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Regio- and Stereoselective N^2-Functionalization with Propanamide Fragment of Aromatic and Heteroaromatic Aldehydes Thiosemicarbazones

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Abstract—Aiming at the synthesis of new potentially pharmacologically active compounds combining in the molecule structures of thiosemicarbazone and 3-hydrazinylpropionic acid, we performed a regio- and stereoselective N^2-functionalization of thiosemicarbazones of aromatic and heteroaromatic aldehydes by alkaline hydration of the corresponding (*E*)-N^2-cyanoethyl derivatives (propanenitriles) prepared by a regio- and stereoselective cyanoethylation with acrylonitrile. The hydration proceeds with the retention of the *E*-configuration of the initial propanenitriles.

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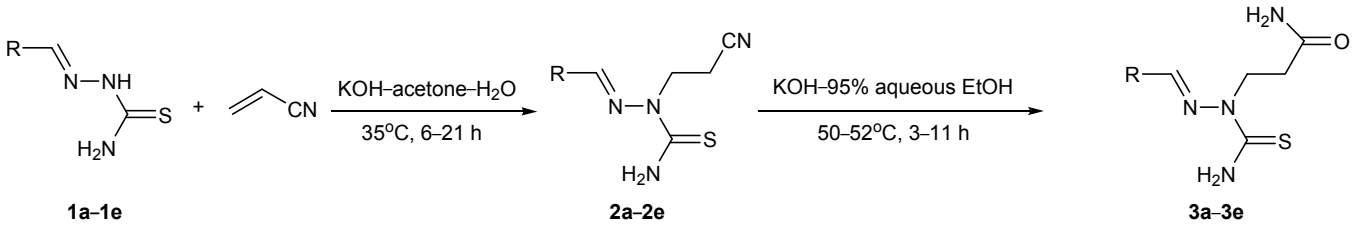
Thiosemicarbazones of aromatic and heteroaromatic aldehydes are potential drugs and drug precursors [1–12]. Among them compounds were found exhibiting antitumor [6, 8, 13–15], antibacterial [4, 7, 12, 13, 16], anticonvulsant [17], antioxidant [18], fungicidal and antihelminthic [16] action, urease inhibitors [12, 19]. Well known drugs like thioacetazone (tuberculocidal medicine) [20] and ambazone (faringosept, antiseptic and bacteriostatic) [21] contain thiosemicarbaside fragments. Recently a new tuberculocidal drug appeared, perchlozone [22–26], active agains micobacteria resistant to the other tuberculosis drugs.

Functionalization of thiosemicarbazones with pharmacoactive structural moieties, in particular, the combination of thiosemicarbazone and propanamide fragments in one molecule may open new possibilities for the targeted drug designing, since the propionamide derivatives exhibit antiphlogistic and anticonvulsant action [27], and also are used in the treatment of psoriasis, ulcerative colitis, glomerulonephritis, acute respiratory failure, idiopathic fibrosis, and rheumatoid arthritis [28]. Besides the amides of propionic acid favor better functioning of cognitive functions: processes of perception, concentration, memory, and learning in total [29].

We performed a regio- (at the atom N^2) and stereo- (with the retention of the initial *E*-configuration) functionalization of thiosemicarbazones of aromatic and heteroaromatic aldehydes by the introduction of a fragment of propanamide aiming at the preparation of hybrid molecules combining pharmacophore structure of thiosemicarbazone as well as 3-hydrazinylpropanamide, the main structural element of the known mildronate (meldonium) drug [30–33]. Regio- and stereoselective cyanoethylation of thiosemicarbazones of aromatic and heteroaromatic aldehydes **1** with acrylonitrile followed by alkaline hydration of obtained nitriles **2a**–**2e** to the corresponding propanamide derivatives was carried out. The experimental details of the first stage of this synthetic protocol are described in [34]. The cyanoethylation was performed in aqueous acetone in the presence of KOH (yield up to 74%, Scheme 1).

The molecules of thiosemicarbazones **1** have three nucleophilic sites (NH, NH_2, C=S) that theoretically may be involved in the addition to the electrophilic double bond of acrylonitrile. In these reactions thiol

Scheme 1.



R = Ph (**a**), 3-$NO_2C_6H_4$ (**b**), 3-phenylethenyl (**c**), furan-2-yl (**d**), pyridin-4-yl (**e**).

group is usually active, which forms due to tautomerism from the thione fragment [35, 36]. We found conditions that made it possible to carry out the cyanoethylation chemo- and regioselectively at the NH group of the hydrazine fragment.

The cyanoethylation occurs with the conservation of the *E*-configuration of initial thiosemicarbazones **1a–1e**. The regio- and stereoslectivity of the reaction was proved by X-ray diffraction analysis of the cyanoethylation products [34].

