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Synthesis and Antitumor Activity of New 5-Ylidene Derivatives of 3-(Furan-2-ylmethyl)-2-sulfanylidene-1,3-thiazolidin-4-one

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Abstract—Reactions of 3-(furan-2-ylmethyl)-2-sulfanyidene-1,3-thiazolidin-4-one with aromatic and heterocyclic aldehydes afforded a series of previously unknown 5-[(het)arylmethylidene]-3-(furan-2-ylmethyl)-2-sulfanylidene-1,3-thiazolidin-4-ones. Treatment of 3-(furan-2-ylmethyl)-2-sulfanylidene-1,3-thiazolidin-4-one with thionyl chloride gave in a good yield 3,3′-bis(furan-2-ylmethyl)-2,2′-disulfanylidene-5,5′-bi-1,3-thiazolidinylidene-4,4′-dione which was reduced with zinc in acetic acid to 3,3′-bis(furan-2-ylmethyl)-2,2′-disulfanylidene-5,5′-bi-1,3-thiazolidine-4,4′-dione. The synthesized compounds were screened for antitumor activity.

Keywords: rhodanine, 2-sulfanylidene-1,3-thiazolidin-4-one, furan, thionyl chloride, antitumor activity

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Design of highly efficient and low-toxic medicines and their implementation into medical practice constitute one of the most important problems of organic and medicinal chemistry. The results of recent studies of the chemistry and biological activity of rhodanine (2-sulfanylidene-1,3-thiazolidin-4-one) derivatives convincingly showed that compounds of this series are promising as pharmacological agents with a broad spectrum of activity. Lead compounds exhibiting antimicrobial, antitubercular, antiviral, antidiabetic, anti-inflammatory, antitumor, anticonvulsant, and other activities have been identified among rhodanine derivatives. Therefore, rhodanine fragment is considered a privileged structure in medicinal chemistry [1–3].

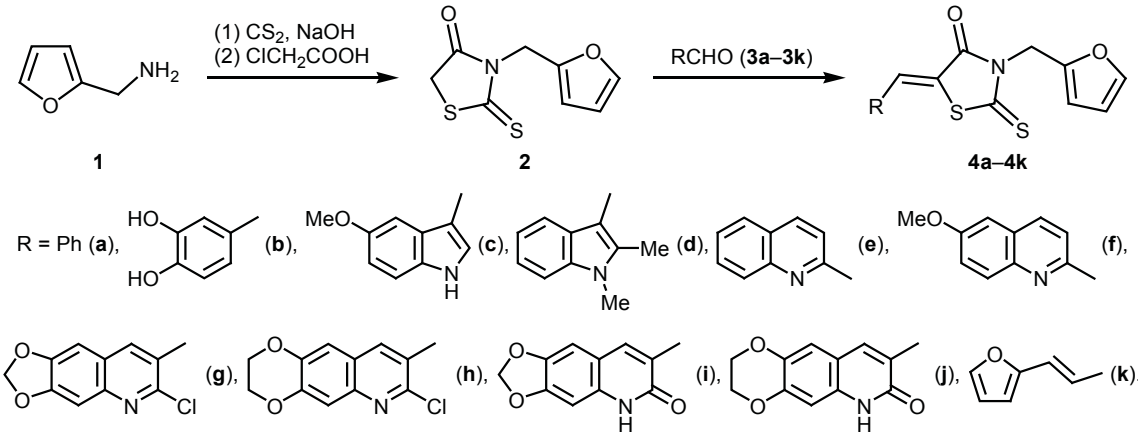
On the other hand, furan compounds have found applications in various fields of chemistry and technology, in particular in pharmacy, due to their unique physicochemical, chemical, and biological properties [4–6]. First of all, a broad range of biological activity of natural and synthetic furan compounds, as well as of its fused derivatives (benzofuran, naphthofurans, anthrafurans, etc.), should be noted. In view of the above stated, there is great interest in the use of furan heterocycle as an important building block in the design of medicines.

