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Acylation and Carbamoylation of 2-Hydrazinothiazole Derivatives. Identification of Isomeric Structures

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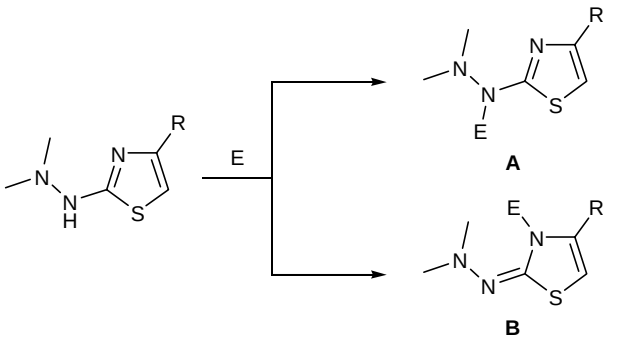
Abstract—Acylation and carbamoylation of 2-(arylmethylidenehydrazino)- and 2-(aroylhydrazino)thiazoles was performed, and structure of the products was established.

2-Hydrazinothiazole derivatives exhibit various kinds of biological activity, in particular antibacterial, antiviral, and antitumor [1]. According to the results of biological studies, compounds having a substituent in the hydrazino group possess stronger biological activity and lower toxicity, as compared to their unsubstituted analogs. Of specific interest are semi- and thiosemicarbazido derivatives, for they are structural analogs of 2-ureidothiazoles some of which exhibit antileukemic activity [2].

The amidrazone fragment in 2-arylmethylidene- and 2-(aroylhydrazino)thiazoles contains two potential nucleophilic centers: the ring and side-chain nitrogen atoms. Therefore, their reactions with electrophiles E could result in formation of isomeric structures **A** and/or **B** (Scheme 1).

The reactivity of monosubstituted hydrazinothiazoles toward electrophiles was studied in [3, 4] where

Scheme 1.



E = ArNCO, RCOCl.

it was shown that carbamoylation and thiocarbamoylation of these compounds occurs at the ring nitrogen atom. However, the data of elemental analysis, IR and ^{1}H NMR spectroscopy, and mass spectrometry are insufficient to rigorously assign isomeric structures **A** and **B**; these data indicate only the presence of an acyl (or carbamoyl) moiety in the product.

In order to examine the relative reactivity of the nitrogen atoms in the thiazole ring and side chain in 2-hydrazinothiazole derivatives having a substituent at the terminal hydrazine nitrogen atom, we performed chloroacetylation and carbamoylation of 2-arylmethylidenehydrazino- and 2-(aroylhydrazino)thiazoles **Ia**–**Ic** and **IIa**–**IIc** (Schemes 2, 3). The structure of products **III**–**V** thus obtained was determined using ^{13}C NMR spectroscopy, and the structure of **Va** was proved by the X-ray diffraction data. In addition, we synthesized model compounds **VI**–**VIII** (Schemes 4, 5) already containing substituent at the ring nitrogen atom (**VI**) or in the side chain (**VII**, **VIII**) [5–8] and examined their spectral parameters.

The reactions of 2-arylmethylidenethiazoles **Ia**–**Ic** and 2-(aroylhydrazino)thiazoles **IIa**–**IId** with chloroacetyl chloride at room temperature gave the corresponding *N*-chloroacetyl derivatives **IIIa**–**IIIc** and **IVa**–**IVd** as individual products. Under analogous conditions, carbamoylation of 2-aroylhydrazinothiazoles **IIa**–**IId** with phenyl and *p*-chlorophenyl isocyanates afforded *N*-arylcarbamoylhydrazides **Va**–**Vc** as the only products.

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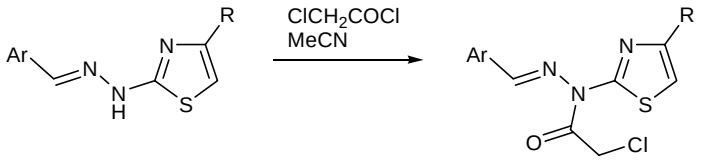
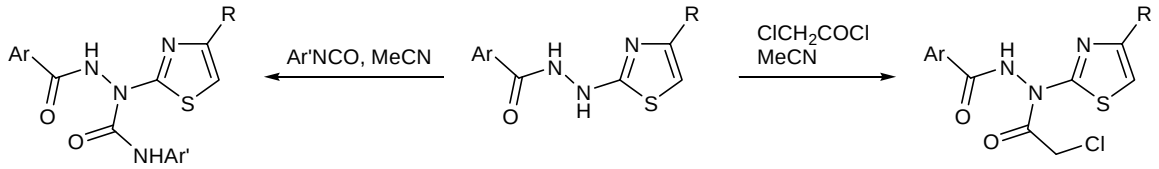
Scheme 2.



Ia–Ic **IIIa–IIIc**

Ar = *p*-$O_2NC_6H_4$, R = Ph (**a**); Ar = 3,4,5-$(MeO)_3C_6H_2$, R = *p*-MeC_6H_4 (**b**), CO_2Et (**c**).

Scheme 3.



Va–Vc **IIa–IId** **IVa–IVd**

II, **IV**, Ar = Ph, R = CO_2Et (**a**), *p*-ClC_6H_4 (**b**), *p*-MeC_6H_4 (**c**); Ar = 3,4,5-$(MeO)_3C_6H_2$, R = *p*-MeC_6H_4 (**d**); **V**, Ar = Ar' = Ph, R = H (**a**); Ar = Ph, Ar' = *p*-ClC_6H_4 (**b**); R = *p*-ClC_6H_4, *p*-MeC_6H_4 (**c**).

