DOI 10.1515/hc-2013-0055 — Heterocycl. Commun. 2013; 19(4): 275–280

Karine A. Eliazyan, Ruzanna S. Hakobyan, Vergush A. Pivazyan, Emma A. Ghazaryan, Siranush V. Harutyunyan and Aleksandr P. Yengoyan*

Synthesis of novel 2-arylsulfonylimino-3,4-dimethyl-5-(5-*S*-substituted [1,3,4]oxadiazol-2-yl)-2,3-dihydrothiazole derivatives and their plant growth stimulant activity

Abstract: 2-Arylsulfonylimino-3,4-dimethyl-2,3-dihydrothiazole-5-carboxylic acid hydrazides **2** were obtained from corresponding 2-arylsulfonylimino-4-methyl-2,3-dihydrothiazole-5-carboxylic acid ethyl esters **1** in a two-step synthesis. Heterocyclization of the hydrazide moiety yielded 2-arylsulfonylimino-3,4-dimethyl-5-(5-thioxo-4,5-dihydro-[1,3,4]oxadiazol-2-yl)-2,3-dihydro-thiazoles **3**. Treatment of compounds **3** with various alkyl halides gave corresponding *S*-substituted derivatives **4–6**. The plant growth stimulant activities of synthesized compounds were compared with those of similar [1,2,4]triazol- and [1,3,4,]thiadiazol-2-yl-thiazoles.

Keywords: 2-arylsulfonylimino-3,4-dimethyl-2,3-dihydrothiazole-5-carboxylic acid hydrazides; heterocyclization; [1,3,4]oxadiazol-2-yl-thiazoles; plant growth stimulant activity.

***Corresponding author: Aleksandr P. Yengoyan,** Armenian National Agrarian University, Teryan, 74, Yerevan 0009, Armenia; and Armenian-Russian (Slavonic) State University, H. Emin, 123, Yerevan 0051, Armenia, e-mail: ayengoyan@mail.ru
Karine A. Eliazyan, Ruzanna S. Hakobyan, Vergush A. Pivazyan, Emma A. Ghazaryan and Siranush V. Harutyunyan: Armenian National Agrarian University, Teryan, 74, Yerevan 0009, Armenia

Introduction

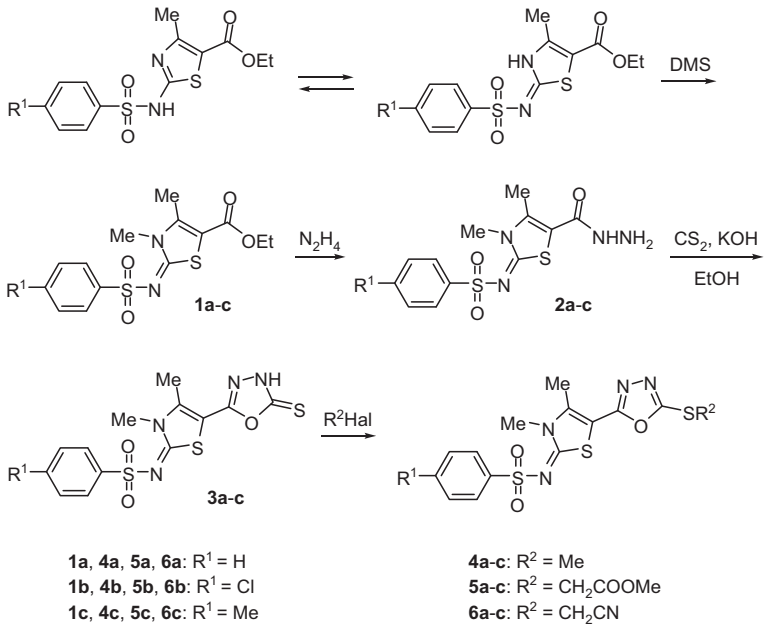
Derivatives of N,S,O-containing five-membered heterocycles, in particular thiazole and [1,3,4]oxadiazole, exhibit a broad spectrum of biological activity. In agriculture, the thiazole derivatives are widely used for chemical means of plant protection and growth regulation. They are known as herbicides (benazolin, benzthiazuron, fenthiaprop mefenacet, metabenzthiazuron, thiazopir), fungicides (ethaboxam, fluthianil, isotianil, metsulfovax, octhilinone, thiabendazole, thiadifluor, thifluzamide,), insecticides (clothianidin, imidaclothiz, tazimcarb, thiacloprid, thiamethoxam, thiapronil), acaricides (flubenzimine, hexythiazox), and bactericides (amicarthiazol). The arsenal of pesticides based on [1,3,4]oxadiazole is more limited and includes oxadiazolone herbicides (dimefuron, oxadiargyl, oxadiazon) and insecticide (metoxadiazone) (http://www.alanwood.net/pesticides/class_pesticides.html). However, the search for new biologically active compounds continues among the new, previously unexplored series of thiazole [1–9] and [1,3,4]oxadiazole derivatives [10–21].

The aim of the present investigation was to develop facile and efficient methods for the synthesis of non-condensed 2-arylsulfonylimino-substituted biheterocyclic systems with combination of [1,3,4]oxadiazole and thiazole rings and to study their physiological activity.

