Synthesis of 2-thioxo-1,3-thiazolidin-4-one derivatives*

V. N. Yarovenko,[a] A. S. Nikitina,[b] I. V. Zavarzin,[a] M. M. Krayushkin,[a] and L. V. Kovalenko[b]*

[a]N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences,
47 Leninsky prosp., 119991 Moscow, Russian Federation.
Fax: +7 (495) 137 6939. E-mail: yarov@mail.ioc.ac.ru
[b]D. I. Mendeleev Russian University of Chemistry and Technology,
9 Miusskaya pl., 125047 Moscow, Russian Federation.
Fax: +7 (495) 978 6132. E-mail: lvkcpf@muctr.edu.ru

A series of new 2-thioxo-1,3-thiazolidin-4-one derivatives containing arylidene, arylazo, and aminomethylene fragments in position 5 of the rhodanine cycle was synthesized.

Key words: thiohydrazides of oxamic acids, thiorhodanines, 2-thioxothiazolidin-4-ones, azorhodanines.

The Knoevenagel condensation, acylation, and azo-coupling reactions at the active methylene group of rhodanines afford 5-substituted derivatives manifesting a wide range of pharmacological properties, in particular, possessing anticancer properties.[1,2]

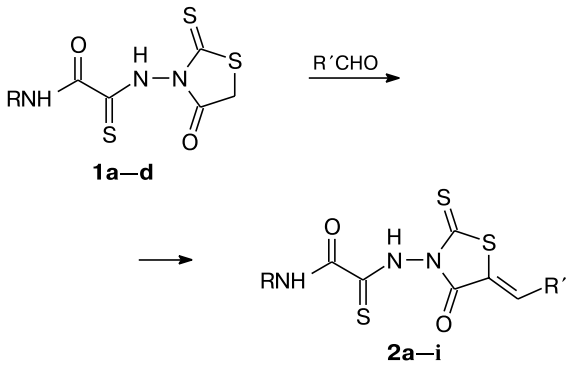
We have previously[3] synthesized new derivatives of 2-thioxo-1,3-thiazolidin-4-ones **1** by the reaction of thiohydrazides of oxamic acids with trithiocarbonyldiglycolic acid in the presence of dicyclohexylcarbodiimide or carbonyldiimidazole.

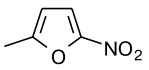
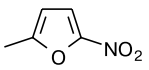
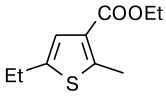
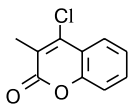
In the present work, we studied the reactivity of the active methylene group in position 5 of rhodanines **1** and synthesized their 5-arylidene-, 5-arylazo-, and 5-aminomethyl-substituted derivatives.

The influence of the catalyst and solvent on the reaction of rhodanines **1** with aldehydes was studied. The reactions of 2-thioxo-1,3-thiazolidin-4-ones **1a—d** with aromatic and heterocyclic aldehydes in methanol in the presence of ethylenediammonium diacetate at ambient temperature afford 5-arylidene-2-thioxo-1,3-thiazolidin-4-ones **2a—i** in 85—95% yields (Scheme 1). The use of sodium acetate in acetic acid or acetic anhydride gives lower yields of products **2a—i** (45—65%), whereas the latter are not formed at all when the reaction is carried out in ethanol in the presence of piperidine.

The treatment of 2-thioxo-1,3-thiazolidin-4-ones **1a—d** with triethyl orthoformate in acetic anhydride gave 5-ethoxymethylenerhodanines **3a—d** in 60—75% yields. They are convenient synthons for the synthesis of azomethines. The reactions of compounds **3a—d** with sec-

Scheme 1



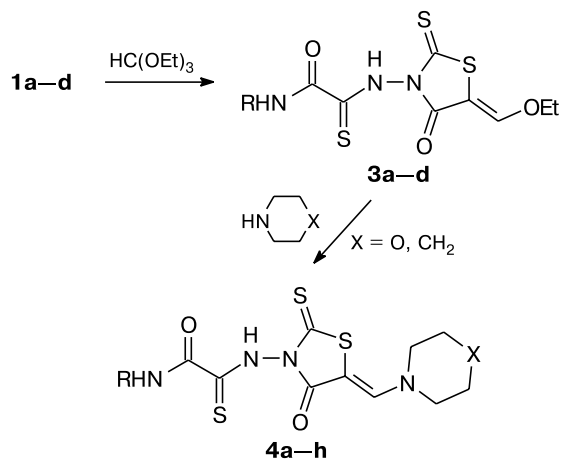
2	R	R′
a	Ph	Ph
b	Ph	
d	*p*-ClC$_6$H$_4$	
c	*p*-ClC$_6$H$_4$	Ph
e	*p*-MeC$_6$H$_4$	Ph
f	*p*-MeC$_6$H$_4$	
h		
g		Ph
i	Ph	

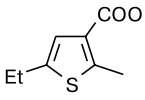
* Dedicated to Academician V. A. Tartakovsky on the occasion of his 75th birthday.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 8, pp. 1564—1569, August, 2007.

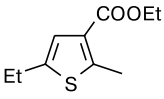
ondary amines afford 5-aminomethylenerhodanines **4a—h** in 70—80% yields (Scheme 2).