The presence of a chloroacetyl or arylcarbamoyl moiety in compounds **III**–**V** was confirmed by their analytical data and ^{1}H NMR and mass spectra (see Experimental). However, rigorous identification of possible isomeric structures cannot be performed on the basis of these data. It should also be noted that the ^{1}H NMR spectra of **III**–**V** are characterized by an appreciable downfield shift of signals from the thiazole ring proton ($\Delta\delta$ = 0.7–0.9 ppm), proton of the CH=N fragment ($\Delta\delta$ = 0.8–1.2 ppm), and carboxamide NH proton ($\Delta\delta$ = 0.78–0.97 ppm) relative to the corresponding signals of the initial compounds (see Experimental). These data may be treated only as an indirect evidence that the reaction occurred at the exocyclic nitrogen atom (N'), and additional proofs are necessary.

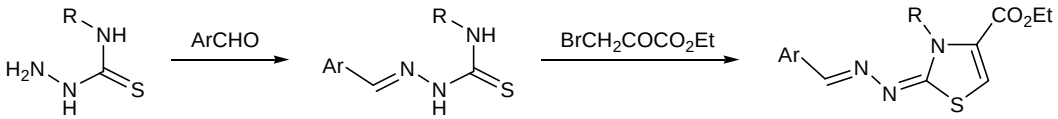
Therefore, we examined the ^{13}C NMR spectra of the following pairs: **Ic**, **IIIc**; **Ia**, **IVa**; and **IIa**, **Va**. Specific attention was given to variation of chemical shifts of the carbon atoms in the thiazole ring of products **III**–**V** relative to the corresponding parameters of initial compounds **I** and **II**. The ^{13}C NMR spectra of the above compounds are given in Experimental. The following variations in the ^{13}C chemical shifts were observed for chloroacetylation product **IIIc** relative to initial compound **Ic**: C^5, 7.4 ppm downfield; C^2, 13.3 ppm upfield; C^4, unchanged.

Analysis of the ^{13}C NMR spectra of ethyl 2-benzoylhydrazino-4-thiazolecarboxylate (**IIa**) and its chloroacetyl and carbamoyl derivatives **IVa** and **Va** showed that the C^2 and C^5 atoms in the thiazole ring are also the most sensitive to introduction of a carbonyl-contaning group into the initial structure. As a result, the C^2 signal was displaced upfield by 12.70–15.00 ppm, and the C^5 signal suffered a downfield shift by 6.51–7.42 ppm. The chemical shifts of C^4 and carbon atoms of the two carbonyl groups (at C^4 in the thiazole ring and in the benzoylhydrazide fragment) remained almost unchanged. The observed variations are similar to those found for **Ic**/**IIIc**; therefore, we presumed that both acylation and carbamoylation of monosubstituted 2-hydrazinothiazole derivatives **Ic** and **IIa** involves electrophilic attack at the same nitrogen atom.

Signals in the ^{13}C NMR spectra of compounds **IIa** and **Va** were assigned using HETCOR and HMBC two-dimensional correlation techniques. Initial benzoylhydrazine **IIa** showed an interaction between the C^2 atom and NH proton, which is rarely observed in ^{13}C NMR spectra; as a result, the C^2 signal appears as a doublet of doublets. The C^2 signal in the spectra of **IVa** and **Va** is a doublet, presumably due to the lack of interaction between C^2 and NH proton (for the latter is replaced by acyl group).

To estimate the effect of substituent on the ring nitrogen atom on the chemical shifts of carbon atoms in the thiazole ring, we synthesized 3-phenyl- and 3-methyldihydrothiazoles **VIa** and **VIb** according to the procedure described in [5] and recorded their ^{13}C NMR spectra (see Experimental; no relevant data were given in [5]). It is seen that the C^4 and C^5 signals of compounds **VIa** and **VIb** appear in a stronger field relative

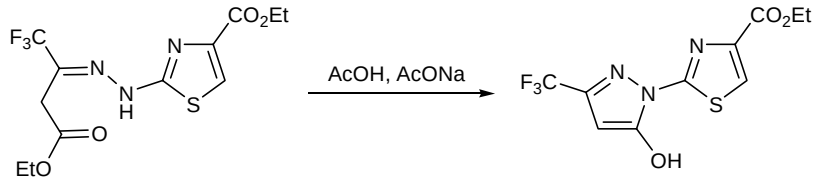
Scheme 4.



VIa, **VIb**

Ar = 3,4,5-$(MeO)_3C_6H_2$, R = Ph (**a**), Me (**b**).

Scheme 5.



VIII **VII**

to those of thiazole **Ic** having no substituent on the ring nitrogen atom. The largest shift is observed or C^4 ($\Delta\delta_C$ = 11.50–12.00 ppm), while the shift of the C^5 signal is smaller in absolute value, $\Delta\delta_C$ = 2.91–3.62 ppm. An upfield shift was also observed for the ester carbonyl carbon signal. Attachment of both phenyl and methyl groups (which possess different electronic properties) to the thiazole nitrogen atom did not change the position of the C^2 signal located at δ_C 169 ppm in the spectra of the three compounds (**Ic**, **VIa**, and **VIb**).