The present study continues our previous works related to the design of biologically active nitrogen heterocycles [7–20]. It was aimed at synthesizing 5-ylidene derivatives of 3-(furan-2-ylmethyl)-2-sulfanylidene-1,3-thiazolidin-4-one and evaluating them for antitumor activity. Compounds exhibiting valuable chemotherapeutic properties such as antiviral [21–23], antifungal [24], trypanocidal [25, 26], and antitumor activities [27–29] have already been found among this series.

The target 5-ylidene-3-(furan-2-ylmethyl)-2-sulfanylidene-1,3-thiazolidin-4-ones **4a**–**4k** were synthesized by reacting 3-(furan-2-ylmethyl)-2-sulfanylidene-1,3-thiazolidin-4-one (**2**) with aromatic and heterocyclic aldehydes **3a**–**3k** (Scheme 1) in boiling acetic acid in the presence of anhydrous sodium acetate. Initial rhodanine **2** was prepared by the dithiocarbamate method (see Experimental). The structure of **4a**–**4k** was confirmed by ^{1}H NMR spectroscopy. For example, the 3-CH_2 methylene protons resonated in their ^{1}H NMR spectra at δ 5.19–5.26 ppm, and the C^5=CH signal was located at δ 7.67–8.19 ppm, indicating *Z* configuration of the exocyclic double bond.

We also found that treatment of 3-(furan-2-ylmethyl)-2-sulfanylidene-1,3-thiazolidin-4-one (**2**) with thionyl chloride leads to is oxidation with the formation of 3,3′-bis(furan-2-ylmethyl)-2,2′-disulfanylidene-5,5′-bi-1,3-thiazolidinylidene-4,4′-dione (**5**). The latter was readily reduced to 3,3′-bis(furan-2-ylmethyl)-2,2′-di-

Scheme 1.



sulfanylidene-5,5′-bi-1,3-thiazolidine-4,4′-dione (**6**) by the action of zinc in acetic acid (Scheme 2).

Compounds **4a**–**4k** and **5** were evaluated for their in vitro antitumor activity against 60 human cancer cell lines by highly efficient biological screening according to the International Scientific Program of the US National Institutes of Health (DTP, Developmental Therapeutic Program), National Cancer Institute (Bethesda, Maryland, USA) [30–33]. The tested cell lines cover almost the entire spectrum of human malignant tumors, including leukemia, non-small-cell lung carcinoma, melanoma, and CNS, breast, prostate, renal, and epithelial colon cancers. Compounds **4a**–**4k** and **5** were tested at a concentration of 10^{-5} M, and their activity was evaluated as cancer cell growth percentage (% GP) relative to control [30–33]. The results are collected in Table 1.

Compounds **4a**–**4k** and **5** showed different levels of antitumor activity. In particular, 5-(3,4-dihydroxybenzylidene) derivative **4b** generally showed a moderate antitumor activity, but it appreciably inhibited NST-15 and NST-116 epithelial colon cancer cell lines. 5-(Indol-3-ylmethylidene) derivatives **4c** and **4d** were highly active against A-498 (renal cancer), VT-549, and MDA-MB-468 (breast cancer) cell lines, and compound **4c** showed the highest cytotoxicity against MDA-MB-435 melanoma (GP = –32.74%). Quinoline derivatives **4e**–**4j** and 3-(furan-2-yl)prop-2-en-1-ylidene derivative **4k** showed a low activity against most cancer cell lines tested, but selective sensitivity of CHB-75 CNS and K-562 leukemia cell lines to these compounds was observed. Compound **5** showed a moderate activity against MCF7 breast cancer and SR leukemia cell lines.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Varian Mercury VX-400 spectrometer at 400 MHz using DMSO-d_6 as solvent and tetramethylsilane as internal standard.