Scheme 2



3: R = Ph (**a**), *p*-ClC_6H_4 (**b**), *p*-MeC_6H_4 (**c**),  (**d**)

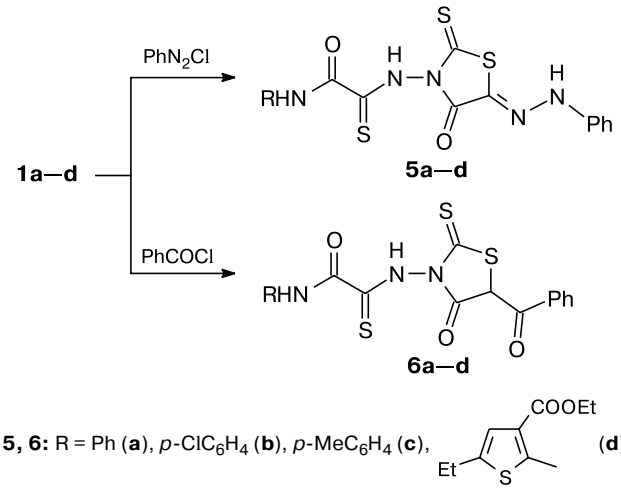
4: R = Ph (**a**, **b**), *p*-ClC_6H_4 (**c**, **d**),

p-MeC_6H_4 (**e**, **f**),  (**g**, **h**)

X = O (**a**, **c**, **e**, **g**), CH_2 (**b**, **d**, **f**, **h**)

Phenylhydrazones **5a—d** were synthesized by the reaction of rhodanines **1a—d** with phenyldiazonium salt in 70—75% yields, and this reaction with benzoyl chloride afforded 5-benzoylthiazolidin-4-ones **6a—d** in 70—80% yields (Scheme 3).

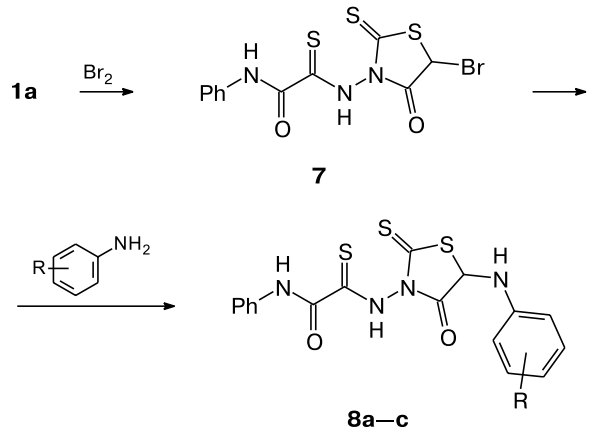
Scheme 3



5, 6: R = Ph (**a**), *p*-ClC_6H_4 (**b**), *p*-MeC_6H_4 (**c**), (**d**)

We failed to synthesize 5-bromorhodanine according to the described procedure[4] (in acetic acid at 80—90 °C). Resinification of the product occurs at the isolation stage. We showed that the process occurred successfully in dioxane at ambient temperature. Since bromination product **7a** is unstable and decomposes in air, the reaction mixture was treated with aniline or haloanilines without isolating this bromide, and 5-arylaminorhodanines **8a—c** are formed (Scheme 4).

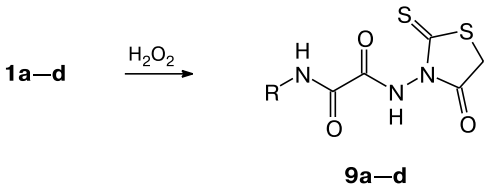
Scheme 4

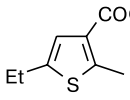


8: R = H (**a**), 3-F (**b**), 3,5-Cl_2 (**c**)

The thioamide group was modified into the amide group with the formation of the corresponding amides **9a—d** using the treatment of rhodanines **1a—d** with hydrogen peroxide in acetonitrile at ambient temperature (Scheme 5).

Scheme 5



9: R = Ph (**a**), *p*-ClC_6H_4 (**b**), *p*-MeC_6H_4 (**c**),  (**d**)

The structures of the synthesized compounds were confirmed by the ^1H, ^{13}C NMR and mass spectral data. The ^1H NMR spectra of rhodanines **1a—d** contain no chemical shift of the proton of secondary amine near the thiocarbonyl group because of screening of the latter, whereas in the spectra of compounds **9a—d** the signal from this proton appears at 12 ppm.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-300 instrument (working frequency 300 MHz) in DMSO-d_6. Mass spectra were recorded on a Kratos instrument with direct injection of a sample into the ion source with an ionization energy of 70 eV and a controlling voltage of 1.75 kV. Melting points were measured on a Boetius heating stage and were not corrected. The reaction mixtures were analyzed and purity of the isolated products was monitored by TLC (EtOAc—hexane (1 : 1) mixture as eluent) on Merck 60 F_{254} plates.

2-Thioxo-1,3-thiazolidin-4-ones **1a—d** were synthesized according to an earlier described procedure.[3]

The characteristics of the primarily synthesized compounds are given in Tables 1 and 2.

2-[(5-Benzylidene-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)amino]-2-thioxo-*N*-phenylacetamide (2a). Rhodanine **1a**

Table 1. Characteristics of synthesized compounds **2a—i**, **3a—d**, **4a—h**, **5a—d**, **6a—d**, **8a—c**, and **9a—d**