Results and discussion

Synthesis

The treatment of 2-arylsulfonylimino-4-methyl-2,3-dihydrothiazole-5-carboxylic acid ethyl esters with dimethyl sulfate gave the corresponding *N*-methylated derivatives **1a–c** (Scheme 1). In principle, alkylation can proceed on both exocyclic and endocyclic nitrogen atoms of the substrate. The structure determination could not be based on analysis of ^{13}C NMR spectra due to lack of model compounds. Therefore, X-ray diffraction analysis of methyl derivative **1a** was carried out, which showed that methylation occurs exclusively at the endocyclic nitrogen atom (Figure 1). The reaction of compounds **1a–c** with hydrazine hydrate yielded corresponding hydrazides **2a–c**. By their heterocyclization with carbon disulfide and potassium hydroxide in ethanol



Scheme 1

2-arylsulfonylimino-3,4-dimethyl-5-(5-thioxo-4,5-dihydro-[1,3,4]oxadiazol-2-yl)-2,3-dihydro-thiazoles **3a–c** were obtained. These compounds have thione structure because their ^{13}C NMR spectra contain the signal for the C=S moiety at 176 ppm. Treatment of **3a–c** with dimethyl sulfate, chloroacetic acid methyl ester or chloroacetonitrile yielded the *S*-substituted derivative **4a–c**, **5a–c**, or **6a–c**, respectively. Alkylation of these compounds occurs at the sulfur atom because ^{13}C NMR spectra display new signals for a C=N bond of [1,3,4]oxadiazole and the C=S signals are not observed.

Biological activity

The object of study was the seeds and seedlings of dicotyledonous common bean (*Phaseolus vulgaris* L.) collected in September 2012 from the Syunik region of Armenia. At preliminary screening, the possible herbicidal, fungicidal, and growth regulatory activities of novel compounds **3–6** were studied. All preparations did not show noticeable herbicidal or antifungal properties, but they showed a growth stimulant effect. Subsequently, more detailed studies of the activity of compounds **3–6** on the germination, growth, and survivability of seeds and seedlings of common bean were performed.

In the first set of experiments, the effect of aqueous solutions of compounds **3–6** and heteroauxin (indole-3-acetic acid, IAA) in concentrations of 25 and 50 mg/L was studied. The seeds were incubated for 24 h in an appropriate medium in the dark at 25°C. Then, the seeds were transplanted into soil and watered daily.

In the second experimental setup, the bean seeds were placed in the soil in small vessels. When the length of the stems reached 15–20 cm, the plants were dug out, the root parts were washed with water and cut off. A series of 8–10 cut plants were immersed in the prepared aqueous solutions of IAA or **3–6** at concentrations of 25 mg/L and 50 mg/L. After 24 h, they were washed and dipped into the vessels with water. Water in the vessels was changed every day. For every compound, the two experimental schemes were repeated three times. The experiments were conducted for 20–25 days. The number of plant roots of each series, and their length and weight in the moist and dry

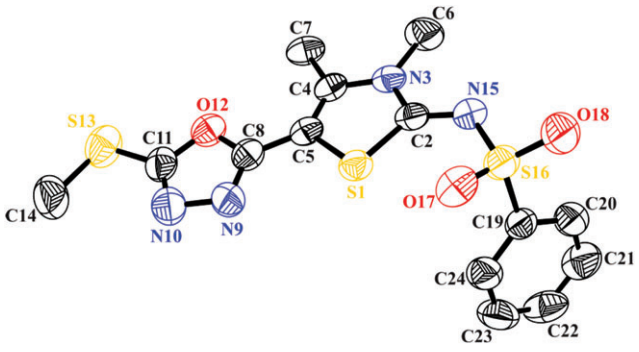


Figure 1 Molecular structure of compound **1a**.

forms were calculated. The results were compared with similar data of plants placed in IAA solutions, and the activities of preparations in comparison with IAA (in %) were determined (Table 1). The data show that the growth stimulant properties increase in the following order **4** ≈ **6** < **3** < **5**.

Conclusions

This research is the continuation of our previous efforts on the synthesis of new non-condensed biheterocyclic systems with 1,2,3-triazole, 1,3,4-thiadiazole, or 1,3,4-oxadiazole moieties, additionally substituted with a thiazolyl, arylsulfonylimino [22], arylsulfonylethylamino [23], or thioxo [24–26] group. Practically, all derivatives of these systems manifest growth stimulant activity, in certain cases equal to the activity of heteroauxin. The triazolylthiazole derivatives also possess fungicidal properties [24]. The results of preliminary bioassays show that the obtained new compounds show promise for the development as new growth stimulators and fungicides.

Table 1 Growth stimulant activity of compounds **3–6.**

Compound	Concentration, mg/L	Activity
IAA	50	100
	25	100
3a	50	74.6
	25	75.3
3b	50	73.8
	25	63.4
3c	50	47.2
	25	49.5
4a	50	60.5
	25	55.5
4b	50	40.2
	25	41.7
4c	50	41.1
	25	42.2
5a	50	93.0
	25	85.1
5b	50	73.8
	25	62.1
5c	50	81.7
	25	59.6
6a	50	62.3
	25	79.9
6b	50	60.1
	25	73.5
6c	50	42.6
	25	60.5

Experimental

General

^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz, decoupled and coupled modes) spectra were recorded on a Varian Mercury 300 spectrometer in the mixture of DMSO-d_6 and CCl_4 (1:3) or in pure DMSO-d_6. The reaction progress and purity of the obtained substances were checked by using TLC on 'Silufol UV-254' plates with an acetone/hexane mixture (2:1) as eluent. Melting points were determined in open capillaries and are uncorrected. An X-ray diffraction experiment was carried out at room temperature on an Enraf-Nonius automatic diffractometer CAD-4.

