,4-dihydro-3H-1,2,4-triazole-3-thiones (6–9)

General procedure. To compounds **2–5** 0.005 mol 2% solution of NaOH 10 mL was added. The mixture was refluxed for 2 h. The solution was filtered off. After cooling filtrate was acidified by diluted HCl to pH = 3–4. The resulting precipitate was recrystallized from ethanol.

5-{2-[(furan-2-ylmethyl)sulfanyl]ethyl}-4-phenyl-2,4-dihydro-3H-1,2,4-triazole-3-thione (6)

Yield 57%, mp 118–120°C. IR (KBr) ν(cm^{-1}): 3090, 3040 ($CH_{ar.}$); 2923 ($CH_{al.}$); 1340 (C=S). ^{1}H NMR (DMSO-d$_6$) δ (ppm): 2.65 (m, 4H, CH_2CH_2S); 3.67 (s, 2H, CH_2S); 6.15, 6.33 (2m, 2H, furan ring); 7.51 (dd, 1H, furan ring, $J = 1.8$ Hz, $J = 0.8$ Hz); 7.38, 7.56 (2m, 5H, C_6H_5); 13.75 (s, 1H, NH). ^{13}C NMR (DMSO-d$_6$) δ (ppm): 26.0, 27.0, 27.2 ($3CH_2$); 107.6, 110.5 (2C, furan ring), 128.2, 129.5, 129.6, 133.5 ($4C_{ar.}$), 142.5 (C, furan ring), 150.8 (C=N), 151.2 (C, furan ring), 167.7 (C=S). Elemental anal. (%), Calcd for $C_{15}H_{15}N_3OS_2$ (317.43): C 56.76, H 4.76, N 13.24; Found: C 56.68, H 4.69, N 13.25

5-{2-[(furan-2-ylmethyl)sulfanyl]ethyl}-4-(4-methylphenyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (7)

Yield 78%, mp 110–112°C. IR (KBr) ν(cm^{-1}): 3112, 3055 ($CH_{ar.}$); 2947 ($CH_{al.}$); 1318 (C=S). ^{1}H NMR (DMSO-d$_6$) δ (ppm): 2.38 s (3H, CH_3); 2.58, 2.63 (2m, 4H, CH_2CH_2S); 3.67 (s, 2H, CH_2S); 6.14 (dd, 1H, furan ring, $J = 3.2$ Hz, $J = 0.8$ Hz); 6.33 (dd, 1H, furan ring, $J = 3.2$ Hz, $J = 1.9$ Hz); 7.24, 7.35 (dd, 4H, 4-$CH_3C_6H_4$, $J = 7.5$ Hz); 7.51 (dd, 1H, furan ring, $J = 1.9$ Hz, $J = 0.9$ Hz); 13.71 s (1H, NH). ^{13}C NMR (DMSO-d$_6$) δ (ppm):20.8 (CH_3), 26.0, 27.1, 27.2 ($3CH_2$), 107.6, 110.5 (2C, furan ring), 127.9, 130.0, 130.9, 139.2 ($4C_{ar.}$), 142.5 (C, furan ring), 150.9 (C=N), 151.2 (C, furan ring), 167.7 (C=S). Elemental anal. (%), Calcd for $C_{16}H_{17}N_3OS_2$ (331.46): C 57.98, H 5.17, N 12.68; Found: C 58.04, H 5.09, N 12.61

4-benzyl-5-{2-[(furan-2-ylmethyl)sulfanyl]ethyl}-2,4-dihydro-3H-1,2,4-triazole-3-thione (8)