3-(Furan-2-ylmethyl)-2-sulfanylidene-1,3-thiazolidin-4-one. A round-bottom flask equipped with a reflux condenser was charged with 9.7 g (0.1 mol) of (furan-2-yl)methanamine and a cold solution of 5.6 g (0.1 mol) of potassium hydroxide in 30 mL of water. Carbon disulfide, 8.4 g (0.11 mol), was added dropwise with stirring over a period of 15 min, the mixture was stirred for 30 min more, and a solution of 10.4 g (0.11 mol) of chloroacetic acid and 9.3 g (0.11 mol) of sodium hydrogen carbonate in 60 mL of water was added. The mixture was left to stand at room temperature for 4 days, 50 mL of concentrated aqueous HCl was added, and the mixture was heated at 95°C for 1 h. The mixture was cooled, and the precipitate was

Scheme 2.

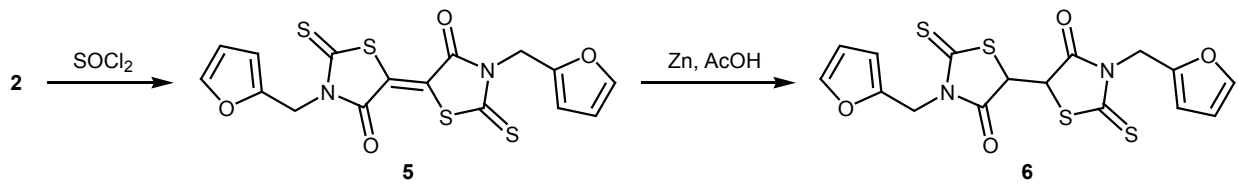


Table 1. Cytotoxicity of compounds **4b**–**4k** and **5** at a concentration of 10^{-5} M against most sensitive cancer cell lines

Compound no.	Mitotic activity, % GP		Most sensitive cancer cell lines, % GP
	average	range	
4b	69.33	20.59–109.83	HCT-15 (Epithelial colon cancer) 20.59 CCRF-CEM (Leukemia) 25.46 HCT-116 (Epithelial colon cancer) 29.57 OVCAR-3 (Melanoma) 30.41 NCI-H522 (Non-small-cell lung carcinoma) 32.26
4c	36.17	–32.74 to 89.04	MDA-MB-435 (Melanoma) –32.74 A498 (Renal cancer) –9.18 CHB-75 (CNS cancer) 1.19 MDA-MB-468 (Breast cancer) 3.03 BT-549 (Breast cancer) 7.24
4d	93.06	55.04–111.42	A498 (Renal cancer) 55.04
4e	88.94	50.37–133.54	CHB-75 (CNS cancer) 50.37
4f	94.72	84.88–115.54	K-562 (Leukemia) 84.88
4g	93.70	67.65–116.34	K-562 (Leukemia) 67.65
4h	92.72	57.04–127.71	HOP-92 (CNS cancer) 57.04
4i	83.53	29.53–131.64	CH12C (Renal cancer) 29.53 CHB-75 (CNS cancer) 32.96 HCT-116 (Epithelial colon cancer) 50.32
4j	93.70	67.65–106.86	K-562 (Leukemia) 67.65
4k	99.19	67.55–141.65	CHB-75 (CNS cancer) 67.55
5	92.18	50.13–129.58	MCF7 (Breast cancer) 50.13 SR (Leukemia) 54.84

filtered off and recrystallized from propan-2-ol. Yield 80%, mp 72–74°C; published data [34]: mp 73–74°C.

5-Ylidene 3-(furan-2-ylmethyl)-2-sulfanylidene-1,3-thiazolidin-4-ones 4a–4k (*general procedure*). A round-bottom flask equipped with a reflux condenser was charged with a solution of 0.64 g (3 mmol) of compound **2**, 3.6 mmol of the corresponding aldehyde **3a**–**3k**, and 0.25 g (3 mmol) of anhydrous sodium acetate in 5 mL of acetic acid. The mixture was refluxed for 1.5–2 h and cooled, and the precipitate was filtered off, washed with acetic acid and water, dried, and recrystallized from acetic acid or a mixture of DMF and acetic acid.