General procedure for 1a–c

2-Arylsulfonylimino-3-methylthiazol-5-carboxylic acid ethyl ester potassium salts were obtained by treatment of esters (0.01 mol) with KOH (0.01 mol) at 0°C. These products (0.01 mol) in water (10 mL) were allowed to react with dimethyl sulfate for 24 h at 20–25°C. The precipitate was filtered off, washed with water, and dried.

2-Benzenesulfonylimino-3,4-dimethyl-2,3-dihydrothiazol-5-carboxylic acid ethyl ester (1a) Flesh-colored crystals; mp 125–127°C; yield 3.05 g (90%); ^{1}H NMR: δ 1.36 (t, 3H, J = 7.0 Hz, OCH_2CH_3), 2.58 (s, 3H, 4-CH_3), 3.47 (s, 3H, 3-NCH_3), 4.32 (q, 2H, J = 7.0 Hz, OCH_2CH_3), 7.45–7.90 (m, 5H, C_6H_5). Anal. Calcd for $C_{14}H_{16}N_2O_4S_2$: C, 49.40; H, 4.74; N, 8.23; S, 18.84. Found: C, 49.26; H, 4.63; N, 7.88; S, 18.48.

Crystal data for 1a $C_{14}H_{14}N_4O_3S_3$, monoclinic, space group $P2_1/c$, a = 10.914(2), b = 15.176(3), c = 10.285(2) Å, β = 92.45(3)°, V = 1702.0(6) Å^3, Z = 4, T = 293(2)K, d_x = 1.493 g cm^{-3}, μ(MoKα) = 0.71073 mm^{-1}, 4967 data were collected up to θ_{max} = 30° (R_{int} = 0.0675, R_σ = 0.1575). Final R-indices for 1802 reflections with $I > 2\sigma(I)$ and 220 refined parameters are: R_1 = 0.0626, wR_2 = 0.1150 (R_1 = 0.2395, wR_2 = 0.1532 for all 4967 data). Crystallographic data for compound **1a** have been deposited with the Cambridge Crystallographic Data Centre, deposition no. CCDC 940247.

2-(4-Chlorobenzenesulfonylimino)-3,4-dimethyl-2,3-dihydrothiazole-5-carboxylic acid ethyl ester (1b) Flesh-colored crystals; mp 156–158°C; yield 3.08 g (82%); ^{1}H NMR: δ 1.35 (t, 3H, J = 7.0 Hz, OCH_2CH_3), 2.59 (s, 3H, 4-CH_3), 3.48 (s, 3H, 3-NCH_3), 4.31 (q, 2H, J = 7.0 Hz, OCH_2CH_3), 7.47–7.87 (m, 4H, C_6H_4). Anal. Calcd for $C_{14}H_{15}ClN_2O_4S_2$: C, 44.86; H, 4.03; N, 7.47; S, 17.11. Found: C, 44.72; H, 3.91; N, 7.08; S, 16.77.

2-(4-Methylbenzenesulfonylimino)-3,4-dimethyl-2,3-dihydrothiazole-5-carboxylic acid ethyl ester (1c) Flesh-colored crystals; mp 184–186°C; yield: 3.18 g (90%); ^{1}H NMR: δ 1.35 (t, 3H, J = 7.0 Hz, OCH_2CH_3), 2.42 (s, 3H, $CH_3C_6H_4$), 2.61 (s, 3H, 4-CH_3), 3.48 (s, 3H,

NCH_3), 4.30 (q, 2H, J = 7.0 Hz, OCH_2CH_3), 7.26–7.75 (m, 4H, C_6H_4); ^{13}C NMR (coupled): δ 12.9 (4-CH_3); 14.0 (OCH_2CH_3), 20.8 ($CH_3C_6H_4$), 32.7 (3-NCH_3), 61.2 (OCH_2CH_3), 106.0 (C-5; ^3J = 4.2 Hz), 125.9; 129.4, 138.7; 146.6, (Ar); 142.8 (C-4; ^2J = 6.6 Hz), 160.4 (C=O, ^3J = 3.2 Hz), 165.2 (C-2, ^3J = 3.2 Hz). Anal. Calcd for $C_{15}H_{18}N_2O_4S_2$: C, 50.83; H, 5.12; N, 7.90; S, 18.09. Found: C, 50.60; H, 5.06; N, 7.69; S, 17.88.

General procedure for 2a–c

The suspension of 2-arylsulfonylimino-3,4-dimethylthiazol-5-carboxylic acid ethyl ester **1** (0.01 mol) in 15 mL of hydrazine hydrate (48%) was stirred at 20°C for 2 days. The precipitate was filtered off, washed with water, and dried. Compounds **2** were purified by boiling in hexane.