Product	Yield (%)	M.p/°C	Found / Calculated (%)					Molecular formula
			C	H	N	S	Cl	
2a	95	158—159	54.12	3.28	10.52	24.08	—	$C_{18}H_{13}N_3O_2S_3$
			54.17	3.32	10.48	23.93		
2b	85	173—174	44.23	2.32	12.90	22.14	—	$C_{16}H_{10}N_4O_5S_3$
			44.23	2.38	12.81	22.02		
2c	93	168—169	49.82	2.79	8.17	22.17	8.17	$C_{18}H_{12}ClN_3O_2S_3$
			49.90	2.85	8.21	22.10	8.21	
2d	85	154—155	40.98	1.93	11.95	20.51	7.56	$C_{16}H_9ClN_4O_5S_3$
			41.06	2.00	11.85	20.42	7.63	
2e	89	168—169	53.13	3.52	9.78	22.39	—	$C_{19}H_{15}N_3O_3S_3$
			53.19	3.50	9.71	22.30		
2f	85	149—150	43.96	2.60	12.06	20.71	—	$C_{17}H_{12}N_4O_6S_3$
			44.04	2.66	12.13	20.61		
2g	93	181—182	49.88	3.79	8.31	25.36	—	$C_{21}H_{19}N_3O_4S_4$
			49.96	3.85	8.23	25.32		
2h	86	178—179	42.21	2.98	10.36	23.72	—	$C_{19}H_{16}N_4O_7S_4$
			42.31	2.91	10.43	23.61		
2i	75	165—166	50.25	2.41	8.37	19.16	7.06	$C_{21}H_{12}ClN_3O_4S_3$
			50.35	2.37	8.25	19.09	7.15	
3a	75	115—116	45.76	3.57	11.43	26.18	—	$C_{14}H_{13}N_3O_3S_3$
			45.78	3.51	11.38	26.23		
3b	65	133—134	41.84	3.01	10.45	23.93	8.82	$C_{14}H_{12}ClN_3O_3S_3$
			41.76	2.91	10.43	24.01	8.76	
3c	62	125—126	45.33	3.80	10.57	24.20	—	$C_{15}H_{15}N_3O_4S_3$
			45.41	3.83	10.51	24.23		
3d	70	146—147	43.11	4.04	8.87	27.08	—	$C_{17}H_{19}N_3O_5S_4$
			43.22	4.10	8.81	27.03		
4a	80	173—174	47.04	3.95	13.71	23.55	—	$C_{16}H_{16}N_4O_3S_3$
			47.09	3.91	13.78	23.61		
4b	72	166—167	50.22	4.46	13.78	23.66	—	$C_{17}H_{18}N_4O_2S_3$
			50.31	4.51	13.73	23.70		
4c	79	189—190	43.38	3.41	12.65	21.72	8.00	$C_{16}H_{15}ClN_4O_3S_3$
			43.43	3.51	12.73	21.67	7.95	
4d	70	171—172	46.30	3.89	12.70	21.81	8.04	$C_{17}H_{17}ClN_4O_2S_3$
			46.38	3.93	12.77	21.70	7.98	
4e	77	163—164	46.56	4.14	12.78	21.93	—	$C_{17}H_{18}N_4O_4S_3$
			46.64	4.19	12.77	21.88		
4f	75	158—159	49.52	4.62	12.83	22.03	—	$C_{18}H_{20}N_4O_3S_3$
			49.59	4.60	12.77	22.00		
4g	80	192—193	44.34	4.31	10.89	24.92	—	$C_{19}H_{22}N_4O_5S_4$
			44.42	4.27	10.96	24.87		
4h	70	174—175	46.85	4.72	10.93	25.02	—	$C_{20}H_{24}N_4O_4S_4$
			46.92	4.60	10.99	24.96		

(*to be continued*)

Table 1 (*continued*)

Product	Yield (%)	M.p/°C	Found / Calculated (%)					Molecular formula
			C	H	N	S	Cl	
5a	75	217—218	49.14	3.15	16.85	23.15	—	$C_{17}H_{13}N_5O_2S_3$
			49.16	3.11	16.97	23.18		
5b	70	221—222	45.38	2.69	15.56	21.38	7.88	$C_{17}H_{12}ClN_5O_2S_3$
			45.48	2.63	15.69	21.32	7.79	
5c	73	203—204	48.53	3.39	15.72	21.59	—	$C_{18}H_{15}N_5O_3S_3$
			48.62	3.42	15.86	21.53		
5d	70	212—213	46.05	3.67	13.43	24.59	—	$C_{20}H_{19}N_5O_4S_4$
			46.15	3.70	13.45	24.51		
6a	73	130—131	52.03	3.15	10.11	23.15	—	$C_{18}H_{13}N_3O_3S_3$
			52.16	3.18	10.18	23.05		
6b	70	126—127	48.05	2.69	9.34	21.38	7.88	$C_{18}H_{12}ClN_3O_3S_3$
			48.09	2.65	9.48	21.33	7.81	
6c	79	110—111	51.22	3.39	9.43	21.59	—	$C_{19}H_{15}N_3O_4S_3$
			51.30	3.34	9.52	21.51		
6d	72	138—139	48.35	3.67	8.06	24.59	—	$C_{21}H_{19}N_3O_5S_4$
			48.46	3.62	8.11	24.53		
	68	227—228	50.73	3.51	13.92	23.90	—	$C_{17}H_{14}N_4O_2S_3$
			50.79	3.46	14.03	23.87		
8b	72	205—206	48.56	3.12	13.32	22.88	—	$C_{17}H_{13}FN_4O_2S_3$
			48.63	3.09	13.42	22.85		
8c	70	241—242	43.31	2.57	11.88	20.41	15.04	$C_{17}H_{12}Cl_2N_4O_2S_3$
			43.38	2.51	11.96	20.37	15.00	
9a	93	164—165	42.43	2.91	13.49	30.89	—	$C_{11}H_9N_3O_2S_3$
			42.52	2.87	13.58	30.86		
9b	93	177—178	38.20	2.33	12.15	27.81	10.25	$C_{11}H_8ClN_3O_2S_3$
			38.29	2.29	12.22	27.76	10.23	
9c	89	156—157	42.21	3.25	12.31	28.17	—	$C_{12}H_{11}N_3O_3S_3$
			42.25	3.21	12.36	28.24		
9d	85	197—198	41.88	3.77	10.47	23.96	—	$C_{14}H_{15}N_3O_5S_3$
			41.93	3.74	10.42	24.03		