The best yields of propanamides **3a–3e** (47–60%) were obtained at performing the alkaline hydration of the cyanoethyl derivatives of thiosemicarbazones of aromatic and heteroaromatic aldehydes **2a–2e** in 95% aqueous ethanol, with 30–100 mol% KOH, at 50–52°C within 3–11 h. In the course of hydration the *E*-configuration of the initial propanenitriles does not change. The main trends in the influence of the structure of initial propanenitriles **2a–2e** and reaction conditions on the yield of propanamides **3a–3e** are shown in the table.

In the presence of 30 mol % of KOH (50–52°C, 3 h) the conversion of propanenitrile **2a** was incomplete (81%), and the yield of propanamide **3a** was 58% (with respect to reacted propanenitrile **2a**, run no. *1*). In 11 h a complete conversion of initial propanenitrile **2a** was achieved, yet the yield of the hydration product decreased to 46%, evidently due to deeper transformations of the formed propanamide **3a** (run no. *2*). Under the same conditions at the increased concentration of KOH (100 mol %) propanamide **3a** was not at all found in the reaction mixture indicating the total alkaline destruction of propanenitrile **2a** (run no. *5*). At the reaction temperature increased to 78°C (3.5 h) the side hydrolytic decomposition of initial propanenitrile **2a** became more pronounced, and the yield of amide **3a** reduced to 34% (run no. *3*). The same relationship was observed with the other propanenitrile derivatives, for example, with furan derivative **2d** (runs nos. *8–10*).

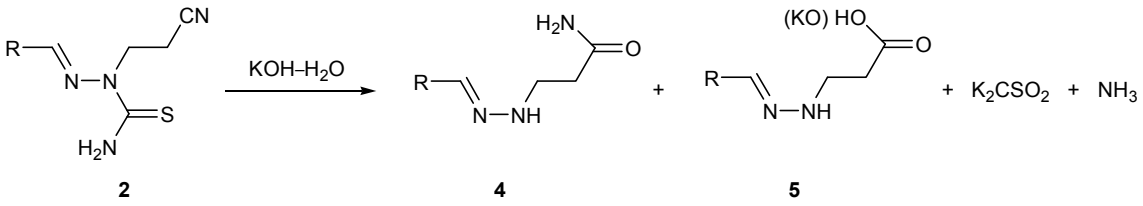
Due to the polyfunctional character of propanenitriles **2a–2e** their reaction with alkali in aqueous ethanol should take several paths. Along with

Hydration conditions of propanenitriles **2a–2e** and the yield of propanamides **3a–3e**

Run no.	Propanenitriles **2a–2e**[a]	KOH, mol %	Ethanol, mL	Reaction time, h	T, °C	Propanamides **3a–3e**	Yield of propanamides **3a–3e** (%)
1	**2a**	30	12	3	50–52	**3a**	58[b, c]
2	**2a**	30	12	11	50–52	**3a**	46
3	**2a**	30	12	3.5	78	**3a**	34[c]
4	**2a**	100	12	7	50–52	**3a**	42[c]
5	**2a**	100	12	11[d]	50–52	**3a**	–
6	**2b**	100	12	5	50–52	**3b**	47[b]
7	**2c**	50	6	6	50–52	**3c**	49
8	**2d**	30	12	11	50–52	**3d**	60
9	**2d**	50	6	11	50–52	**3d**	36[c]
10	**2d**	100	12	11	50–52	**3d**	18[c]
11	**2e**	30	6	3	60	**3e**	60

[a] Thiosemicarbazones **2a–2e** (1 mmol).
[b] Conversion of propionitriles **2a** 81%, **2b**, 97%.
[c] Yield calculated from the data of ^{1}H NMR spectra.
[d] After 7 h the reaction mixture contained thiosemicarbazone **1a**, propanenitrile **2a**, and propanamide **3a** (^{1}H NMR data).

Scheme 2.



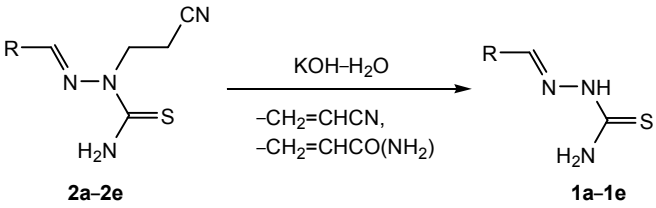
2 **4** **5**

the expectable hydration of the cyano group into amide and further hydrolysis to acid function a deep hydrolysis may occur of the thioamide fragment with the liberation respectively of hydrazinylpropanamide **4**, hydrazinylpropionic acid **5**, and its potassium salt, close structural analogs of meldonium (Scheme 2).

We did not identify the products of propanenitriles **2a–2e** deep hydrolysis, yet further they might be of pharmacologic interest.

Unexpectedly a removal of cyanoethyl group (retro-cyanoethylation) occurs and a formation of thiosemicarbazones **1a–1e** (yields 2–45%). On top of this, as showed a special experiment, analogous by the chemical nature elimination of acrylamide occurred: from propanamide **3a** under the hydration conditions of propanenitrile **2a** (run no. *2*) formed 14% of thiosemicarbazone **1a** (R = Ph). The liberated acrylonitrile and acryl amide (Scheme 3) evidently underwent polymerization as showed a polymer formation.