2-Benzenesulfonylimino-3,4-dimethyl-2,3-dihydrothiazole-5-carboxylic acid hydrazide (**2a**) White crystals; mp 174–176°C (with decomp.); yield 2.28 g (70%); ^1H NMR: δ 2.45 (s, 3H, 4-CH_3), 3.42 (s, 3H, 3-NCH_3), 4.50 and 4.84 (brs, 2H, NH_2), 7.50–7.87 (m, 5H, C_6H_5), 8.85 and 9.50 (brs, 1H, NH); ^{13}C NMR: δ 13.0 (4-CH_3), 32.7 (3-NCH_3), 109.7 (C-5), 125.9, 128.9, 132.3, 140.0 (Ph), 141.7 (C-4), 160.2 (C=O), 164.8 (C-2). Anal. Calcd for $C_{12}H_{14}N_4O_3S_2$: C, 44.16; H, 4.32; N, 17.17; S, 19.65. Found: C, 44.02; H, 4.20; N, 16.89; S, 19.44.

2-(4-Chlorobenzenesulfonylimino)-3,4-dimethyl-2,3-dihydrothiazole-5-carboxylic acid hydrazide (**2b**) White crystals; mp 191–193°C (with decomp.); yield 3.25 g (90%); ^1H NMR: δ 2.50 (s, 3H, 4-CH_3), 3.43 (s, 3H, 3-NCH_3), 4.50 and 4.80 (brs, 2H, NH_2), 7.61–7.92 (m, 4H, C_6H_4), 8.80 and 9.40 (brs, 1H, NH); ^{13}C NMR: δ 13.0 (4-CH_3), 32.7 (3-NCH_3), 109.7 (C-5), 127.8, 129.3, 137.3, 140.1 (Ar), 141.7 (C-4), 160.2 (C=O), 164.8 (C-2). Anal. Calcd for $C_{12}H_{13}ClN_4O_3S_2$: C, 39.94; H, 3.63; N, 15.53; S, 17.77. Found: C, 39.85; H, 3.54; N, 15.30; S, 17.52.

2-(4-Methylbenzenesulfonylimino)-3,4-dimethyl-2,3-dihydrothiazole-5-carboxylic acid hydrazide (2c) White crystals; mp 190–192°C (with decomp.); yield 2.70 g (79%); ^1H NMR: δ 2.36 (s, 3H, PhCH_3), 2.45 (s, 3H, 4-CH_3), 3.41 (s, 3H, 3-NCH_3), 4.51 and 4.83 (brs, 2H, NH_2), 7.30–7.78 (m, 4H, C_6H_4), 8.83 and 9.49 (brs, 1H, NH); ^{13}C NMR (coupled): δ 13.0 (4-CH_3), 20.9 (PhCH_3), 32.6 (2-NCH_3), 109.6 (m, C-5), 125.9, 129.4, 138.9 (t, ^2J =8.3 Hz), 140.0 (m) (Ar), 142.6 (q, ^3J = 6.6 Hz, C-4), 160.3 (brs, C=O), 164.7 (q, ^3J = 3.0 Hz, C-2). Anal. Calcd for $C_{13}H_{16}N_4O_3S_2$: C, 45.87; H, 4.74; N, 16.46; S, 18.84. Found: C, 45.69; H, 4.62; N, 16.20; S, 18.61.

General procedure for 3a–c

To a mixture of hydrazide **2** and 1.2 mL (0.02 mol) of carbon disulfide in 20 mL of ethanol, at boiling, 1.12 g (0.02 mol) of KOH in 10 mL of ethanol was added dropwise with continuous stirring. After 7 h ethanol was evaporated, 10 mL of water was added, and the resultant suspension was acidified with HCl to pH 4. After 2–3 h the precipitate was filtered off, washed with water, and purified by boiling in ethanol (50%).

2-Benzenesulfonylimino-3,4-dimethyl-5-(5-thioxo-4,5-dihydro-[1,3,4]oxadiazol-2-yl)-2,3-dihydrothiazole (3a) Yellow crystals; mp 236–238°C (with decomp.); yield 2.87 g (78%); ^1H NMR: δ 2.60 (s, 3H, 4-CH_3), 3.55 (s, 3H, 3-NCH_3), 7.50–7.90 (m, 5H, C_6H_5), 14.50 (brs, 1H, NH); ^{13}C NMR (coupled): δ 13.2 (4-CH_3), 32.8 (3-NCH_3), 99.0 (q, ^3J = 4.8 Hz, C-5), 125.8, 128.4, 131.8, 140.3 (Ph), 141.5 (q, ^2J = 6.6 Hz, C-4), 154.5 (C-2′), 164.6 (q, ^3J = 3.1 Hz, C-2), 176.4 (C=S). Anal. Calcd for $C_{13}H_{12}N_4O_3S_3$: C, 42.38; H, 3.28; N, 15.21; S, 26.11. Found: C, 42.21; H, 3.16; N, 15.00; S, 25.92.

2-(4-Chlorobenzenesulfonylimino)-3,4-dimethyl-5-(5-thioxo-4,5-dihydro-[1,3,4]oxadiazol-2-yl)-2,3-dihydrothiazole (3b) Yellow crystals; mp 242–244°C (with decomp.); yield 3.30 g (82%); ^1H NMR: δ 2.61 (s, 3H, 4-CH_3), 3.53 (s, 3H, 3-NCH_3), 7.60–7.92 (m, 4H, C_6H_4), 14.55 (brs, 1H, NH); ^{13}C NMR (coupled): δ 13.12 (4-CH_3), 32.8 (3-NCH_3), 99.3 (q, ^3J = 4.8 Hz, C-5), 127.6, 128.5, 137.5, 140.1 (Ar), 140.3 (q, ^2J = 6.6 Hz, C-4), 154.3 (C-2′), 160.0 (q, ^3J= 3.1 Hz, C-2), 176.35 (C=S). Anal. Calcd for $C_{13}H_{11}ClN_4O_3S_3$: C, 38.75; H, 2.75; N, 13.91; S, 23.88. Found: C, 38.62; H, 2.69; N, 13.70; S, 23.61.