Table 2. Spectral data for compounds **2a—i**, **3a—d**, **4a—h**, **5a—d**, **6a—d**, **8a—c**, and **9a—d**

Product	^{1}H NMR (300.13 MHz, DMSO-d_6), δ (*J*/Hz)	MS, *m/z*
2a	7.10, 7.25 (both t, 1 H each, 2 CH_{arom}, J = 7.3, J = 7.5); 7.40 (t, 2 H, 2 CH_{arom}, J = 7.2); 7.55 (t, 2 H, 2 CH_{arom}, J = 7.8); 7.75 (d, 2 H, 2 CH_{arom}, J = 7.8); 7.85 (d, 2 H, 2 CH_{arom}, J = 7.9); 8.05 (s, 1 H, CH_{aliph}); 11.05 (s, 1 H, NH)	399
2b	7.20 (t, 1 H, CH_{arom}, J = 7.3); 7.31 (d, 1 H, CH_{arom}, J = 3.6); 7.45 (t, 2 H, 2 CH_{arom}, J = 7.2); 7.65 (d, 1 H, CH_{arom}, J = 3.5); 7.90 (d, 2 H, 2 CH_{arom}, J = 7.4); 8.05 (s, 1 H, CH_{aliph}); 10.90 (s, 1 H, NH)	434
2c	7.20 (t, 1 H, CH_{arom}, J = 7.4); 7.35 (d, 2 H, 2 CH_{arom}, J = 8.7); 7.55 (t, 2 H, 2 CH_{arom}, J = 9.0); 7.75 (d, 2 H, 2 CH_{arom}, J = 7.8); 7.95 (d, 2 H, 2 CH_{arom}, J = 8.74); 8.10 (s, 1 H, CH_{aliph}); 10.90 (s, 1 H, NH)	433
2d	7.20 (d, 1 H, CH_{arom}, J = 3.6); 7.50 (d, 2 H, 2 CH_{arom}, J = 8.7); 7.75 (d, 1 H, CH_{arom}, J = 3.5); 7.95 (d, 2 H, 2 CH_{arom}, J = 8.7); 8.05 (s, 1 H, CH_{aliph}); 11.2 (s, 1 H, NH)	468
2e	3.75 (s, 3 H, OCH_3); 6.95 (d, 2 H, 2 CH_{arom}, J = 8.9); 7.35 (t, 1 H, CH_{arom}, J = 7.8); 7.05 (d, 2 H, 2 CH_{arom}, J = 9.0); 7.75 (t, 2 H, 2 CH_{arom}, J = 9.0); 7.95 (d, 2 H, 2 CH_{arom}, J = 8.7); 8.10 (s, 1 H, CH_{aliph}); 10.70 (s, 1 H, NH)	429

(*to be continued*)

Table 2 (*continued*)