As model compound having a substituent at the side-chain nitrogen atom we selected ethyl 2-(5-hydroxy-3-trifluoromethyl-1-pyrazolyl)thiazole-4-carboxylate (**VII**), which is the product of intramolecular acylation (cyclization) of ethyl 4,4,4-trifluoro-3-(4-ethoxycarbonylthiazol-2-ylhydrazono)butanoate (**VIII**) (Scheme 5). The chemical shifts of the carbon atoms in the thiazole ring of compound **VIII** were almost identical to those found for structurally similar thiazolylhydrazone **Ic** (see Experimental). Comparison of the ^{13}C NMR spectra of model compounds **VII** and **VIII** shows that the intramolecular cyclization is accompanied by an appreciable ($\Delta\delta_C$ = 11.50 ppm) upfield shift of the C^2 signal and slightly smaller downfield shift ($\Delta\delta_C$ = 7.10 ppm) of the C^5 signal, while the position of the C^4 signal does not change. The chemical shifts of carbon atoms in the pyrazole ring coincided with those found for 5-substituted 3-trifluoromethyl-1-(2-thiazolyl)pyrazoles whose ^{13}C NMR spectra characteristically contain a quartet at δ_C 143.1 ppm due to the C^3 atom [6, 7]. It should be added that the intramolecular cyclization of 2-thiazolylhydrazone derived from 1-(2-thienyl)-4,4,4-trifluorobutane-1,3-dione (an analog of **VIII**) to the corresponding 3-trifluoromethyl-substituted pyrazole (an analog of **VII**) revealed the same trends in variation of the carbon chemical shifts [6].

As follows from analysis of our results and published data [9, 10], substituents at the endo- and exocyclic nitrogen atoms produce different (in both absolute value and sign) changes of the chemical shifts of the thiazole carbon atoms. The presence of a substituent on N^3 induces upfield shifts of the C^4 and C^5 signals, the effect on C^4 being stronger, while the chemical shift of C^2 remains unchanged. Attachment of an electron-acceptor group to the exocyclic nitrogen atom leads to an upfield shift of the C^2 signal and a downfield shift of the C^5 signal, whereas the position of the C^4 signal does not change. These relations could help us to identify acyl, alkyl, and carbamoyl derivatives of monosubstituted hydrazinothiazoles. The observed chemical shifts of the thiazole carbon atoms in the ^{13}C NMR spectra of **IIIc**, **IVa**, and **Va** are similar to those found for model structure **VII** (in comparison with the initial compounds) and strongly different from the corresponding parameters of 3-substituted dihydrothiazoles **VIa** and **VIb**. Therefore, compounds **III**–**V** are products of electrophilic attack at the exocyclic nitrogen atom.

Our conclusions were confirmed by the X-ray diffraction data obtained for ester **Va** [11] (see figure). Colorless monoclinic crystals of **Va** were isolated from an oversaturated solution in chloroform; the following unit cell parameters were found: a = 13.618(2), b = 11.870(2), c = 24.588(4) Å; α = 90, β = 95.546, γ = 90°; V = 3955.9(11) $Å^3$; Z = 8; space group $P2_1/n$ (no. 14). The molecule of **Va** is not planar. There are

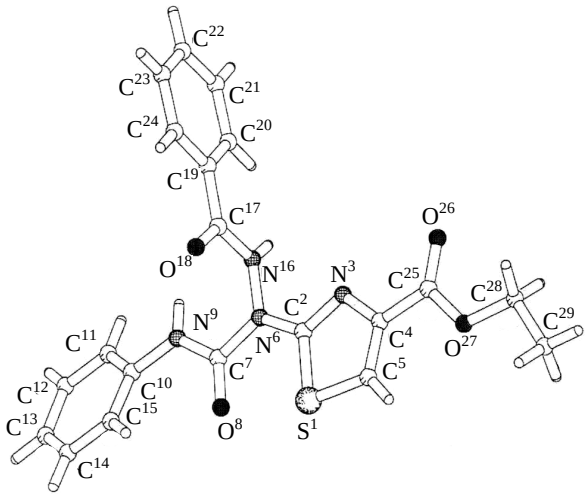
two conformations differing by arrangement of the mean plane of the thiazole ring and benzene ring in the phenylcarbamoyl group with respect to the benzoylhydrazine fragment. One of these conformations is characterized by coplanar arrangement of the thiazole ring and benzene ring of the phenylcarbamoyl fragment, while in the other conformation the thiazole and benzene ring planes form a dihedral angle of 24.8°. The benzene ring in the benzoylhydrazine fragment is almost orthogonal to the mean plane of the thiazole and phenylcarbamoyl rings. No hydrogen bond is formed between the carbonyl group and NH proton, for these groups are located in different planes. The thiazole ring approaches a regular pentagon. The bond lengths and bond angles therein are typical of five-membered aromatic heterocycles: the C–C and C–N bond lengths range from 1.30 to 1.39 Å. The bond angles in the thiazole ring range from 88° (C^2SC^5) to 116° (SC^2N^3). The benzene rings deviate from planarity by no more than 2°. The complete set of crystallographic parameters, including bond lengths and bond and dihedral angles, is available from the authors (see also [11]).