2-(4-Methylbenzenesulfonylimino)-3,4-dimethyl-5-(5-thioxo-4,5-dihydro-[1,3,4]oxadiazol-2-yl)-2,3-dihydrothiazole (3c) Yellow crystals; mp 242–244°C (with decomp.); yield 3.30 g (82%); ^1H NMR: δ 2.43 (s, 3H, PhCH_3), 2.60 (s, 3H, 4-CH_3), 3.53 (s, 3H, 3-NCH_3), 7.28–7.78 (m, 4H, C_6H_4), 14.50 (brs, 1H, NH); ^{13}C NMR (coupled): δ 13.3 (4-CH_3), 20.9 (PhCH_3), 33.1 (2-NCH_3), 98.6 (q, ^3J = 4.8 Hz, C-5), 125.9, 129.4, 138.4, 141.4 (Ar), 142.7 (q, ^2J = 6.6 Hz, C-4), 154.9 (C-2′), 164.6 (q, ^3J = 3.2 Hz, C-2), 176.4 (C=S). Anal. Calcd for $C_{14}H_{14}N_4O_3S_3$: C, 43.96; H, 3.69; N, 14.65; S, 25.15. Found: C, 43.82; H, 3.57; N, 14.31; S, 24.85.

General procedure for 4a–c

To a solution of compound **3** (0.01 mol) and KOH (0.01 mol) in 20 mL of water at 20°C, 1 mL (0.01 mol) of dimethyl sulfate was added portion-wise. The mixture was stirred at 20°C for 24 h, and the resultant precipitate of compound **3** was filtered off, washed with water, dried, and crystallized from benzene.

2-Benzenesulfonylimino-3,4-dimethyl-5-(5-methylsulfanyl-[1,3,4]oxadiazol-2-yl-)-2,3-dihydro-thiazole (4a) White crystals; mp 180–182°C; yield 2.98 g (78%); ^1H NMR: δ 2.62 (s, 3H, 4-CH_3), 2.78 (s, 3H, SCH_3), 3.57 (s, 3H, 3-NCH_3), 7.48–7.90 (m, 5H, C_6H_5); ^{13}C NMR: δ 13.1 (4-CH_3), 14.1 (SCH_3), 32.8 (3-NCH_3), 99.3 (C-5), 125.7, 128.2, 131.6, 139.6 (Ph); 141.5 (C-4), 158.9 (C-2′), 163.3 (C-5′), 164.7 (C-2). Anal. Calcd for $C_{14}H_{14}N_4O_3S_3$: C, 43.96; H, 3.69; N, 14.65; S, 25.15. Found: C, 43.82; H, 3.60; N, 14.32; S, 24.84.

2-(4-Chlorobenzenesulfonylimino)-3,4-dimethyl-5-(5-methylsulfanyl-[1,3,4]oxadiazol-2-yl-)-2,3-dihydrothiazole (4b) White crystals; mp 158–160°C; yield 3.12 g (75%); ^1H NMR: δ 2.57 (s, 3H, 4-CH_3), 2.75 (s, 3H, SCH_3), 3.50 (s, 3H, 3-NCH_3), 7.60–7.92 (m, 4H, C_6H_4); ^{13}C NMR (coupled): δ 13.3 (4-CH_3), 14.3 (SCH_3), 33.3 (3-NCH_3), 99.3 (q, ^3J = 4.8 Hz, C-5), 127.8, 129.2, 137.3, 140.2 (Ar), 141.0 (q, ^2J = 6.6 Hz, C-4), 159.1 (C-2′), 164.0 (C-5′), 165.0 (q, ^3J = 3.1 Hz, C-2). Anal. Calcd for $C_{14}H_{13}ClN_4O_3S_3$: C, 40.33; H, 3.14; N, 13.44; S, 23.07. Found: C, 40.20; H, 3.05; N, 13.21; S, 22.79.

2-(4-Methylbenzenesulfonylimino)-3,4-dimethyl-5-(5-methylsulfanyl-[1,3,4]oxadiazol-2-yl-)-2,3-dihydrothiazole (4c) White crys-

tals; mp 230–232°C; yield 3.37 g (85%); ^{1}H NMR: δ 2.42 (s, 3H, PhCH_3), 2.62 (s, 3H, 4-CH_3), 2.78 (s, 3H, SCH_3), 3.54 (s, 3H, 3-NCH_3), 7.27–7.78 (m, 4H, C_6H_4); ^{13}C NMR: δ 13.1 (4-CH_3), 14.2 (SCH_3), 20.8 (PhCH_3), 32.9 (3-NCH_3), 99.1 (C-5); 125.8, 129.0; 138.6, 140.1 (Ar), 142.3 (C-4), 159.0 (C-2′), 163.6 (C-5′), 164.6 (C-2). Anal. Calcd for $C_{15}H_{16}N_4O_3S_3$: C, 45.44; H, 4.07; N, 14.13; S, 24.26. Found: C, 45.22; H, 3.97; N, 13.88; S, 24.01.