5-Benzylidene-3-(furan-2-ylmethyl)-2-sulfanylidene-1,3-thiazolidin-4-one (4a). Yield 89%, mp 135–136°C. ^{1}H NMR spectrum, δ, ppm: 5.23 s (2H, CH_2), 6.38–6.46 m (2H, H_{Fu}), 7.50–7.60 m (4H, Ph, H_{Fu}), 7.63–7.67 m (2H, Ph), 7.86 s (1H, CH=). Found, %: C 59.89; H 3.61; N 4.72. $C_{15}H_{11}NO_2S_2$. Calculated, %: C 59.78; H 3.68; N 4.65.

5-(3,4-Dihydroxybenzylidene)-3-(furan-2-ylmethyl)-2-sulfanylidene-1,3-thiazolidin-4-one (4b). Yield 60%, mp 224–225°C. ^{1}H NMR spectrum, δ, ppm: 5.21 s (2H, CH_2), 6.40 s (2H, H_{Fu}), 6.40 s (2H, H_{Fu}), 6.89 d (1H, H_{Fu}, J = 7.9 Hz), 7.05 d (2H, H_{arom}, J = 8.1 Hz), 7.59 s (1H, H_{arom}), 7.67 s (1H, CH=). Found, %: C 53.91; H 3.40; N 4.11. $C_{15}H_{11}NO_4S_2$. Calculated, %: C 54.04; H 3.33; N 4.20.

3-(Furan-2-ylmethyl)-5-(5-methoxy-1*H*-indol-3-ylmethylidene)-2-sulfanylidene-1,3-thiazolidin-4-one (4c). Yield 60%, mp 227–229°C. ^{1}H NMR spectrum, δ, ppm: 3.83 s (3H, CH_3), 5.24 s (2H, CH_2), 6.41 d (2H, H_{Fu}, J = 3.5 Hz), 6.88 d.d (1H, H_{Fu}, J = 8.8, 2.2 Hz), 7.39 d (1H, H_{arom}, J = 8.8 Hz), 7.54 d (1H, H_{arom}, J = 2.1 Hz), 7.59 s (1H, H_{arom}), 7.84 s (1H, H_{arom}), 8.19 s (1H, CH=), 12.30 s (1H, NH). Found, %: C 58.36; H 3.81; N 7.56. $C_{18}H_{14}N_2O_3S_2$. Calculated, %: C 58.47; H 3.89; N 7.49.

5-(1,2-Dimethyl-1*H*-indol-3-ylmethylidene)-3-(furan-2-ylmethyl)-2-sulfanylidene-1,3-thiazolidin-4-one (4d). Yield 68%, mp 179–180°C. ^{1}H NMR spec-

trum, δ, ppm: 3.74 s (3H, CH_3), 3.82 s (3H, CH_3), 5.24 s (2H, CH_2), 6.41 s (2H, H_{Fu}), 6.92 d (1H, H_{Fu}, J = 8.8 Hz), 7.32 s (1H, H_{arom}), 7.48 d (1H, H_{arom}, J = 8.9 Hz), 7.58 s (1H, H_{arom}), 7.76 s (1H, H_{arom}), 8.02 s (1H, CH=). Found, %: C 62.05; H 4.29; N 7.49. $C_{19}H_{16}N_2O_2S_2$. Calculated, %: C 61.93; H 4.38; N 7.60.

3-(Furan-2-ylmethyl)-5-(quinolin-2-ylmethylidene)-2-sulfanylidene-1,3-thiazolidin-4-one (4e). Yield 70%, mp 198–200°C. ^{1}H NMR spectrum, δ, ppm: 5.26 s (2H, CH_2), 6.42 s (2H, H_{Fu}), 7.59 s (1H, H_{Fu}), 7.65–7.72 m (1H, H_{arom}), 7.81–7.88 m (1H, H_{arom}), 7.95–8.03 m (3H, CH=, H_{arom}), 8.16 d (1H, H_{arom}, J = 8.6 Hz), 8.49 d (1H, H_{arom}, J = 7.0 Hz). Found, %: C 61.45; H 3.36; N 7.86. $C_{18}H_{12}N_2O_2S_2$. Calculated, %: C 61.34; H 3.43; N 7.95.