Scheme 3.



2a–2e **1a–1e**

The reaction progress was monitored by TLC and IR spectroscopy by the disappearance of the absorption band in the region 2247–2252 cm^{-1} corresponding to the cyano group of propanenitriles **2**.

The structure of compounds **2a–2e** and **3a–3e** was established by ^{1}H, ^{13}C, ^{15}N NMR and IR spectroscopy, the composition was confirmed by the data of elemental analysis. The application of 2D homonuclear $^{1}H–^{1}H$ (COSY), and also heteronuclear $^{1}H–^{13}C$ (HSQC, HMBC) procedures made it possible to unambiguously assign all signals in the ^{1}H and ^{13}C NMR spectra. The chemical shifts of the atoms ^{15}N were measured and assigned owing to the 2D experiment $^{1}H–^{15}N$ HMBC.

The proton chemical shifts of the azomethine group (HC=NN) in the ^{1}H NMR spectra were used as a spectral criterion for the configurational assignment. In propanenitriles **2a–2e** these values regularly decrease by 0.1–0.2 ppm with respect to analogous values in the thiosemicarbazones **1a–1e** [34] because of the electron effect of the CN group. The obtained propanenitriles **2a–2e** conserve the *E*-configuration for the formation of the *Z*-isomer should result in significantly larger upfield shift of the proton signal of the azomethine group (0.6–0.8 ppm) [37, 38]. In propanamides **3a–3e** the values of the chemical shifts of this proton vary in the range 7.80–8.13 ppm. Consequently, propanamides **3a–3e** also retain the *E*-configuration. In the ^{13}C NMR spectra of propanamides **3a–3e** the signals of the carbonyl group appear in the region 172 ppm, and the signals of cyano group at 118 ppm disappear. In the ^{15}N NMR spectra a signal was found of the second amino group (of amide fragment) in the region –269 to –270 ppm, and the signals of CN group in the region –129 to –130 ppm were absent.

IR spectra of propanamides **3a–3e** lacked the absorption band of the CN group (2247–2252 cm^{-1}), and the presence of a conjugated carbonyl fragment was confirmed by the absorption bands in the region 1669–1685 cm^{-1} (C=O).

Therefore the regio- and stereoselective functionalization of pharmacoactive thiosemicarbazones of aromatic and heteroaromatic aldehydes provides a possibility to introduce to the nitrogen in the position *2* a propanamide fragment retaining the *E*-configuration of the initial compounds with a preliminary regio- and stereoselective cyanoethylation of thiosemicarbazones in the position N^{2}. The prepared compounds combine in their molecule two important pharmacophore structures, thiosemicarbazone and propanamide, thus opening new ways to drugs designing. Their pharmacologic investigation is planned.

EXPERIMENTAL

^{1}H, ^{13}C, and ^{15}N NMR spectra were registered on spectrometers Bruker DPX-400 and Bruker AV-400 (400, 100, and 40.56 MHz respectively) in DMSO-d_6, internal references HMDS (^{1}H, ^{13}C), nitromethane (^{15}N). IR spectra were recorded on a spectrophotometer Bruker Vertex-70. Elemental analysis was carried out on a Koeffler heating block. The reaction progress was monitored by TLC on Silufol plates (eluent acetone–hexane, 1 : 1, 5 : 2). Thiosemicarbazones **1a–1e** and **2a–2e** were prepared as described in [34]. Aqueous 95% ethanol was used. The ratio of compounds **1a–1e** and **3a**, **3c–3e** in mixtures was determined from the data of ^{1}H NMR spectra.

3-[(2*E*)-2-Benzylidene-1-carbamothioylhydrazinyl]propanamide (3a). *a.* A slurry of 0.232 g (1 mmol) of (2*E*)-2-benzylidene-1-(2-cyanoethyl)hydrazine-1-carbothioamide **2a** and 0.020 g (0.3 mmol) of KOH·0.5H_2O in 12 mL of ethanol was vigorously stirred for 3 h at 50–52°C. Ethanol was removed in a vacuum. The dry residue was washed with water (2 mL), dried in a vacuum to obtain 0.188 g of yellow powder containing 23% of thiosemicarbazone **2a** (conversion 81%), 62% of propanamide **3a** (yield 58%), and 15% of thiosemicarbazone **1** (yield 19%) (^{1}H NMR data, see the table, run no. *1*).