General procedure for 5a–c and 6a–c

A potassium salt of **3a–c** (0.01 mol) was obtained by treatment of compound **3a–c** (0.01 mol) with KOH (0.01 mol) in 30 mL of acetone at 10–15°C. A suspension of this salt was treated with chloroacetic acid methyl ester or chloroacetonitrile (0.011 mol), and the mixture was heated at 50–60°C for 3 h. After filtration the solution was concentrated, and the residue was treated with water. The resultant precipitate was filtered off and dried. Compounds **5a** and **6a** were crystallized from benzene and others were purified by boiling in hexane.

2-Benzenesulfonylimino-3,4-dimethyl-5-(5-methoxycarbonyl-methylsulfanyl-[1,3,4]oxadiazol-2-yl)-2,3-dihydrothiazole (5a) White crystals; mp 168–169°C; yield 3.87 g (88%); ^{1}H NMR: δ 2.62 (s, 3H, 4-CH_3), 3.53 (s, 3H, 3-NCH_3), 3.80 (s, 3H, OCH_3), 4.20 (s, 2H, SCH_2), 7.47–7.88 (m, 5H, C_6H_5); ^{13}C NMR: δ 13.1 (4-CH_3); 32.7 (3-NCH_3); 33.5 (SCH_2); 52.2 (OCH_3); 99.2 (C-5); 125.7, 128.2, 131.6, 139.6 (Ph); 142.1 (C-4); 159.2 (C-2′); 162.3 (C-5′); 164.6 (C-2); 167.2 (C=O). Anal. Calcd for $C_{16}H_{16}N_4O_5S_3$: C, 43.62; H, 3.66; N, 12.72; S, 21.84. Found: C, 43.50; H, 3.55; N, 12.46; S, 21.56.

2-(4-Chlorobenzenesulfonylimino)-3,4-dimethyl-5-(5-methoxycarbonyl-methylsulfanyl-[1,3,4]oxadiazol-2-yl)-2,3-dihydrothiazole (5b) White crystals; mp 190–192°C; yield 3.94 g (83%); ^{1}H NMR: δ 2.60 (s, 3H, 4-CH_3), 3.50 (s, 3H, 3-NCH_3), 3.80 (s, 3H, OCH_3), 4.20 (s, 2H, SCH_2), 7.60–7.92 (m, 4H, C_6H_4); ^{13}C NMR: δ 13.1 (4-CH_3); 32.9 (3-NCH_3); 33.4 (SCH_2); 52.3 (OCH_3); 99.2 (C-5); 127.8, 129.1, 137.3, 140.3 (Ar); 141.6 (C-4); 159.0 (C-2′); 162.5 (C-5′); 164.6 (C-2); 167.2 (C=O). Anal. Calcd for $C_{16}H_{15}ClN_4O_5S_3$: C, 40.46; H, 3.18; N, 11.80; S, 20.25. Found: C, 40.29; H, 3.07; N, 11.52; S, 20.02.

2-(4-Methylbenzenesulfonylimino)-3,4-dimethyl-5-(5-methoxycarbonyl-methylsulfanyl-[1,3,4]oxadiazol-2-yl)-2,3-dihydrothiazole (5c) White crystals; mp 194–196°C; yield 4.10 g (90%); ^{1}H NMR: δ 2.42 (s, 3H, PhCH_3), 2.62 (s, 3H, 4-CH_3), 3.55 (s, 3H, 3-NCH_3), 3.78 (s, 3H, OCH_3), 4.18 (s, 2H, SCH_2), 7.25–7.78 (m, 4H, C_6H_4); ^{13}C NMR: δ 13.1 (4-CH_3), 20.8 (PhCH_3), 32.8 (3-NCH_3), 33.4 (SCH_2), 52.2 (OCH_3), 99.1 (C-5), 125.8, 128.8; 138.7, 140.0 (Ar), 142.0 (C-4), 159.2 (C-2′), 161.6 (C-5′), 164.6 (C-2), 167.1 (C=O). Anal. Calcd for $C_{17}H_{18}N_4O_5S_3$: C, 44.92; H, 3.99; N, 12.33; S, 21.16. Found: C, 44.79; H, 3.88; N, 12.03; S, 20.90.

2-Benzenesulfonylimino-3,4-dimethyl-5-(5-cyanomethylsulfanyl-[1,3,4]oxadiazol-2-yl)-2,3-dihydro-thiazole (6a) Flesh-colored crystals; mp 198–200°C; yield 3.38 g (83%); ^{1}H NMR: δ 2.62 (s, 3H, 4-CH_3), 3.55 (s, 3H, 3-NCH_3), 4.42 (s, 2H, SCH_2), 7.48–7.89 (m, 5H, C_6H_5); ^{13}C NMR: δ 13.2 (4-CH_3); 17.7 (SCH_2); 32.7 (3-NCH_3); 99.9 (C-5); 115.6 (C≡N); 125.7, 128.1, 131.6, 139.6 (Ph); 142.1 (C-4); 159.9 (C-2′); 160.3 (C-5′); 164.6 (C-2). Anal. Calcd for $C_{15}H_{13}N_5O_3S_3$: C, 44.21; H, 3.22; N, 17.19; S, 23.61. Found: C, 44.09; H, 3.13; N, 16.88; S, 23.30.