Product	^{1}H NMR (300.13 MHz, DMSO-d_6), δ (*J*/Hz)	MS, *m/z*
2f	3.75 (s, 3 H, OCH_3); 7.00 (d, 2 H, 2 CH_{arom}, J = 8.9); 7.35 (d, 1 H, CH_{arom}, J = 3.7); 7.60 (d, 2 H, 2 CH_{arom}, J = 9.0); 7.85 (d, 1 H, CH_{arom}, J = 3.6); 8.00 (s, 1 H, CH_{aliph}); 11.10 (s, 1 H, NH)	464
2g	1.25 (t, 3 H, $CH_{3(aliph);}$ J = 7.4); 1.35 (t, 3 H, $CH_{3(aliph);}$ J = 7.1); 2.70 (q, 2 H, $CH_{2(aliph)}$); 4.35 (q, 2 H, $CH_{2(aliph)}$); 7.0 (s, 1 H, CH_{arom}); 7.20 (t, 1 H, CH_{arom}, J = 7.8); 7.40 (t, 2 H, 2 CH_{arom}, J = 8.9); 7.70 (d, 2 H, 2 CH_{arom}, J = 8.9); 8.10 (s, 1 H, CH_{aliph}); 11.50 (s, 1 H, NH)	505
2h	1.25 (t, 3 H, $CH_{3(aliph);}$ J = 7.4); 1.35 (t, 3 H, $CH_{3(aliph);}$ J = 7.1); 2.70 (q, 2 H, $CH_{2(aliph)}$); 4.35 (q, 2 H, $CH_{2(aliph)}$); 7.10 (s, 1 H, CH_{arom}); 7.35 (d, 1 H, CH_{arom}, J = 3.7); 7.85 (d, 1 H, CH_{arom}, J = 3.6); 8.20 (s, 1 H, CH_{aliph}); 11.40 (s, 1 H, NH)	540
2i	7.20—7.95 (m, 9 H, Ar); 8.20 (s, 1 H, CH_{aliph}); 11.40 (s, 1 H, NH)	501
3a	1.33 (t, 3 H, $CH_{3(aliph);}$ J = 7.0); 4.45 (q, 2 H, $CH_{2(aliph)}$); 7.20 (t, 1 H, CH_{arom}, J = 7.0); 7.40 (t, 2 H, 2 CH_{arom}, J = 7.8); 7.85 (d, 2 H, 2 CH_{arom}, J = 8.1); 8.20 (s, 1 H, CH_{aliph}); 10.90 (s, 1 H, NH)	367
3b	1.35 (t, 3 H, $CH_{3(aliph);}$ J = 7.0); 4.40 (q, 2 H, $CH_{2(aliph)}$); 7.50 (d, 2 H, 2 CH_{arom}, J = 8.7); 7.75 (both d, 1 H each, 2 CH_{arom}, J = 7.8); 8.15 (s, 1 H, CH_{aliph}); 10.70 (s, 1 H, NH)	401
3c	1.33 (t, 3 H, $CH_{3(aliph);}$ J = 7.1); 3.75 (s, 3 H, $OCH_{3(aliph)}$); 4.45 (q, 2 H, $CH_{2(aliph)}$); 7.00 (d, 2 H, 2 CH_{arom}, J = 8.9); 7.70 (d, 2 H, 2 CH_{arom}, J = 9.0); 8.10 (s, 1 H, CH_{aliph}); 10.80 (s, 1 H, NH)	397
3d	1.25 (t, 3 H, $CH_{3(aliph);}$ J = 7.4); 1.35 (t, 6 H, 2 $CH_{3(aliph);}$ J = 7.2); 2.70 (q, 2 H, $CH_{2(aliph)}$); 4.35 (q, 4 H, 2 $CH_{2(aliph)}$); 7.00 (s, 1 H, CH_{arom}); 8.20 (s, 1 H, CH_{aliph}); 10.80 (s, 1 H, NH)	473
4a	3.25—3.40 (m, 4 H, 2 $CH_{2(aliph)}$); 3.60—3.75 (m, 4 H, 2 $CH_{2(aliph)}$); 7.20 (t, 1 H, CH_{arom}, J = 7.6); 7.40 (t, 2 H, 2 CH_{arom}, J = 7.6); 7.75 (d, 2 H, 2 CH_{arom}, J = 7.7); 8.05 (s, 1 H, CH_{aliph}); 10.35 (s, 1 H, NH)	408
4b	1.50—1.70 (m, 4 H, 3 $CH_{2(aliph)}$); 3.60—3.75 (m, 4 H, 2 $CH_{2(aliph)}$); 7.20 (t, 1 H, CH_{arom}, J = 7.6); 7.40 (t, 2 H, 2 CH_{arom}, J = 7.6); 7.75 (d, 2 H, 2 CH_{arom}, J = 7.9); 8.05 (s, 1 H, CH_{aliph}); 10.35 (s, 1 H, NH)	406
4c	3.20—3.40 (m, 4 H, 2 $CH_{2(aliph)}$); 3.60—3.75 (m, 4 H, 2 $CH_{2(aliph)}$); 7.45 (both d, 2 H, 2 CH_{arom}, J = 8.7); 7.85 (d, 2 H, 2 CH_{arom}, J = 8.7); 8.20 (s, 1 H, CH_{aliph}); 10.35 (s, 1 H, NH)	440
4d	1.35—1.75 (m, 4 H, 3 $CH_{2(aliph)}$); 3.15—3.35 (m, 4 H, 2 $CH_{2(aliph)}$); 7.50 (d, 2 H, 2 CH_{arom}, J = 8.7); 7.90 (d, 2 H, 2 CH_{arom}, J = 8.7); 8.15 (s, 1 H, CH_{aliph}); 10.30 (s, 1 H, NH)	442
4e	3.20—3.40 (m, 4 H, 2 $CH_{2(aliph)}$); 3.60—3.70 (m, 4 H, 2 CH_{aliph}); 3.75 (s, 3 H, $OCH_{3(aliph)}$); 6.95 (d, 2 H, 2 CH_{arom}, J = 8.9); 7.70 (d, 2 H, 2 CH_{arom}, J = 9.0); 8.15 (s, 1 H, CH_{aliph}); 10.20 (s, 1 H, NH)	438
4f	1.30—1.70 (m, 4 H, 3 $CH_{2(aliph)}$); 3.15—3.35 (m, 4 H, 2 CH_{aliph}); 3.75 (s, 3 H, $OCH_{3(aliph)}$); 6.95 (d, 2 H, 2 CH_{arom}, J = 8.9); 7.70 (d, 2 H, 2 CH_{arom}, J = 9.0); 8.15 (s, 1 H, CH_{aliph}); 10.20 (s, 1 H, NH)	436
4g	1.25 (t, 3 H, $CH_{3(aliph);}$ J = 7.4); 1.35 (t, 3 H, $CH_{3(aliph);}$ J = 7.1); 2.70 (q, 2 H, $CH_{2(aliph)}$); 3.20—3.40 (m, 4 H, 2 $CH_{2(aliph)}$); 3.60—3.80 (m, 4 H, 2 $CH_{2(aliph)}$); 4.35 (q, 2 H, $CH_{2(aliph)}$); 7.00 (s, 1 H, CH_{arom}); 8.00 (s, 1 H, CH_{aliph}); 11.40 (s, 1 H, NH)	514
4h	1.25 (t, 3 H, $CH_{3(aliph);}$ J = 7.4); 1.35 (t, 3 H, $CH_{3(aliph);}$ J = 7.1); 1.40—1.70 (m, 4 H, 3 $CH_{2(aliph)}$); 2.70 (q, 2 H, $CH_{2(aliph)}$); 3.20—3.30 (m, 4 H, 2 $CH_{2(aliph)}$); 4.35 (q, 2 H, $CH_{2(aliph)}$); 7.10 (s, 1 H, CH_{arom}); 8.00 (s, 1 H, CH_{aliph}); 11.40 (s, 1 H, NH)	512
5a	6.90 (t, 1 H, CH_{arom}, J = 7.5); 7.15 (t, 2 H, 2 CH_{arom}, J = 7.5); 7.35 (t, 1 H, CH_{arom}, J = 7.6); 7.55 (t, 2 H, 2 CH_{arom}, J = 7.8); 7.75 (d, 2 H, 2 CH_{arom}, J = 7.8); 7.95 (d, 2 H, 2 CH_{arom}, J = 7.9); 11.10, 11.80 (s, 2 H, NH)	415
5b	6.90 (t, 1 H, CH_{arom}, J = 7.6); 7.20 (t, 2 H, 2 CH_{arom}, J = 7.5); 7.45 (d, 2 H, 2 CH_{arom}, J = 8.7); 7.60 (d, 2 H, 2 CH_{arom}, J = 7.8); 7.80 (d, 2 H, CH_{arom}, J = 7.8); 7.95 (d, 2 H, 2 CH_{arom}, J = 8.7); 10.90, 11.60 (both s, 1 H each, NH)	449
5c	3.75 (s, 3 H, $OCH_{3(aliph)}$); 6.95—7.60 (m, 9 H, Ar); 11.10, 11.7 (both s, 1 H each, NH)	445
5d	1.25 (t, 3 H, $CH_{3(aliph)}$, J = 7.4); 1.35 (t, 3 H, $CH_{3(aliph)}$, J = 7.1); 2.7 (q, 2 H, $CH_{2(aliph)}$); 4.35 (q, 2 H, $CH_{2(aliph)}$); 6.90 (t, 1 H, CH_{arom}, J = 7.7); 7.0 (s, 1 H, CH_{arom}); 7.20 (t, 2 H, 2 CH_{arom}, J = 7.7); 7.70 (d, 2 H, 2 CH_{arom}, J = 8.8); 11.50, 12.20 (both s, 1 H each, NH)	521
6a	6.50 (s, 1 H, CH_{aliph}); 7.15 (t, 1 H, CH_{arom}, J = 7.3); 7.35 (t, 2 H, 2 CH_{arom}, J = 7.5); 7.55 (t, 1 H, CH_{arom}, J = 7.8); 7.75 (d, 2 H, 2 CH_{arom}, J = 7.8); 7.85 (t, 2 H, 2 CH_{arom}, J = 7.9); 8.00 (d, 2 H, 2 CH_{arom}, J = 7.8); 11.15 (s, 1 H, NH)	415