b. A slurry of 0.232 g (1 mmol) of compound **2a** and 0.020 g (0.3 mmol) of KOH·0.5H_2O in 12 mL of ethanol was vigorously stirred for 11 h at 50–52°C. Ethanol was removed in a vacuum. The dry residue was washed with water (2 mL), dried in a vacuum to obtain yellow powder that was chromatographed on a column packed with silica gel (eluent acetone–hexane, 5 : 2). Yield of compound **3a** 0.115 g (46%), R_f 0.60–0.62, mp 167–169°C (see the table, run no. *2*). IR spectrum (KBr), cm^{-1}: 3488, 3420, 3399, 3265, 3202, 3139, 2959, 2926, 2856, 1664, 1588, 1462, 1447, 1400, 1383, 1359, 1341, 1309, 1295, 1231, 1201, 1165, 1127, 1088, 988, 938, 921, 870, 751, 687, 616, 575, 499, 463. ^{1}H NMR spectrum, δ, ppm: 2.42 t [2H, C$\underline{H}_2$CO(NH$_2$), *J* 7.8 Hz], 4.66 t (2H, NCH$_2$, *J* 7.8 Hz), 7.41, 6.88 br.s (2H, NH$_2$), 7.44–7.40 m (3H, H^{3,4,5}), 7.92–7.90 m (2H, H^{2,6}), 7.98 s (1H, HC=N), 8.32, 8.17 br.s (2H, NH$_2$). ^{13}C NMR spectrum, δ, ppm: 31.22 [$\underline{C}$H$_2$CO(NH$_2$)], 40.49 (NCH$_2$), 127.87 (C^{2,6}), 128.63 (C^{3,5}), 129.92 (C^4), 134.45 (C^1), 140.84 (HC=N), 172.08 (C=O), 180.32 (C=S). ^{15}N NMR spectrum, δ, ppm: –268.7 [CO(NH$_2$)], –266.8 (NH$_2$), –208.2 (N$\underline{N}$C=S), –65.9 (HC=N). Found, %: C 52.97; H 5.90; N 22.41; S 12.53. $C_{11}H_{14}N_4OS$. Calculated, %: C 52.78; H 5.64; N 22.38; S 12.81.

Yield of (2*Z*)-2-benzylidenehydrazine-1-carbothioamide **1a** 0.054 g (30%), R_f 0.80–0.82, melting point and spectral characteristics coincided with those described in [39].

c. A slurry of 0.232 g (1 mmol) of compound **2a** and 0.020 g (0.3 mmol) of KOH·0.5H_2O in 12 mL of ethanol was vigorously stirred at boiling for 3.5 h. Ethanol was removed in a vacuum. The dry residue was washed with water (2 mL), dried in a vacuum. Yellow powder (0.214 g) was washed with ethyl ether, dried in a vacuum to obtain 0.190 g of colorless substance containing 45% of propanamide **3a** (yield 34%), 43% of thiosemicarbazone **1a** (yield 45%), and 12% of unidentified compound (^{1}H NMR data, see the table, run no. *3*).

3-{(2*E*)-1-Carbamothioyl-2-[(3-nitrophenyl)methylidene]hydrazinyl}propanamide (3b). A slurry of 0.277 g (1 mmol) of (2*E*)-[2-(3-nitrophenyl)methylidene]-1-(2-cyanoethyl)hydrazine-1-carbothioamide **2b** and 0.065 g (1 mmol) of KOH·0.5H_2O in 12 mL of ethanol was stirred for 5 h at 50–52°C. The precipitate separated at cooling the reaction mixture was filtered off and washed in succession with ethyl ether and water, dried in a vacuum to obtain 0.142 g of light yellow substance containing 6% of thiosemicarbazone **2b** (conversion 97%) and 94% of propanamide **3b** (^{1}H NMR data). After chromatographing on a column with silica gel (eluent acetone–hexane, 1 : 1) we isolated compound **2b**, R_f 0.72–0.74, then **3b**, R_f 0.21–0.22. Yield of compound **3b** 0.135 g (47%), mp 218–220°C (decomp.) (see the ttable, run no. *6*), IR spectrum (KBr), cm^{-1}: 3430, 3323, 3231, 3177, 3063, 2962, 2923, 2854, 1685, 1596, 1532, 1475, 1460, 1430, 1406, 1383, 1357, 1338, 1280, 1250, 1205, 1162, 1093, 1081, 997, 951, 900, 875, 837, 809, 789, 737, 682, 646, 625, 593, 523, 506, 464. ^{1}H NMR spectrum, δ, ppm: 2.44 t [2H, C$\underline{H}_2$CO(NH$_2$), *J* 7.6 Hz], 4.66 t (2H, NCH$_2$, *J* 7.6 Hz), 6.94, 7.44 br.s (2H, NH$_2$), 7.70 t (1H, H^5, *J* 7.9 Hz), 8.13 s (1H, HC=N), 8.22 d (1H, H^4, *J* 8.1 Hz), 8.47 d (1H, H^6, *J* 7.8 Hz), 8.44, 8.52 br.s (2H, NH$_2$), 8.70 s (1H, H^2). ^{13}C NMR spectrum, δ, ppm: 31.00 [$\underline{C}$H$_2$CO(NH$_2$)], 40.85 (NCH$_2$), 122.80 (C^2), 124.14 (C^4), 130.14 (C^5), 133.49 (C^6), 136.51 (C^1), 138.83 (HC=N), 148.41 (C^3), 172.14 (C=O), 180.56 (C=S). ^{15}N NMR spectrum, δ, ppm: –269.9 [CO(NH$_2$)], –265.4 (NH$_2$), –207.3 (N$\underline{N}$C=S), –59.9 (HC=N), –8.0 (NO$_2$). Found, %: C 44.76; H 4.61; N

23.57; S 10.62. $C_{11}H_{13}N_5O_3S$. Calculated, %: C 44.74; H 4.44; N 23.71; S 10.86.