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were measured on Bruker WM-250 (^1H, 250.13 MHz), Bruker DRX-400 (^{13}C, 100.61 MHz; ^1H, 400.13 MHz), and Bruker AMX-400 spectrometers (^{13}C, 100.61 MHz; ^1H, 400.13 MHz) using $CDCl_3$ and DMSO-d_6 as solvents and tetramethylsilane as internal reference. The mass spectra (electron impact, 70 eV) were recorded on a Varian MAT-311A spectrometer (accelerating voltage 3 kV). The progress of reactions and the purity of products were monitored by TLC on Sorbfil UV-254 and Silufol UV-254 plates using chloroform–ethanol (15:1 and 9:1) as eluent. The melting points were not corrected.

4-Substituted 2-(*N′*-arylmethylidenehydrazino)-thiazoles Ia–Ic (*general procedure*). Appropriate aromatic aldehyde, 2.70 mmol, was added to a solution of 2.66 mmol of the corresponding 4-substituted 2-hydrazinothiazole in 30 ml of ethanol, and the mixture was heated for 15 min under reflux. The mixture was cooled, and the precipitate was filtered off, dried, and recrystallized from ethanol.

2-[*N′*-(4-Nitrobenzylidene)hydrazino]-4-phenylthiazole (Ia). Yield 95%, yellow crystals, mp 249–251°C. ^1H NMR spectrum, δ, ppm: 7.27–7.45 m (3H, C_6H_5), 7.39 s (1H, 5-H), 7.90–7.92 m (2H, C_6H_5), 7.87 d and 8.27 d (4H, *AA′BB′* system, ^3J = 8.7 Hz), 8.13 s (1H, CH=N), 12.54 s (1H, NH). Found, %: N 17.21; S 9.54. $C_{16}H_{12}N_4O_2S$. Calculated, %: N 17.28; S 9.89.



Structure of the molecule of ethyl 2-(*N′*-benzoyl-*N*-phenylcarbamoylhydrazino)thiazole-4-carboxylate (**Va**).

4-(4-Methylphenyl)-2-[*N′*-(3,4,5-trimethoxybenzylidene)hydrazino]thiazole (Ib). Yield 82%, colorless crystals, mp 255–257°C. ^1H NMR spectrum, δ, ppm: 2.32 s (3H, Me), 3.70 s (3H, 4-OMe), 3.84 s (6H, 3-OMe, 5-OMe), 6.97 s (2H, 2-H, 6-H), 7.20 s (1H, 5-H), 7.21 d and 7.74 d (4H, *AA′XX′* system, ^3J = 7.9 Hz), 7.96 s (1H, CH=N), 12.07 s (1H, NH). Found, %: N 11.26; S 7.97. $C_{20}H_{21}N_3O_3S$. Calculated, %: N 10.96; S 8.36.

Ethyl 2-[*N′*-(3,4,5-trimethoxybenzylidene)hydrazino]thiazole-4-carboxylate (Ic). Yield 78%, colorless crystals, mp 209–211°C. ^1H NMR spectrum, δ, ppm: 1.34 t (3H, Me, ^3J = 7.1 Hz), 3.71 s (3H, 4-OMe), 3.84 s (6H, 3-OMe, 5-OMe), 4.25 q (2H, CH_2, ^3J = 7.1 Hz), 6.91 s (2H, C_6H_2), 7.59 s (1H, 5-H), 7.85 s (1H, CH=N), 12.25 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 118.5 d (C^5, ^1J = 192 Hz), 143.0 d (C^4, ^2J = 4.0 Hz), 143.2 d.t (HC=N, ^1J = 161, ^3J = 5.5 Hz), 161.6 t.d (4-CO, ^3J = 3.3, ^3J = 1.8 Hz), 169.2 d (C^2, ^3J = 10 Hz). Found, %: N 11.73; S 8.56. $C_{16}H_{19}N_3O_5S$. Calculated, %: N 11.50; S 8.77.

4-Substituted 2-(*N′*-aroylhydrazino)thiazoles IIa–IId (*general procedure*). Substituted benzoyl chloride, 2.70 mmol, and triethylamine, 2.70 mmol, were added dropwise under stirring to a solution of 2.66 mmol of 4-substituted 2-hydrazinothiazole in 15 ml of dioxane. The solvent was removed, the residue was treated with water, and the precipitate was

filtered off, dried, and recrystallized from ethanol–water (4:1).

Ethyl 2-(*N'*-benzoylhydrazino)thiazole-4-carboxylate (IIa). Yield 75%, colorless crystals, mp 194–196°C. ^{1}H NMR spectrum, δ, ppm: 1.26 t (3H, Me, ^3J = 7.1 Hz), 4.25 q (2H, OCH_2, ^3J = 7.1 Hz), 7.30–7.75 m (3H, C_6H_5), 7.70 s (1H, 5-H), 7.80–8.10 m (2H, C_6H_5), 9.80 s (1H, NH), 10.90 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 118.4 d (C^5, ^1J = 194 Hz), 142.8 d (C^4, ^2J = 4.3 Hz), 160.9 t.d (4-CO, ^3J = 3.2, ^3J = 1.8 Hz), 166.4 d.t (Ph**C**ON, ^3J = 10.6, ^3J = 3.8 Hz), 172.5 d.d (C^2, ^3J = 9.2, ^3J = 5.1 Hz). Found, %: N 14.21; S 10.88. $C_{13}H_{13}N_3O_3S$. Calculated, %: N 14.43; S 11.01.