3-(Furan-2-ylmethyl)-5-(6-methoxyquinolin-2-ylmethylidene)-2-sulfanylidene-1,3-thiazolidin-4-one (4f). Yield 85%, mp 226–227°C. ^{1}H NMR spectrum, δ, ppm: 3.93 s (3H, CH_3), 5.26 s (2H, CH_2), 6.41 s (2H, H_{Fu}), 7.40 d (1H, H_{Fu}, J = 2.2 Hz), 7.47 d (1H, H_{arom}, J = 9.2 Hz), 7.58 s (1H, H_{arom}), 7.89–7.92 m (3H, CH=, H_{arom}), 8.04 d (1H, H_{arom}, J = 9.2 Hz). Found, %: C 59.78; H 3.60; N 7.24. $C_{19}H_{14}N_2O_3S_2$. Calculated, %: C 59.67; H 3.69; N 7.32.

5-(6-Chloro[1,3]dioxolo[4,5-*g*]quinolin-7-ylmethylidene)-3-(furan-2-ylmethyl)-2-sulfanylidene-1,3-thiazolidin-4-one (4g). Yield 90%, mp 220–221°C. ^{1}H NMR spectrum, δ, ppm: 5.25 s (2H, CH_2), 6.27 s (2H, CH_2), 6.44 d (2H, H_{Fu}, J = 7.8 Hz), 7.34 s (1H, H_{Fu}), 7.60 s (1H, H_{arom}), 7.63 s (1H, H_{arom}), 7.90 s (1H, CH=), 8.27 s (1H, H_{arom}). Found, %: C 52.79; H 2.51; N 6.38. $C_{19}H_{11}ClN_2O_4S_2$. Calculated, %: C 52.96; H 2.57; N 6.50.

5-(7-Chloro-2,3-dihydro[1,4]dioxino[2,3-*g*]quinolin-8-ylmethylidene)-3-(furan-2-ylmethyl)-2-sulfanylidene-1,3-thiazolidin-4-one (4h). Yield 99%, mp 222–223°C. ^{1}H NMR spectrum, δ, ppm: 4.41 s (2H, CH_2), 4.43 s (2H, CH_2), 5.26 s (2H, CH_2), 6.44 d (2H, H_{Fu}, J = 7.9 Hz), 7.37 s (1H, H_{Fu}), 7.60 s (1H, H_{arom}), 7.74 s (1H, H_{arom}), 7.93 s (1H, CH=), 8.34 s (1H, H_{arom}). Found, %: C 54.11; H 2.90; N 6.42. $C_{20}H_{13}ClN_2O_4S_2$. Calculated, %: C 53.99; H 2.95; N 6.30.

7-[3-(Furan-2-ylmethyl)-4-oxo-2-sulfanylidene-1,3-thiazolidin-5-ylidenemethyl]-5*H*-[1,3]dioxolo-[4,5-*g*]quinolin-6-one (4i). Yield 97%, mp >270°C. ^{1}H NMR spectrum, δ, ppm: 5.21 s (2H, CH_2), 6.14 s (2H, CH_2), 6.40 s (2H, H_{Fu}), 6.81 s (1H, H_{arom}), 7.25 s (1H, H_{Fu}), 7.57 s (1H, H_{arom}), 7.68 s (1H, H_{arom}), 8.14 s (1H, CH=), 12.12 s (1H, NH). Found, %: C 55.46; H 2.99; N 6.68. $C_{19}H_{12}N_2O_5S_2$. Calculated, %: C 55.33; H 2.93; N 6.79.