3-{(2*E*)-1-Carbamothioyl-2-[(*2E*)-3-phenylprop-2-en-1-ylylidene]hydrazinyl}propanamide (3c). A slurry of 0.258 g (1 mmol) of (2*E*)-2-[(*2E*)-3-phenylprop-2-en-1-ylilidene]-1-(2-cyanoethyl)hydrazine-1-carbothioamide **2c** and 0.033 g (0.5 mmol) of KOH·0.5H_2O in 6 mL of ethanol was vigorously stirred for 6 h at 50–52°C. Ethanol was removed in a vacuum. The residue was dissolved in 10 mL of water. To the obtained solution 0.1 N HCl solution (pH 5–6) was added and the mixture was left standing for 1 h. The separated precipitate was isolated by decanting, washed with water, and dried in a vacuum. Light yellow substance (0.165 g) contained 90% of propanamide **3c** and 10% of thiosemicarbazone **1c** (^{1}H NMR data). It was washed in succession with chloroform and ethyl ether and dried in a vacuum. Yield 0.135 g (49%) of compound **3c**, mp 154–156°C (see the table, run no. *7*). IR spectrum (KBr), cm^{-1}: 3466, 3446, 3317, 3188, 3030, 1652, 1628, 1601, 1570, 1530, 1493, 1456, 1438, 1412, 1364, 1342, 1312, 1287, 1257, 1216, 1171, 1117, 1090, 1071, 1002, 967, 913, 885, 795, 750, 688, 581, 511, 494, 467, 441. ^{1}H NMR spectrum, δ, ppm: 2.37 t [2H, C$\underline{H}_2$CO(NH_2)], 4.55 t (2H, NCH_2, *J* 6.9 Hz), 7.03 d.d (1H, H^8, *J* 8.2, 16.1 Hz), 7.12 d (1H, H^7, *J* 16.1 Hz), 7.33 t (1H, H^4, *J* 7.2 Hz), 7.40 t (2H, $H^{3,5}$, *J* 7.2 Hz), 7.49, 6.96 br.s (2H, NH_2), 7.55 d (2H, $H^{2,6}$, *J* 7.2 Hz), 7.80 d (1H, HC=N, *J* 8.2 Hz), 8.35, 8.06 br.s (2H, NH_2). ^{13}C NMR spectrum, δ, ppm: 31.28 [$\underline{C}H_2CO(NH_2)$], 40.54 (NCH_2), 126.10 (CH=$\underline{C}$HCH=N), 127.02 ($C^{2,6}$), 129.02 (C^4), 129.15 ($C^{3,5}$), 136.16 (C^1), 139.31 (PhCH=), 142.67 (HC=N), 172.20 (C=O), 180.06 (C=S). ^{15}N NMR spectrum, δ, ppm: –269.0 [$CO(NH_2)$], –266.6 (NH_2), –206.9 (N$\underline{N}$C=S), –60.2 (HC=N). Found, %: C 56.27; H 5.90; N 20.43; S 11.33. $C_{13}H_{16}N_4OS$. Calculated, %: C 56.50; H 5.84; N 20.27; S 11.60.

The solvents were removed from the mother liquor in a vacuum to obtain yellow powder subjected to column chromatography on silica gel (eluent acetone–hexane, 1 : 1). Yield of thiosemicarbazone **1c** 0.015 g, R_f 0.70–0.71. From the water solution at standing a substance precipitated that was separated, washed with water, and dried in a vacuum to obtain 0.014 g of thiosemicarbazone **1c**. Overall yield of compound **1c** 0.029 g (14%), its spectral characteristics coincided with those described in [19].