(*to be continued*)

Table 2 (*continued*)

Product	^{1}H NMR (300.13 MHz, DMSO-d_6), δ (*J*/Hz)	MS, *m/z*
6b	6.30 (s, 1 H, CH_{aliph}); 7.35 (t, 2 H, 2 CH_{arom}, *J* = 8.7); 7.40 (t, 1 H, CH_{arom}, *J* = 7.8); 7.60—7.75 (m, 4 H, Ar); 7.95 (d, 2 H, 2 CH_{arom}, *J* = 8.7); 10.70 (s, 1 H, NH)	449
6c	3.75 (s, 3 H, $OCH_{3(aliph)}$); 6.30 (s, 1 H, CH_{aliph}); 6.95 (d, 2 H, 2 CH_{arom}, *J* = 8.9); 7.40 (d, 2 H, 2 CH_{arom}, *J* = 9.0); 7.60 (t, 1 H, CH_{arom}, *J* = 7.8); 7.85 (t, 2 H, 2 CH_{arom}, *J* = 7.8); 8.00 (d, 2 H, 2 CH_{arom}, *J* = 9.0); 11.10 (s, 1 H, NH)	445
6d	1.25 (t, 3 H, $CH_{3(aliph)}$, *J* = 7.4); 1.35 (t, 3 H, $CH_{3(aliph)}$, *J* = 7.1); 2.70 (q, 2 H, $CH_{2(aliph)}$); 4.35 (q, 2 H, $CH_{2(aliph)}$); 6.60 (s, 1 H, CH_{aliph}); 7.00 (s, 1 H, CH_{arom}); 7.60 (t, 1 H, CH_{arom}, *J* = 7.8); 7.75 (t, 2 H, 2 CH_{arom}, *J* = 8.9); 7.90 (d, 2 H, 2 CH_{arom}, *J* = 8.9); 11.9 (s, 1 H, NH)	521
8a	6.55 (s, 1 H, CH_{aliph}); 7.20—7.65 (m, 10 H, Ar); 11.15 (s, 1 H, NH)	402
8b	6.45 (s, 1 H, CH_{aliph}); 7.10 (t, 1 H, CH_{arom}, *J* = 7.4); 7.40 (t, 2 H, 2 CH_{arom}, *J* = 7.3); 7.65 (d, 2 H, 2 CH_{arom}, *J* = 7.9); 7.30 (d, 1 H, CH_{arom}, *J* = 7.9); 7.15—7.25 (m, 2 H, 2 CH_{arom}); 7.85 (d, 1 H, CH_{arom}, *J* = 7.8); 9.45, 10.00 (both s, 1 H each, NH)	420
8c	6.40 (s, 1 H, CH_{aliph}); 7.10 (t, 1 H, CH_{arom}, *J* = 7.4); 7.40 (t, 2 H, 2 CH_{arom}, *J* = 7.3); 7.65 (d, 2 H, 2 CH_{arom}, *J* = 7.9); 7.85 (s, 2 H, 2 CH_{arom}); 8.00 (s, 1 H, CH_{arom}); 9.30, 10.05 (both s, 1 H each, NH)	471
9a	4.50 (s, 2 H, $CH_{2(aliph)}$); 7.20 (t, 1 H, CH_{arom}, *J* = 7.6); 7.40 (t, 2 H, 2 CH_{arom}, *J* = 7.6); 7.90 (d, 2 H, 2 CH_{arom}, *J* = 7.6); 10.85, 12.05 (both s, 1 H each, NH)	295
9b	4.40 (s, 2 H, $CH_{2(aliph)}$); 7.50 (t, 2 H, 2 CH_{arom}, *J* = 8.7); 7.90 (d, 2 H, 2 CH_{arom}, *J* = 8.7); 10.40, 11.9 (both s, 1 H each, NH)	329
9c	3.75 (s, 3 H, $OCH_{3(aliph)}$); 4.50 (s, 2 H, $CH_{2(aliph)}$); 6.95 (t, 2 H, 2 CH_{arom}, *J* = 8.9); 7.70 (d, 2 H, 2 CH_{arom}, *J* = 9.0); 11.60, 12.00 (both s, 1 H each, NH)	325
9d	1.25 (t, 3 H, $CH_{3(aliph)}$, *J* = 7.4); 1.35 (t, 3 H, $CH_{3(aliph)}$, *J* = 7.1); 2.70 (q, 2 H, $CH_{2(aliph)}$); 4.20 (s, 2 H, $CH_{2(aliph)}$); 4.35 (q, 2 H, $CH_{2(aliph)}$); 7.10 (s, 1 H, CH_{arom}); 11.40, 12.1 (both s, 1 H each, NH)	401