8-[(3-(Furan-2-ylmethyl)-4-oxo-2-sulfanylidene-1,3-thiazolidin-5-ylidenemethyl]-2,3-dihydro-6*H*-[1,4]dioxino[2,3-*g*]quinolin-7-one (4j). Yield 99%, mp >270°C. ^{1}H NMR spectrum, δ, ppm: 4.27 d (2H, CH_2, J = 3.5 Hz), 4.35 d (2H, CH_2, J = 3.9 Hz), 5.21 s (2H, CH_2), 6.39 s (2H, H_{Fu}), 6.76 s (1H, H_{arom}), 7.29 s (1H, H_{Fu}), 7.58 s (1H, H_{arom}), 7.68 s (1H, H_{arom}), 8.15 s (1H, CH=), 11.92 s (1H, NH). Found, %: C 56.45; H 3.26; N 6.34. $C_{20}H_{14}N_2O_5S_2$. Calculated, %: C 56.33; H 3.31; N 6.57.

3-(Furan-2-ylmethyl)-5-[3-(furan-2-yl)prop-2-en-1-ylidene]-2-sulfanylidene-1,3-thiazolidin-4-one (4k). Yield 84%, mp 178–179°C. ^{1}H NMR spectrum, δ, ppm: 5.19 s (2H, CH_2), 6.39 d (2H, H_{Fu}, J = 3.7 Hz), 6.61–6.74 m (2H, H_{Fu}), 6.95 d (1H, H_{Fu}, J = 2.6 Hz), 7.28 d (1H, CH=, J = 14.9 Hz), 7.52–7.61 m (2H, CH=, H_{Fu}), 7.87 s (1H, CH=). Found, %: C 56.85; H 3.54; N 4.35. $C_{15}H_{11}NO_3S_2$. Calculated, %: C 56.77; H 3.49; N 4.41.

3,3′-Bis(furan-2-ylmethyl)-2,2′-disulfanylidene-5,5′-bi-1,3-thiazolidinylidene-4,4′-dione (5). Compound **2**, 2.1 g (10 mmol), was dissolved in 5 mL of anhydrous toluene on heating in a round-bottom flask equipped with a reflux condenser, 2.4 g (20 mmol) of thionyl chloride was added, and the mixture was refluxed for 3 h. The mixture was cooled, and the precipitate was filtered off, washed with toluene and petroleum ether, dried, and recrystallized from DMF. Yield 74%, mp 258–260°C. ^{1}H NMR spectrum, δ, ppm: 5.23 s (2H, CH_2), 6.41 s (2H, H_{Fu}), 6.45 d (2H, H_{Fu}, J = 3.1 Hz), 7.59 s (2H, H_{Fu}). Found, %: C 45.56; H 2.31; N 6.58. $C_{16}H_{10}N_2O_4S_4$. Calculated, %: C 45.48; H 2.39; N 6.63.

3,3′-Bis(furan-2-ylmethyl)-2,2′-disulfanylidene-5,5′-bi-1,3-thiazolidine-4,4′-dione (6). Compound **5**, 0.42 g (1 mmol), was dissolved in a 2:1 mixture of DMF and acetic acid on heating in a round-bottom flask equipped with a reflux condenser, 0.4 g of zinc dust was added with stirring to the hot solution, the mixture was slowly heated to the boiling point, the heating bath was removed, and the mixture was stirred for 10 min. The mixture was filtered, the filtrate was diluted with 100 mL of water, and the precipitate was filtered off, washed with water, dried, and recrystallized first from dilute acetic acid and then from benzene–petroleum ether. Yield 67%, mp 140°C (decomp.).

^{1}H NMR spectrum, δ, ppm: 5.07 d (2H, CH, J = 4.4 Hz), 5.55 s (4H, CH_2), 6.36 s (2H, H_{Fu}), 6.39 s (2H, H_{Fu}), 7.56 s (2H, H_{Fu}). Mass spectrum (ESI-MS): m/z 446.8 $[M + H]^+$. Found, %: 45.38; H 2.78; N 6.51. $C_{16}H_{12}N_2O_4S_4$. Calculated, %: 45.27; H 2.85; N 6.60.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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