3-{(2*E*)-1-Carbamothioyl-2-[(furan-2-yl)methylidene]hydrazinyl}propanamide (3d). *a*. A slurry of 0.222 g (1 mmol) of (2*E*)-2-(furan-2-ylmethylidene)-1-(2-cyanoethyl)hydrazine-1-carbothioamide **2d** and 0.020 g (0.3 mmol) of KOH·0.5H_2O in 12 mL ethanol was vigorously stirred for 11 h at 50–52°C. Ethanol was removed in a vacuum. The residue was dissolved in 10 mL of water. To the obtained solution 0.1 N HCl solution (pH 5–6) was added. The light brown precipitate was filtered off, washed with water, and dried in a vacuum (0.149 g). It contained 97% of propanamide **3d** and 3% of thiosemicarbazone **1d** (^{1}H NMR data). The substance was washed in succession with chloroform and ethyl ether and dried in a vacuum. Yield 0.144 g (60%) compound **3d**, mp 158–160°C (decomp.) (see the table, run no. *8*). IR spectrum (KBr), cm^{-1}: 3427, 3348, 3307, 3191, 3154, 2970, 2926, 2855, 1669, 1621, 1583, 1539, 1517, 1481, 1458, 1416, 1366, 1332, 1290, 1259, 1222, 1181, 1150, 1095, 1079, 1015, 996, 935, 916, 884, 825, 751, 634, 612, 593, 544, 517, 461. ^{1}H NMR spectrum, δ, ppm: 2.38 t [2H, C$\underline{H}_2$CO(NH_2), *J* 7.2 Hz], 4.58 t (2H, NCH_2, *J* 7.2 Hz), 6.63 s (1H, H^4), 7.10 d (1H, H^3, *J* 2.6 Hz), 7.48, 6.95 br.s (2H, NH_2), 7.81 s (1H, H^5), 7.88 s (1H, HC=N), 8.40, 7.94 br.s (2H, NH_2). ^{13}C NMR spectrum, δ, ppm: 31.20 [$\underline{C}H_2CO(NH_2)$], 40.50 (NCH_2), 112.55 (C^4), 112.96 (C^3), 131.06 (HC=N), 145.10 (C^5), 150.11 (C^2), 172.22 (C=O), 180.08 (C=S). ^{15}N NMR spectrum, δ, ppm: –268.9 [$CO(NH_2)$], –266.8 (NH_2), –208.5 (N$\underline{N}$C=S), –71.2 (HC=N). Found, %: C 44.66; H 4.97; N 23.61; S 13.38. $C_9H_{12}N_4O_2S$. Calculated, %: C 44.99; H 5.03; N 23.32; S 13.34.

b. By analogous processing from 0.222 g (1 mmol) of compound **2d** and 0.033 g (0.5 mmol) of KOH·0.5H_2O in 6 mL of ethanol we obtained 0.087 g (36%) of propanamide **3d** (see the table, run no. *9*). The residue obtained after distilling off chloroform and ethyl ether was chromatographed on the column packed with silica gel (eluent acetone–hexane, 1 : 1). Yield 0.011 g (7%) of (2*Z*)-2-(furan-2-ylmethylidene)-hydrazine-1-carbothioamide **1d**, whose spectral characteristics coincided with those described in [40].

c. Similarly from 0.222 g (1 mmol) of compound **2d** and 0.065 g (1 mmol) of KOH·0.5H_2O in 12 mL of ethanol we obtained 0.044 g (18%) of propanamide **3d** and 0.005 g (2%) of thiosemicarbazone **1d** (see the table, run no. *10*).

Water from the mother liquors was removed in a vacuum. Dry residues were treated with anhydrous

acetone. Acetone was removed in a vacuum to isolate 0.089 g (*a*), 0.128 g (*b*), and 0.149 g (*c*) of polymer respectively.

3-{1-Carbamothioyl-(2*E*)-2-[(pyridin-4-yl)methylidene]hydrazinyl}propanamide (3e). A slurry of 0.234 g (1 mmol) of (2*E*)-2-[(pyridin-4-yl)methylidene]-1-(2-cyanoethyl)hydrazine-1-carbothioamide **2e**, and 0.020 g (0.3 mmol) of KOH·0.5H_2O in 6 mL of ethanol was vigorously stirred for 3 h at 60°C. On cooling the reaction mixture to room temperature a precipitate formed, it was separated by decanting and washed successively with ethyl ether and water, dried in a vacuum to obtain 0.064 g of propanamide **3e**. Ethanol was removed in a vacuum, the residue was washed with dry ethyl ether and dried to isolate 0.154 g of substance chromatographed on a column packed with silica gel (eluent acetone–hexane, 1 : 1). We isolated compound **3e**, R_f 0.21–0.22, and thiosemicarbazone **1e**, R_f 0.71–0.73. Overall yield of compound **3e** 0.150 g (60%), mp 210–211°C (decomp.) (see the table, run no. *11*). IR spectrum (KBr), cm^{-1}: 3419, 3352, 3331, 3240, 3177, 3111, 3030, 2997, 2964, 2923, 2857, 1683, 1658, 1619, 1596, 1548, 1451, 1407, 1367, 1341, 1310, 1261, 1240, 1203, 1177, 1080, 1026, 995, 969, 953, 921, 883, 816, 766, 712, 670, 626, 536, 511, 460. ^{1}H NMR spectrum, δ, ppm: 2.42 t [2H, C$\underline{H}_2$CO(NH_2), *J* 7.6 Hz], 4.65 t (2H, NCH_2, *J* 7.6 Hz), 7.42, 6.93 br.s (2H, NH_2), 7.90 d (2H, $H^{3,5}$, *J* 5.8 Hz), 7.95 s (1H, HC=N), 8.60, 8.39 br.s (2H, NH_2), 8.60 d (2H, $H^{2,6}$, *J* 5.8 Hz). ^{13}C NMR spectrum, δ, ppm: 30.90 [$\underline{C}H_2CO(NH_2)$], 40.66 (NCH_2), 121.70 ($C^{3,5}$), 138.12 (HC=N), 141.67 (C^4), 150.04 ($C^{2,6}$), 171.94 (C=O), 180.69 (C=S). ^{15}N NMR spectrum, δ, ppm: –268.8 [$CO(NH_2)$], –263.0 (NH_2), –205.7 (N$\underline{N}$C=S), –76.2 (HC=N). Found, %: C 47.97; H 4.99; N 27.61; S 12.90. $C_{10}H_{13}N_5OS$. Calculated, %: C 47.79; H 5.21; N 27.87; S 12.76.