(0.1 g, 0.32 mmol) in methanol (10 mL) was mixed with ethylenediammonium diacetate (0.01 g, 0.0055 mmol) and benzaldehyde (0.034 g, 0.32 mmol) at ambient temperature. The reaction mixture was kept at room temperature for 20 min, and then poured into water (30 mL). The precipitate was filtered off and recrystallized from acetic acid (2 mL). Compounds **2b—i** were synthesized analogously.

2-{5-[(5-Nitro-2-furyl)methylene]-4-oxo-2-thioxo-1,3-thiazolidin-3-yl}amino-2-thioxo-*N*-phenylacetamide (2b) was synthesized from rhodanine **1a**.

2-[(5-Benzylydene-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)amino]-2-thioxo-*N*-(4-chlorophenyl)acetamide (2c) and **2-{5-[(5-nitro-2-furyl)methylene]-4-oxo-2-thioxo-1,3-thiazolidin-3-yl}amino-2-thioxo-*N*-(4-chlorophenyl)acetamide (2d)** were synthesized from rhodanine **1b**.

2-[(5-Benzylydene-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)amino]-2-thioxo-*N*-(4-methoxyphenyl)acetamide (2e) and **2-{5-[(5-nitro-2-furyl)methylene]-4-oxo-2-thioxo-1,3-thiazolidin-3-yl}amino-2-thioxo-*N*-(4-methoxyphenyl)acetamide (2f)** were synthesized from rhodanine **1c**.

Ethyl 2-(5-benzylydene-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)amino-5-ethyl-2-thioxoacetylaminothiophene-3-carboxylate (2g) and **ethyl 5-ethyl-2-[5-(5-nitro-2-furyl)methylene-4-oxo-2-thioxo-1,3-thiazolidin-3-yl]amino-2-thioxoacetylaminothiophene-3-carboxylate (2h)** were synthesized from rhodanine **1d**.

2-{4-Oxo-5-[(2-oxo-4-chloro-2*H*-chromen-3-yl)methylene]-2-thioxo-1,3-thiazolidin-3-yl}amino-2-thioxo-*N*-phenylacetamide (2i) was synthesized from rhodanine **1a**.

2-(5-Ethoxymethylene-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)amino-2-thioxo-*N*-phenylacetamide (3a). A mixture of rhodanine **1a** (0.1 g, 0.32 mmol) and triethyl orthoformate (0.048 g, 0.32 mmol) in acetic acid with sodium acetate was refluxed for 3 h. Then the reaction mixture was poured into water. The precipitate was filtered off and recrystallized from acetic acid (1 mL). Compounds **3b—d** were synthesized analogously.

2-(5-Ethoxymethylene-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)amino-2-thioxo-*N*-(4-chlorophenyl)acetamide (3b) was synthesized from rhodanine **1b**.

2-(5-Ethoxymethylene-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)amino-2-thioxo-*N*-(4-methoxyphenyl)acetamide (3c) was synthesized from rhodanine **1c**.

Ethyl 2-(5-ethoxymethylene-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)amino-5-ethyl-2-thioxoacetylaminothiophene-3-carboxylate (3d) was synthesized from rhodanine **1d**.

2-(5-Morpholinomethylene-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)amino-2-thioxo-*N*-phenylacetamide (4a). A mixture of 5-oxomethylenerhodanine **3a** (0.05 g, 0.14 mmol) in ethanol (2 mL) with morpholine (0.014 g, 0.16 mmol) was kept for 1 h at ambient temperature. Then the reaction mixture was poured into water. The precipitate was filtered off and recrystallized from acetic acid. Compounds **4b—d** were synthesized analogously.

2-(4-Oxo-5-piperidinomethylene-2-thioxo-1,3-thiazolidin-3-yl)amino-2-thioxo-*N*-phenylacetamide (4b) was synthesized from rhodanine **1a**.

2-(5-Morpholinomethylene-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)amino-2-thioxo-*N*-(4-chlorophenyl)acetamide (4c) and **2-(4-oxo-5-piperidinomethylene-2-thioxo-1,3-thiazolidin-3-yl)amino-2-thioxo-*N*-(4-chlorophenyl)acetamide (4d)** were synthesized from rhodanine **1b**.

2-(5-Morpholinomethylene-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)amino-2-thioxo-*N*-(4-methoxyphenyl)acetamide (4e) and **2-(4-oxo-5-piperidinomethylene-2-thioxo-1,3-thiazolidin-3-yl)amino-2-thioxo-*N*-(4-methoxyphenyl)acetamide (4f)** were synthesized from rhodanine **1c**.