2-(*N'*-Benzoylhydrazino)-4-(4-chlorophenyl)-thiazole (IIb). Yield 77%, colorless crystals, mp 215–217°C. ^{1}H NMR spectrum, δ, ppm: 7.28 s (1H, 5-H), 7.40 d and 7.78 d (4H, *AA'BB'*, ^3J = 8.5 Hz), 7.45–7.75 m (3H, C_6H_5), 7.87–8.13 m (2H, C_6H_5), 9.56 s (1H, NH), 10.77 s (1H, NH). Found, %: Cl 10.86; N 12.56; S 9.61. $C_{16}H_{12}ClN_3OS$. Calculated, %: Cl 10.75, N 12.74; S 9.72.

2-(*N'*-Benzoylhydrazino)-4-(4-methylphenyl)-thiazole (IIc). Yield 75%, colorless crystals, mp 238–240°C. ^{1}H NMR spectrum, δ, ppm: 2.30 s (3H, Me), 7.18 d and 7.75 d (4H, *AA'XX'*, ^3J = 8.2 Hz), 7.25 s (1H, 5-H), 7.40–7.70 m (3H, C_6H_5), 7.85–8.10 m (2H, C_6H_5), 9.50 s (1H, NH), 10.75 s (1H, NH). Found, %: N 13.42; S 10.25. $C_{17}H_{15}N_3OS$. Calculated, %: N 13.58; S 10.36.

4-(4-Methylphenyl)-2-[*N'*-(3,4,5-trimethoxybenzoyl)hydrazino]thiazole (IId). Yield 74%, colorless crystals, mp 186–188°C. ^{1}H NMR spectrum, δ, ppm: 2.32 s (3H, Me), 3.74 s (3H, 4-OMe), 3.85 s (6H, 3-OMe, 5-OMe), 7.17 s (1H, 5-H), 7.20 d and 7.72 d (4H, *AA'XX'*, ^3J = 8.2 Hz), 7.28 s (2H, C_6H_2), 10.89 s (1H, NH). Found, %: N 10.68; S 7.89. $C_{20}H_{21}N_3O_4S$. Calculated, %: N 10.52; S 8.03.

4-Substituted 2-(*N'*-arylmethylidene)- and 2-[*N'*-aroyl-*N*-(chloroacetyl)hydrazino]thiazoles IIIa–IIIc and IVa–IVd (*general procedure*). Triethylamine, 2.80 mmol, was added to a mixture of 2.66 mmol of thiazole **Ia–Ic** or **IIa–IId** and 2.75 mmol of chloroacetyl chloride in 30 ml of anhydrous acetonitrile (or ethyl acetate), and the mixture was heated for 15 min under reflux. The solvent was distilled off, the residue was treated with water, and the precipitate was filtered off and dried.

2-[*N*-Chloroacetyl-*N'*-(4-nitrobenzylidene)hydrazino]-4-phenylthiazole (IIIa). Yield 85%, colorless crystals, mp 132–135°C. ^{1}H NMR spectrum, δ, ppm: 5.16 s (2H, CH_2), 7.35–7.50 m (3H, C_6H_5), 7.90–8.02 m (2H, C_6H_5), 8.12 d and 8.32 d (4H, *AA'BB'*, ^3J = 8.9 Hz), 8.25 s (1H, 5-H), 7.83 s (1H, CH=N). Mass spectrum, *m*/z (I_{rel}, %): 399/401 (47/18) $[M]^+$, 323 (91) [*M* – 76], 323 (91), 322 (17), 248 (17), 202 (49), 201 (18), 175 (48), 174 (18), 161 (19), 133 (100), 128 (14). Found, %: Cl 8.96; N 13.95; S 7.88. $C_{18}H_{13}ClN_4O_3S$. Calculated, %: Cl 8.88; N 14.04; S 8.03.

2-[*N*-Chloroacetyl-*N'*-(3,4,5-trimethoxybenzylidene)hydrazino]-4-(4-methylphenyl)thiazole (IIIb). Yield 84%, colorless crystals, mp 188–190°C. ^{1}H NMR spectrum, δ, ppm: 2.33 s (3H, Me), 3.73 s (3H, 4-OMe), 3.83 s (6H, 3-OMe, 5-OMe), 5.09 s (2H, CH_2), 7.19 s (2H, C_6H_2), 7.26 d and 7.82 d (4H, *AA'XX'*, ^3J = 8.1 Hz), 8.12 s (1H, 5-H) 8.48 s (1H, CH=N). Mass spectrum, *m*/*z* (I_{rel}, %): 459/461 (3/1) $[M]^+$, 383 (10) [*M* – 76], 266/268 (23/9), 218 (14), 217 (100), 190 (56), 178 (11), 150 (10), 148 (27), 147 (17). Found, %: Cl 7.54; N 9.35; S 7.35. $C_{22}H_{22}ClN_3O_4S$. Calculated, %: Cl 7.71; N 9.14; S 6.97.