Yield of (2*E*)-2-[(pyridin-4-yl)methylidene]hydrazine-1-carbothioamide **1e** 0.036 g (20%), melting point and spectral characteristics coincided with those described in [34].

Alkaline decomposition of 3-[(2*E*)-2-benzylidene-1-carbamothioylhydrazinyl]propanamide (3a). A slurry of 0.025 g (0.1 mmol) of propanamide **3a** and 0.002 g (0.03 mmol) of KOH·0.5H_2O in 1.2 mL of ethanol was vigorously stirred for 11 h at 50–52°C. Ethanol was removed in a vacuum, the residue was washed with ethyl ether and dried in a vacuum to obtain 0.026 g of light yellow powder containing 90% of propanamide **3a** and 10% of thiosemicarbazone **1a** (yield 14%) (^{1}H NMR data).

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REFERENCES

1. Youssef, A.S.A., *Phosph. Sulfur, Silicon*., 2002, vol. 177, p. 173.
2. Gomaa, M.A.-M., Hassan, A.A., and Shehatta, H.S., *Heteroatom Chem*., 2006, vol. 17, p. 261.
3. Alahari, A., Trivelli, X., Guérardel, Y., Dover, L.G., Besra, G.S., Sacchettini, J.C., Reynolds, R.C., Coxon, G.D., and Kremer, L., *PLoS ONE*, 2007, vol. 2, p. 1343. doi 10.1371/journal.pone.0001343
4. Kizilcikli, Ý., Kurt, Y.D., Akkurt, B., Genel, A.Y., Birteksöz, S., Ötük, G., and Ülküseven, B., *Folia Microbiol*., 2007, vol. 52, p. 15.
5. Darehkordi, A., Saidi, K., and Islami, M.R., *Arkivoc*, 2007, vol. i, p. 180.
6. Điloviæ, I., Rubèiæ, M., Vrdoljak, V., Paveliæ, S.K., Kralj, M., Piantanidab, I., and Cindriæ, M., *Bioorg. Med. Chem*., 2008, vol. 16, p. 5189.
7. De Aquino, T.M., Liesen, A.P., da Silva, R.E.A., Lima, V.T., Carvalho, C.S., de Faria, A.R., de Araujo, J.M., de Lima, J.G., Alves, A.J., de Melo, E.J.T., and Goes, A.J.S., *Bioorg. Med. Chem*., 2008, vol. 16, p. 446. doi 10.1016/j.bmc.2007.09.025
8. Matesanz, A.I. and Souza, P., *Med. Chem*., 2009, vol. 9, p. 1389.
9. Gazieva, G.A. and Kravchenko, A.N., *Russ. Chem. Rev*., 2012, vol. 81, p. 494. doi 10.1070/RC2012v081n06ABEH004235
10. Ahmadi, S.A. and Ghazanfari, D., *Iran. J. Cat*., 2013, vol. 3, p. 177.
11. Singhal, S., Arora, S., Agarwal, S., Sharma, R., and Singhal, N., *World J. Pharm. Pharm. Sci*., 2013, vol. 2, p. 4661.
12. Macegoniuk, K., *Folia Biol. Oecol*., 2013, vol. 9, p. 9. doi 10.2478/fobio-2013-0004
13. Beraldo, H. and Gambino, D., *Mini Rev. Med. Chem*., 2004, vol. 4, p. 31.
14. Tsimberidou, A.-M., Alvarado, Y., and Giles, F.J., *Expert Rev. Anticancer Ther*., 2002, vol. 2, p. 437. doi 10.1586/14737140.2.4.437
15. Heffeter, P., Pirker, C., Kowol, C.R., Herrman, G., Dornetshuber, R., Miklos, W., Jungwirth, U.,

Koellensperger, G., Keppler, B.K., and Berger, W., *Leuk. Res*., 2003, vol. 27, p. 1077.