Ethyl 5-ethyl-2-(5-morpholinomethylene-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)amino-2-thioxoacetylaminothiophene-3-carboxylate (4g) and **ethyl 5-ethyl-2-(4-oxo-5-piperidinomethylene-2-thioxo-1,3-thiazolidin-3-yl)amino-2-thioxoacetylaminothiophene-3-carboxylate (4h)** were synthesized from rhodanine **1d**.

2-(4-Oxo-2-thioxo-5-phenylhydrazono-1,3-thiazolidin-3-yl)amino-2-thioxo-*N*-phenylacetamide (5a). Rhodanine **1a** (0.1 g, 0.32 mmol) was dissolved in aqueous ethanol (1 : 1, v/v), and the solution was cooled in an ice-cold bath down to 0 °C. Diazonium salt was prepared from aniline (0.03 g, 0.32 mmol) and sodium nitrite (0.028 g, 0.4 mmol) in aqueous hydrochloric acid (3 mL) at 0 °C. A solution of rhodanine in aqueous alcohol was mixed with the diazonium salt at 0 °C, and the mixture was stirred for 2 h. The precipitate that formed was filtered off and recrystallized from acetic acid. Compounds **5b—d** were synthesized analogously.

2-(4-Oxo-2-thioxo-5-phenylhydrazono-1,3-thiazolidin-3-yl)amino-2-thioxo-*N*-(4-chlorophenyl)acetamide (5b) was synthesized from rhodanine **1b**.

2-(4-Oxo-2-thioxo-5-phenylhydrazono-1,3-thiazolidin-3-yl)amino-2-thioxo-*N*-(4-methoxyphenyl)acetamide (5c) was synthesized from rhodanine **1c**.

Ethyl 5-ethyl-2-(4-oxo-2-thioxo-5-phenylhydrazono-1,3-thiazolidin-3-yl)amino-2-thioxoacetylaminothiophene-3-carboxylate (5d) was synthesized from rhodanine **1d**.

2-(5-Benzoyl-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)amino-2-thioxo-*N*-phenylacetamide (6a). A mixture of rhodanine **1a** (0.1 g, 0.32 mmol) with benzoyl chloride (0.32 mmol) and sodium hydroxide (0.01 g, 0.32 mmol) in anhydrous dioxane (5 mL) was refluxed for 1.5 h. Then the reaction mixture was poured into water. The precipitate was filtered off and recrystallized from an ethanol—petroleum ether (1 : 1, v/v) mixture. Compounds **6b—d** were synthesized analogously.

2-(5-Benzoyl-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)amino-2-thioxo-*N*-(4-chlorophenyl)acetamide (6b) was synthesized from rhodanine **1b**.

2-(5-Benzoyl-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)amino-2-thioxo-*N*-(4-methoxyphenyl)acetamide (6c) was synthesized from rhodanine **1c**.

Ethyl 2-(5-benzoyl-4-oxo-2-thioxo-1,3-thiazolidin-3-yl-amino-2-thioxoacetylamino-5-ethyl)thiophene-3-carboxylate (6d) was synthesized from rhodanine **1d**.

2-(5-Anilino-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)amino-2-thioxo-*N*-phenylacetamide (8a). Rhodanine **1a** (0.1 g, 0.32 mmol) was dissolved in dioxane (5 mL) and mixed with bromine (0.056 g, 0.35 mmol). The reaction mixture was kept for 14 h. Then aniline (0.03 g, 0.32 mmol) was added to the solution at 10 °C, and the reaction mixture was stirred for 1 h. The mixture was poured into water, and the precipitate was filtered off. Compounds **8b,c** were synthesized analogously.

2-(5-Anilino-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)amino-2-thioxo-*N*-(3-fluorophenyl)acetamide (8b) were synthesized from rhodanine **1a** and 3-fluoroaniline.

2-(5-Anilino-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)amino-2-thioxo-*N*-(3,5-dichlorophenyl)acetamide (8c) was synthesized from rhodanine **1a** and 3,5-dichloroaniline.

***N*-(4-Oxo-2-thioxo-1,3-thiazolidin-3-yl)-*N*′-phenylethanediamide (9a).** A solution of rhodanine **1a** (0.05 g, 0.16 mmol) in acetonitrile (5 mL) was mixed with three droplets of hydrogen peroxide at ambient temperature. Then the reaction mixture was poured into water. The precipitate was filtered off and recrystallized from an ethanol—petroleum ether (1 : 1, v/v) mixture. Compounds **9b—d** were synthesized analogously.

***N*-(4-Oxo-2-thioxo-1,3-thiazolidin-3-yl)-*N*′-(4-chlorophenyl)ethanediamide (9b)** was synthesized from rhodanine **1b**.

***N*-(4-Methoxyphenyl)-*N*′-(4-oxo-2-thioxo-1,3-thiazolidin-3-yl)ethanediamide (9c)** was synthesized from rhodanine **1c**.

Ethyl 5-ethyl-2-(4-oxo-2-thioxo-1,3-thiazolidin-3-yl)amino-glyoxylylaminothiophene-3-carboxylate (9d) was synthesized from rhodanine **1d**.

References

1. S. Bondoc, W. Khalifa, and A. A. Fadda, *Eur. J. Med. Chem.*, 2007, **42**, 948.
2. R. Dayam, T. Sanchez, O. Clement, R. Shoemaker, S. Sei, and N. Neamati, *J. Med. Chem.*, 2005, **48**, 111.
3. V. N. Yarovenko, A. S. Nikitina, I. V. Zavarzin, M. M. Krayushkin, and L. V. Kovalenko, *Synthesis*, 2006, **8**, 1246.
4. S. N. Baranov and R. O. Kochkanyan, *Khim.-Farm. Zh.*, 1970, **3**, 25 [*Pharm. Chem. J.*, 1970, **3** (Engl. Transl.)].

Received July 23, 2007