Ethyl 2-[*N*-chloroacetyl-*N'*-(3,4,5-trimethoxybenzylidene)hydrazino]thiazole-4-carboxylate (IIIc). Yield 85%, colorless crystals, mp 147–149°C. ^{1}H NMR spectrum, δ, ppm: 1.31 t (3H, Me, ^3J = 7.1 Hz), 3.73 s (3H, 4-OMe), 3.84 s (6H, 3-OMe, 5-OMe), 4.31 q (2H, OCH_2, ^3J = 7.0 Hz), 5.05 s (2H, CH_2), 7.16 s (2H, C_6H_2), 8.52 s (1H, CH=N), 8.55 s (1H, 5-H). ^{13}C NMR spectrum, δ_C, ppm: 125.9 d (C^5, ^1J = 191 Hz), 142.7 d (C^4, ^2J = 3.0 Hz), 154.3 d.t (HC=N, ^1J = 169, ^3J = 5.5 Hz), 155.9 d (C^2, ^3J = 10 Hz), 161.0 t.d (4-CO, ^3J = 3.3, ^3J = 2.0 Hz). Mass spectrum, *m*/*z* (I_{rel}, %): 441/443 (16/6) $[M]^+$, 365 (67) [*M* – 76], 366/364 (31/18), 320/318 (21/8), 248 (11), 208 (14), 201 (13), 200 (24), 199 (74), 195 (12), 194 (62), 193 (100), 180 (53), 173 (15), 172 (68), 167 (14), 165 (62), 153 (62), 152 (16), 150 (44), 137 (29). Found, %: Cl 8.24; N 9.35; S 7.41. $C_{18}H_{20}ClN_3O_6S$. Calculated, %: Cl 8.02; N 9.51; S 7.26.

Ethyl 2-(*N'*-benzoyl-*N*-chloroacetylhydrazino)-thiazole-4-carboxylate (IVa). Yield 82%, colorless crystals, mp 169–171°C. ^{1}H NMR spectrum, δ, ppm: 1.29 t (3H, Me, ^3J = 7.2 Hz), 4.24 q (2H, OCH_2, ^3J = 7.1 Hz), 4.48 d and 4.76 d (2H, CH_2, ^2J = 15.6 Hz), 7.56 d (2H, ^3J = 7.2 Hz), 7.65 d.d (1H, ^3J = 7.2, ^3J = 7.6 Hz), 7.99 d.d (2H, C_6H_5, ^3J = 7.2, ^4J = 1.2 Hz), 8.13 s (1H, 5-H), 11.83 (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 125.8 d (C^5, ^1J = 193 Hz), 140.6 d (C^4, ^2J = 4.3 Hz), 157.5 d (C^2, ^3J = 6.6 Hz), 160.5 t.d (4-CO, ^3J = 3.2, ^3J = 1.5 Hz), 167.0 d.t (Ph**C**O, ^3J = 8.7, ^3J =

3.8 Hz). Mass spectrum, *m*/*z* (I_{rel}, %): 368/370 (47/22) $[M]^+$, 332 (38), 323/325 (19/8) [*M* – 45], 294 (14), 293 (20), 292 (100) [*M* – 75], 260 (31), 246 (12), 245 (12), 186 (51), 142 (14). Found, %: N 11.73; S 8.54. $C_{15}H_{14}ClN_3O_4S$. Calculated, %: N 11.43; S 8.72.

2-(*N′*-Benzoyl-*N*-chloroacetylhydrazino)-4-(4-chlorophenyl)thiazole (IVb). Yield 81%, colorless crystals, mp 179–181°C. ^{1}H NMR spectrum, δ, ppm: 7.42 d and 7.81 d (4H, *AA′BB′*, ^3J = 8.5 Hz), 4.70 d and 4.90 d (2H, CH_2, ^2J = 15.6 Hz), 7.59–7.80 m (3H, C_6H_5), 7.79–8.12 m (2H, C_6H_5), 7.90 s (1H, 5-H), 11.74 (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 405/407 (2/1.4) $[M]^+$, 369/371 (11/4), 329/331 (5/2) [*M* – 76], 208/210 (5/3), 105 (100). Found, %: Cl 17.65; N 10.25; S 7.76. $C_{18}H_{19}Cl_2N_3O_2S$. Calculated, %: Cl 17.45; N 10.34; S 7.89.

2-(*N′*-Benzoyl-*N*-chloroacetylhydrazino)-4-(4-methylphenyl)thiazole (IVc). Yield 79%, colorless crystals, mp 180–182°C. ^{1}H NMR spectrum, δ, ppm: 2.28 s (3H, Me), 4.70 d and 4.78 d (2H, CH_2, ^2J = 15.6 Hz), 7.17 d and 7.68 d (4H, *AA′BB′*, ^3J = 8.1 Hz), 7.60–7.76 m (3H, C_6H_5), 7.75 s (1H, 5-H), 7.96–8.13 m (2H, C_6H_5), 11.70 (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 385/387 (5/2) $[M]^+$, 309 (7) [*M* – 76], 349 (8), 204 (7), 188 (5), 116 (3), 106 (8). Found, %: Cl 9.02; N 10.77; S 8.03. $C_{19}H_{16}ClN_3O_2S$. Calculated, %: Cl 9.19; N 10.89; S 8.31.

2-[*N*-Chloroacetyl-*N′*-(3,4,5-trimethoxybenzoyl)-hydrazino]-4-(4-methylphenyl)thiazole (IVd). Yield 81%, colorless crystals, mp 220–222°C. ^{1}H NMR spectrum, δ, ppm: 2.29 s (3H, Me), 3.79 s (3H, 4-OMe), 3.89 s (6H, 3-OMe, 5-OMe), 4.59 d and 4.87 d (2H, CH_2, ^2J = 15.6 Hz), 7.39 s (2H, C_6H_2), 7.18 d and 7.72 d (4H, *AA′XX′*, ^3J = 8.3 Hz), 7.77 s (1H, 5-H), 11.67 (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 475/477 (12/5) $[M]^+$, 441 (44), 440/442 (55/9), 424/426 (20/2), 400 (3) [*M* –76], 381 (14), 366 (26), 229 (10), 225 (10), 220 (17), 219 (48), 217 (27), 216 (18), 196 (51), 195 (100), 194 (30), 193 (51), 188 (21). Found, %: Cl 7.31; N 8.97; S 6.68. $C_{22}H_{22}ClN_3O_5S$. Calculated, %: Cl 7.45; N 8.83; S 6.74.