2-(4-Chlorobenzenesulfonylimino)-3,4-dimethyl-5-(5-cyanomethylsulfanyl-[1,3,4]oxadiazol-2-yl)-2,3-dihydrothiazole (6b) Flesh-colored crystals; mp 158–160°C; yield 3.97 g (90%); ^{1}H NMR: δ 2.62 (s, 3H, 4-CH_3), 3.53 (s, 3H, 3-NCH_3), 4.40 (s, 2H, SCH_2), 7.58–7.90 (m, 4H, C_6H_4); ^{13}C NMR: δ 13.21 (4-CH_3); 17.6 (SCH_2); 32.8 (3-NCH_3); 99.9 (C-5); 115.5 (C≡N); 127.8, 129.2, 137.4, 140.3 (Ar); 141.9 (C-4); 159.9 (C-2′); 160.2 (C-5′); 164.6 (C-2). Anal. Calcd for $C_{15}H_{12}ClN_5O_3S_3$: C, 40.77; H, 2.74; N, 15.85; S, 21.77. Found: C, 40.70; H, 2.69; N, 15.62; S, 21.49.

2-(4-Methylbenzenesulfonylimino)-3,4-dimethyl-5-(5-cyanomethylsulfanyl-[1,3,4]oxadiazol-2-yl)-2,3-dihydrothiazole (6c) Flesh-colored crystals; mp 188–190°C; yield 4.0 g (95%); ^{1}H NMR: δ 2.42 (s, 3H, PhCH_3), 2.62 (s, 3H, 4-CH_3), 3.53 (s, 3H, 3-NCH_3), 4.40 (s, 2H, SCH_2), 7.27–7.78 (m, 4H, C_6H_4); ^{13}C NMR (coupled): δ 13.2 (4-CH_3), 17.5 (SCH_2), 20.9 (PhCH_3), 32.8 (3-NCH_3), 100.0 (q, ^3J = 4.8 Hz, C-5), 115.6 (t, ^2J = 8.1 Hz, C≡N), 125.8, 128.8; 138.6, 140.5 (Ar), 142.1 (q, ^2J = 6.6 Hz, C-4), 159.9 (C-2′), 160.2 (t, ^3J = 6.2 Hz, C-5′), 164.6 (q, ^3J = 3.1 Hz, C-2). Anal. Calcd for $C_{16}H_{15}N_5O_3S_3$: C, 45.59; H, 3.59; N, 16.61; S, 22.82. Found: C, 45.41; H, 3.48; N, 16.36; S, 22.58.

Received April 8, 2013; accepted June 7, 2013; previously published online July 10, 2013

References

[1] Kumar, R.; Kotha, V.; Kumar, S. Simple and convenient synthesis of 2-(substituted-benzylsulfanyl)-4,5-dihydrothiazoles and their antimicrobial activity studies. *J. Heterocycl. Chem.* **2005**, *42*, 1191–1193.

[2] Manju, S.; Devi, S.; Rajasekharan, K. Synthesis and antimicrobial studies of novel bis(diamino)thiazoles. *J. Heterocycl. Chem*. **2009**, *46*, 455–458.

[3] El-Aasar, N.; Saied, K. Synthesis of new thiazolidine and imidazolidine derivatives of pharmacological interest. *J. Heterocycl. Chem*. **2008**, *45*, 645–652.

[4] Dayan, F.; Vincent, A.; Romagni, J.; Allen, S.; Duke, S.; Duke, M.; Bowling, J.; Zjawiony, J. Amino- and urea-substituted thiazoles inhibit photosynthetic electron transfer. *J. Agric. Food Chem*. **2000**, *48*, 3689–3693.

[5] Wang, Q.; Li, H.; Li, Y.; Huang, R. Synthesis and herbicidal activity of 2-cyano-3-(2-chlorothiazol-5-yl)methylaminoacrylates. *J. Agric. Food Chem*. **2004**, *52*, 1918–1922.

[6] Sanemitsu, Y.; Kawamura, S.; Satoh, J.; Katayama, T.; Hashimoto, S. Synthesis and herbicidal activity of 2-acylimino-3-phenyl-1,3-thiazolines. A new family of bleaching herbicides. *J. Pestic. Sci*. **2006**, *31*, 305–310.

[7] Mori, M.; Takagi, M.; Noritake, C.; Kagabu, S. 2,4-Dioxo-1,3-thiazolidine derivatives as a lead for new fungicides. *J. Pestic. Sci*. **2008**, *33*, 357–363.