Yield 70%, mp 138–140°C. IR (KBr) ν(cm^{-1}): 3090, 3033 ($CH_{ar.}$); 2925 ($CH_{al.}$); 1310 (C=S). ^{1}H NMR (DMSO-d$_6$) δ (ppm): 2.64 (m, 4H, CH_2CH_2S); 3.68 (s, 2H, CH_2S); 5.19 (s, 2H, $CH_2C_6H_5$); 6.13, 6.28 (2s, 2H, furan ring); 7.25 (m, 5H, C_6H_5); 7.46 (s, 1H, furan ring); 13.72 (s, 1H, NH). ^{13}C NMR (DMSO-d$_6$) δ (ppm): 25.7, 26.8, 27.1, 45.5 ($4CH_2$), 107.6, 110.5 (2C, furan ring), 126.9, 127.8, 128.7, 135.6 ($4C_{ar.}$), 142.5 (C, furan ring), 151.1 (C=N), 151.3 (C, furan ring), 167.3 (C=S). Elemental anal. (%), Calcd for $C_{16}H_{17}N_3OS_2$ (331.46): C 57.98, H 5.17, N 12.68; Found: C 58.11, H 5.21, N 12.71.

4-cyclohexyl-5-{2-[(furan-2-ylmethyl)sulfanyl]ethyl}-2,4-dihydro-3H-1,2,4-triazole-3-thione (9)

Yield 85%, mp 126–127°C. IR (KBr) ν(cm^{-1}): 3110, 3046 ($CH_{ar.}$); 2932, 2855 ($CH_{al.}$); 1322 (C=S). ^{1}H NMR (DMSO-d_6) δ (ppm): 1.26, 1.71 (2m, 10H, cyclohexyl); 2.81, 2.95 (2m, 4H, CH_2CH_2S); 3.83 (s, 2H, CH_2S); 4.39 (s, 1H, cyclohexyl); 6.29, 6.38, 7.57 (3m, 3H, furan ring); 13.52 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ (ppm): 24.5, 25.5 ($2CH_2$, cyclohexyl), 26.7, 27.5, 27.6 ($3CH_2$), 29.1, 55.6 ($2CH_2$, cyclohexyl), 107.7, 110.6, 142.5 (3C, furan ring), 150.7 (C=N), 151.7 (C, furan ring), 166.1 (C=S). Elemental anal. (%), Calcd for $C_{15}H_{21}N_3OS_2$ (323.48): C 55.70, H 6.54, N 12.99; Found: C 55.57, H 6.48, N 13.08.

Microbiology

The antimicrobial activity of the tested **2–9** compounds was screened on the American Type Culture Collection (ATCC) reference strains of the Gram-positive bacteria (*Staphylococcus aureus* ATCC 25923, S*taphylococcus epidermidis* ATCC 12228, *Bacillus subtilis* ATCC 6633, *Micrococcus luteus* ATCC 10240) and of the Gram-negative bacteria (*Escherichia coli* ATCC 25922, *Klebsiella pneumoniae* ATCC 13883, *Proteus mirabilis* ATCC 12453, *Pseudomonas aeruginosa* ATCC 9027).

The methicillin-resistant *Staphylococcus aureus* (MRSA) Microbank 14.001 from the collection of National Medicines Institute in Warsaw was used. All stock solutions of the tested compounds were dissolved in dimethyl sulfoxide (DMSO). Microbial suspensions were prepared in the sterile saline (0.85% NaCl) with an optical density of 0.5 McFarland standard—150 $\times$ 10^6 CFU/mL (CFU—colony forming units). The medium with DMSO at the final concentration and without the tested compounds served as a negative control. In the first step, the antibacterial potency of tested compounds was screened using the agar dilution method on the basis of the growth inhibition on the Mueller–Hinton agar to which the tested compounds at concentrations 1000 μg/mL were added.

Then the antibacterial activity of the compounds with inhibitory effect was determined by broth microdilution technique using 96-well microplates with series of twofold dilution of the tested compounds, according to the method described earlier.[14]

It was shown that DMSO at the final concentration had no influence on the growth of tested microorganisms. Cefuroxime was used as reference antibiotic. The antimicrobial activity of the tested derivatives was expressed as the minimal concentration of the compound that inhibits the visible growth of the bacteria (MIC). The MBC (minimal bactericidal concentration), defined as the lowest concentration of each compound that resulted in >99.9% reduction in CFU of the initial inoculum, was also determined. MBC was determined by a broth microdilution technique by plating out the contents of wells (5 μL) that showed no visible growth of bacteria, onto Mueller–Hinton agar plates and incubating at 35°C for 18 h.

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