4-Substituted 2-(*N′*-aroyl-*N*-arylcarbamoylhydrazino)thiazoles Va–Vc (*general procedure*). To a suspension of 2.66 mmol of 2-aroylhydrazinothiazole **IIa**–**IIc** in 25 ml of anhydrous acetonitrile or ethyl acetate we added under stirring at room temperature 2.72 mmol of phenyl isocyanate (dropwise) or 4-chlorophenyl isocyanate (in portions). The mixture was stirred for 1 h (TLC), and the precipitate was filtered off, washed with anhydrous acetonitrile, and dried.

Ethyl 2-(*N′*-benzoyl-*N*-phenylcarbamoylhydrazino)thiazole-4-carboxylate (Va). Yield 88%, colorless crystals, mp 188–190°C. ^{1}H NMR spectrum, δ, ppm: 1.22 t (3H, Me, ^3J = 7.0 Hz), 4.20 q (2H, OCH_2, ^3J = 7.0 Hz), 7.00–7.80 m (8H, C_6H_5), 7.85–8.40 m (2H, C_6H_5), 8.12 s (1H, 5-H), 9.95 s (1H, NH), 11.43 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 124.9 d (C^5, ^1J = 192 Hz), 140.6 d (C^4, ^2J = 3.8 Hz), 159.8 d (C^2, ^3J = 9.2 Hz), 160.7 t.d (4-CO, ^3J = 3.2, ^3J = 1.7 Hz), 167.0–167.2 m (Ph**C**O). Mass spectrum, *m*/*z* (I_{rel}, %): $[M]^+$ absent, 291 (15), 186 (9), 140 (8), 120 (6), 119 (80), 106 (7), 91 (23), 77 (29). Found, %: N 13.74; S 7.85. $C_{20}H_{18}N_4O_4S$. Calculated, %: N 13.65; S 7.81.

2-[*N′*-Benzoyl-*N*-(4-chlorophenylcarbamoyl)-hydrazino]-4-(4-chlorophenyl)thiazole (Vb). Yield 90%, colorless crystals, mp 232–234°C. ^{1}H NMR spectrum, δ, ppm: 7.39 d and 7.78 d (8H, *AA′BB′*, ^3J = 8.6 Hz), 7.50–7.80 m (3H, C_6H_5), 7.61 s (1H, 5-H), 8.00–8.25 m (2H, C_6H_5), 9.99 s (1H, NH), 11.30 s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): $[M]^+$ absent, 329/331 (14/6), 224/226 (7/3), 153/155 (28/9), 125/127 (9/3), 106 (8), 105 (100), 77 (27). Found, %: Cl 14.53; N 11.74; S 6.44. $C_{23}H_{16}Cl_2N_4O_2S$. Calculated, %: Cl 14.67; N 11.59; S 6.63.

2-[*N′*-Benzoyl-*N*-(4-chlorophenylcarbamoyl)-hydrazino]-4-(4-methylphenyl)thiazole (Vc). Yield 84%, colorless crystals, mp 229–231°C. ^{1}H NMR spectrum, δ, ppm: 7.13 d and 7.70 d (4H, *AA′XX′*, ^3J = 8.6 Hz), 7.39 d and 7.79 d (4H, *AA′BB′*, ^3J = 8.8 Hz), 7.50–7.80 m (3H, C_6H_5), 7.61 s (1H, 5-H), 8.00–8.27 m (2H, C_6H_5), 10.07 s (1H, NH), 11.28 s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): $[M]^+$ absent, 310 (13), 311 (8), 153/155 (35/10), 205 (8), 189 (10), 143 (6), 105 (100), 77 (25). Found, %: Cl 7.73; N 12.34; S 6.82. $C_{24}H_{19}ClN_4O_2S$. Calculated, %: Cl 7.66; N 12.10; S 6.93.

3-Substituted 2-(*N′*-arylmethylidenehydrazono)-2,3-dihydrothiazoles VIa and VIb were synthesized according to the procedure reported in [5].

Ethyl 3-phenyl-2-[*N′*-(3,4,5-trimethoxybenzylidene)hydrazono]-2,3-dihydrothiazole-4-carboxylate (VIa). Yield 78%, light yellow crystals, mp 136–137°C. ^{1}H NMR spectrum, δ, ppm: 1.09 t (3H, Me, ^3J = 7.3 Hz), 3.72 s (3H, 4-OMe), 3.82 s (6H, 3-OMe, 5-OMe), 4.05 q (2H, OCH_2, ^3J = 7.3 Hz), 6.94 s (2H, 2′-H, 6′-H), 7.25–7.35 m (3H, C_6H_5), 7.40–7.55 m (2H, C_6H_5), 7.49 s (1H, 5-H), 8.07 s (1H, CH=N). ^{13}C NMR spectrum, δ_C, ppm: 115.6 d (C^5, ^1J = 195 Hz), 131.5 d (C^4, ^2J = 5.0 Hz), 153.2 d.t (HC=N, ^1J = 163, ^3J = 5.1 Hz), 158.0 t.d (4-CO, ^3J = 3.0, ^3J = 2.8 Hz), 169.2 d

(C^2, ^3J = 6 Hz). Mass spectrum, *m*/*z* (I_{rel}, %): 441 (100) $[M]^+$, 442 (26), 235 (12), 234 (83), 206 (13), 180 (20), 165 (39), 150 (14). Found, %: N 9.36; S 7.02. $C_{22}H_{23}N_3O_5S$. Calculated, %: N 9.52; S 7.26.