[8] Kayagil, I.; Demirayak, S. Synthesis and anticancer activities of some thiazole derivatives. *Phosphorus Sulfur Silicon Relat. Elem.* **2009**, *184*, 2197–2207.
[9] Wang, T.; Bing, G.; Zhang, X.; Qin, Z.; Yu, H.; Qin, X.; Dai, H.; Miao, W.; Wu, S.; Fang, J. Synthesis and herbicidal activities of 2-cyano-3-benzylaminoacrylates containing thiazole moiety. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3348–3351.
[10] Chen, H.; Li, Z.; Han, Y. Synthesis and fungicidal activity against *Rhizoctonia solani* of 2-alkyl (alkylthio)-5-pyrazolyl-1,3,4-oxadiazoles (thiadiazoles). *J. Agric. Food Chem*. **2000**, *48*, 5312–5315.
[11] Liu, F.; Luo, X.-Q.; Song, B.-A.; Bhadury, P. S.; Yang, S.; Jin, L.-H.; Xue, W.; Hu, D.-Y. Synthesis and antifungal activity of novel sulfoxide derivatives containing trimethoxyphenyl substituted 1,3,4-thiadiazole and 1,3,4-oxadiazole moiety. *Bioorg. Med. Chem*. **2008**, *16*, 3632–3640.
[12] Husain, A.; Ajmal, M. Synthesis of novel 1,3,4-oxadiazole derivatives and their biological properties. *Acta Pharm*. **2009**, *59*, 223–233.
[13] Jiang, L.-L.; Tan, Y.; Zhu, X.-L.; Wang, Z.-F.; Zuo, Y.; Chen, Q.; Xi, Z.; Yang, G.-F. Design, synthesis, and 3D-QSAR analysis of novel 1,3,4-oxadiazol-2(3*H*)-ones as protoporphyrinogen oxidase inhibitors. *J. Agric. Food Chem*. **2010**, *58*, 2643–2651.
[14] Macaev, F.; Ribkovskaia, Z.; Pogrebnoi, S.; Boldescu, V.; Rusu, G.; Shvets, N.; Dimoglo, A.; Geronikaki, A.; Reynolds, R. The structure-antituberculosis activity relationships study in series of 5-aryl-2-thio-1,3,4-oxadiazole derivatives. *Bioorg. Med. Chem*. **2011**, *19*, 6792–6807.
[15] Padmavathi, V.; Reddy, S.; Reddy, G.; Venkatesh, B.; Padmaja, A. Synthesis and antimicrobial studies of pyrazolyl oxadiazoles and thiadiazoles. *J. Heterocycl. Chem.* **2011**, *48*, 1197–1201.
[16] Zou, X.-J.; Lai, L.-H.; Jin, G.-Y.; Zhang, Z.-X. Synthesis, fungicidal activity, and 3D-QSAR of pyridazinone-substituted 1,3,4-oxadiazoles and 1,3,4-thiadiazoles. *J. Agric. Food Chem*. **2002**, *50*, 3757–3760.
[17] Zarghi, A.; Hamedi, S.; Tootooni, F.; Amini, B.; Sharifi, B.; Faizi, M.; Tabatabai, S; Shafiee, A. Synthesis and pharmacological evaluation of new 2-substituted-5-{2-[(2-halobenzyl) thio]phenyl}-1,3,4-oxadiazoles as anticonvulsant agents. *Sci. Pharm*. **2008**, *76*, 185–201.
[18] Shashikant, R.; Rabara, P.; Jayashri, S.; Bukitagar, A.; Wakale, V.; Musmade, D. Synthesis and evaluation of some novel substituted 1,3,4-oxadiazole and pyrazole derivatives for antitubercular activity. *Ind. J. Chem*. **2009**, *48B*, 1453–1456.
[19] Almasirad, A.; Shafiee, A.; Abdollahi, M.; Noeparast, A.; Shahrokhinejad, N.; Vousooghi, N.; Tabatabai, S.; Abbas, R. Synthesis and analgesic activity of new 1,3,4-oxadiazoles and 1,2,4-triazoles. *Med. Chem. Res*. **2011**, *20*, 435–442.
[20] Dash, S.; Ashok, B.; Singh, J.; Maiti, B.; Maity, T. Synthesis of some novel 3,5-disubstituted 1,3,4-oxadiazole derivatives and anticancer activity on EAC animal model. *Med. Chem. Res*. **2010**, *20*, 1206–1213.
[21] Tajik, H.; Dadras, A. Synthesis and herbicidal activity of novel 5-chloro-3-fluoro-2-phenoxypyridines with a 1,3,4-oxadiazole ring. *J. Pest. Sci*. **2011**, *36*, 27–32.
[22] Eliazyan, K.; Hakobyan, R.; Pivazyan, V.; Ghazaryan, E.; Yengoyan, A. Synthesis of 2-(arylsulfonylmethylamino)-4-methyl-thiazole-5-carboxylic acids derivatives and their transformations. *Chem. J. Armenia* **2013**, *66*, 90–100.
[23] Eliazyan, K.; Hakobyan, R.; Pivazyan, V.; Ghazaryan, E.; Yengoyan, A. Synthesis and transformations of 1-[2-(toluene-4-sulfonamido)ethyl]-thiourea. *Heterocycl. Commun*. **2013**, *19*, 121–124.
[24] Knyazyan, A. Synthesis of 5-(2-thioxo-3*H*-thiazol-5-yl)-[1,2,4] triazole-3-thion derivatives with fungicidal and growth stimulant activities. *Chem. J. Armenia* **2012**, *65*, 94–104.
[25] Knyazyan, A.; Eliazyan, K.; Pivazyan, V.; Ghazaryan, E.; Harutyunyan, S.; Yengoyan, A. Synthesis and growth regulatory activity of novel 5-(3-alkyl-4-methyl-2-thioxo-2,3-dihydro-thiazol-5-yl)-3*H*-[1,3,4]-thiadiazole(oxadiazole)-2-thiones and their derivatives. *Heterocycl. Commun*. **2012**, *18*, 103–108.
[26] Knyazyan, A.; Eliazyan, K.; Pivazyan, V.; Ghazaryan, E.; Harutyunyan, S.; Yengoyan, A. Synthesis of novel 2-amino-(2-thioxo-3-alkyl-4-methyl-3H-thiazol-5-yl-[1,3,4]-thiadiazole derivatives and their growth stimulant activity. *J. Heterocycl. Chem*. **2013**, in press.