Ethyl 3-methyl-2-[*N'*-(3,4,5-trimethoxybenzylidene)hydrazono]-2,3-dihydrothiazole-4-carboxylate (VIb). Yield 81%, light yellow crystals, mp 135–137°C. ^{1}H NMR spectrum, δ, ppm: 1.30 t (3H, Me, ^3J = 7.3 Hz), 3.62 s (1H, 3-Me), 3.70 s (3H, 4-OMe), 3.82 s (6H, 3-OMe, 5-OMe), 4.27 q (2H, OCH_2, ^3J = 7.3 Hz), 7.04 s (2H, 2-H, 6-H), 7.44 s (1H, 5-H), 8.24 s (1H, CH=N). ^{13}C NMR spectrum, δ_C, ppm: 115.0 d (C^5, ^1J = 196 Hz), 130–132 m (C^4), 151.7 d.t (HC=N, ^1J = 163, ^3J = 5.1 Hz), 158.5 t.d (4-CO, ^3J = 3.1, ^3J = 2.8 Hz), 169.5 d.q (C^2, ^3J = 5.8, ^3J = 3.0 Hz). Mass spectrum, *m*/*z* (I_{rel}, %): 379 (100) $[M]^+$, 380 (22), 194 (5), 190 (6), 180 (20), 172 (51), 165 (41), 160 (9), 150 (15), 144 (11). Found, %: N 11.30; S 8.35. $C_{17}H_{18}N_3O_5S$. Calculated, %: N 11.07; S 8.45.

Ethyl 2-(5-hydroxy-3-trifluoromethylpyrazol-1-yl)thiazole-4-carboxylate (VII). A mixture of 3 mmol of compound **VIII**, 3 mmol of sodium acetate, and 30 ml of glacial acetic acid was heated for 40 min under reflux. A part of the solvent was distilled off, the precipitate of compound **VII** sodium salt was filtered off and dispersed in water, and the mixture was acidified to pH 3–4 with hydrochloric acid and stirred for 3 h. The precipitate was filtered off, washed with water, and dried. Yield 75%, colorless crystals, mp 145–146°C. ^{1}H NMR spectrum, δ, ppm: 1.32 t (3H, Me, ^3J = 7.0 Hz), 4.35 q (2H, OCH_2, ^3J = 7.0 Hz), 5.81 s (1H, 4-H, pyrazole), 8.28 s (1H, 5-H, thiazole). ^{13}C NMR spectrum, δ_C, ppm: 120.8 q (CF_3, ^1J = 269.3 Hz), 126.9 d (C^5, thiazole, ^1J = 195.3 Hz), 142.7 d (C^4, thiazole, ^2J = 5.6 Hz), 143.1 q (C^3, pyrazole, ^2J = 37.5 Hz), 156.6 d (C^2, thiazole, ^3J = 10.1 Hz), 160.4 t.d (4-CO, ^3J = 3.4, ^2J = 1.5 Hz). Mass spectrum, *m*/*z* (I_{rel}, %): 307 (26) $[M]^+$, 263 (6), 262 (18), 261 (100), 108 (8). Found, %: N 13.62; S 10.73. $C_{10}H_8F_3N_3O_3S$. Calculated, %: N 13.67; S 10.43.

Ethyl 2-[*N'*-(2-ethoxycarbonyl-1-trifluoromethylethylidene)hydrazino]thiazole-4-carboxylate (VIII). Ethyl 4,4,4-trifluoro-3-oxobutanoate, 3.3 mmol, and concentrated hydrochloric acid, 0.5 mmol, were added to a mixture of 3 mmol of ethyl 2-hydrazinothiazole-4-carboxylate and 30 ml of ethanol, and the mixture was heated for 30–40 min under reflux. A part of the solvent was distilled off, and the precipitate was filtered off and recrystallized from ethanol–water (5:1). Yield 87%, light yellow crystals, mp 96–97°C. ^{1}H NMR spectrum, δ, ppm: 1.28 t (3H, Me, ^3J = 7.0 Hz), 1.39 t (3H, Me, ^3J = 7.0 Hz), 3.52 s (2H, CH_2), 4.22 q (2H, OCH_2, ^3J = 7.0 Hz), 4.38 q (3H, OCH_2, ^3J = 7.0 Hz), 7.26 s (1H, 5-H), 7.64 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 119.8 d (C^5), 120.8 q (CF_3, ^1J = 273.0 Hz), 129.5 q ($F_3C\mathbf{C}$, ^2J = 33.5 Hz), 142.8 d (C^4), 160.0–161.5 m (4-CO), 168.1 (C^2). Mass spectrum, *m*/*z* (I_{rel}, %): 353 (15) $[M]^+$, 308 (12), 307 (20), 288 (10), 284 (55), 262 (27), 261 (100), 259 (11), 235 (17), 234 (13), 210 (10), 206 (15). Found, %: N 11.26; S 9.55. $C_{12}H_{14}F_3N_3O_4S$. Calculated, %: N 11.89; S 9.08.

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