16. Gopalakrishnan, M., Sureshkumar, P., Thanusu, J., and Kanagarajan, V., *Pharm. Chem. J*., 2008, vol. 42, p. 271.
17. Rastogi, S. and Rastogi, H., *Ind. J. Chem*., 2010, vol. 49B, p. 547.
18. Barcelos, R.P., de Lima Portella, R., da Rosa, E.J.F., de Souza Fonseca, A., Bresolin, L., and Carratu, V., *Life Sci*., 2011, vol. 89, p. 20.
19. Aslam, M.A.S., Mahmood, S., Shahid, M., Saeed, A., and Iqbal, J., *Eur. J. Med. Chem*. 2011, *46*, 5473. doi 10.1016/j.ejmech.2011.09.009
20. Mashkovskii, M.D., *Lekarstvennye sredstva* (Drugs), Moscow: Novaya Volna, 2003, vol. 3.
21. Kleemann, A., Engel, J., Kutscher, B., and Reichert, D., *Pharmaceutical Substances: Syntheses, Patents, Applications*, Stuttgart, New York: Thieme, 2001.
22. Elokhina, V.N., Aleksandrova, A.E., Nakhmanovich, A.S., Shchegoleva, R.A., Karnaukhova, R.V., Vinogradova, T.I., and Kalikhman, I.D., RF Patent no. 1621449, 1989; *Byull. Izobret*., 1996, no. 25.
23. Nakhmanovich, A.S., Elokhina, V.N., Dolgushin, G.V., Gushchin, A.S., Polyakov, R.A., Volkova, K.A., and Puniya, V.S., RF Patent no. 2265014, 2004, *Byull. Izobret*., 2005, no. 33.
24. Gushchin, A.S., Vinogradova, T.I., Yablonskii, P.K., Batyunin, G.A., Zabolotnykh, N.V., Vasil'eva, S.N., and Malygin, A.V., RF Patent no. 2423977, 2010; *Byull. Izobret*., 2011, no. 20.
25. Smolentsev, A.I., Lavrenova, L.G., Elokhina, V.N., Nakhmanovich, A.S., and Larina, L.I., *J. Struct. Chem*., 2009, vol. 50, p. 500.
26. Trofimov, B.A., Amosova, S.V., Elokhina, V.N., Yaroshenko, T.I., and Potapov, V.A., RF Patent no. 2476426, 2011; *Byull. Izobret*., 2013, no. 6.
27. Amit, S., *Int. J. Med. Sci. Clin. Inven*., 2014, vol. 1, p. 15.
28. Allegretti, M., Bertini, R., Colotta, F., Caselli, G., Cesta, M.C., Sabbatini, V., and Bizzarri, C., Canad. Patent no. 2420585, 2009; *Chem. Abstr*., 2001, vol. 135, p. 331442.
29. Luithle, J., Bob, F.-G., Erb, C., Schnizler, K., Flessner, T., Kampen, M.V., and Methfessel, C., Canad. Patent no. 2479097, 2002; *Chem. Abstr*., 2003, vol. 139, p. 277049.
30. Eremeev, A., Kalvinsh, I.Y., Semenikhina, V.G., Liepinsh, E.E., Latvietis, Y.Y., Anderson, P.P., Astapenok, E.B., Spruzh, Y.Y., Trapentsiers, P.T., Podoprigora, G.I., and Giller, S.A., US Patent no. 4481218, 1984; *Chem. Abstr*., 1981, vol. 94, p. 30198d.
31. Kalvinsh, I. and Birmans, A., WO App. no. 2005012233, 2005; *Chem. Abstr*., 2005, vol. 142, p. 218963.
32. Görgens, C., Guddat, S., Dib, J., Geyer, H., Schänzera, W., and Thevisa, M., *Drug Test. Analysis*, 2015, vol. 7, p. 973. doi 10.1002/dta.1788
33. Dambrova, M., Makrecka-Kuka, M., Vilskersts, R., Makarova, E., Kuka, J., and Liepinsh, E., *Pharm. Res*., 2016, vol. 113, p. 771.
34. Mal'kina, A.G., Nosyreva, V.V., Albanov, A.I., Afonin, A.V., Vashchenko, A.V., Amosova, S.V., and Trofimov, B.A., *Synth. Commun*., 2017, vol. 47, p. 159. doi 10.1080/00397911.2016.1257723
35. Tenório, R.P., Carvalho, C.S., Pessanha, C.S., de Lima, J.G., de Faria, A.R., Alves, A.J., de Melo, E.J.T., and Góes, A.J.S., *Bioorg. Med. Chem. Lett*., 2005, vol. 15, p. 2575.
36. Ali, T.E.-S. and Abdel-Monem, W.R., *Phosph. Sulfur, Silicon Relat. Elem*., 2008, vol. 183, p. 2161.
37. Afonin, A.V., Ushakov, I.A., Pavlov, D.V., Ivanov, A.V., and Mikhaleva, A.I., *Magn. Res. Chem*., 2010, vol. 48, p. 685.
38. Afonin, A.V., Pavlov, D.V., Ushakov, I.A., and Keiko, N.A., *Magn. Res. Chem*., 2012, vol. 50, p. 502.
39. Jatav, V., Mishra, P., Kashaw, S., and Stables, J.P., *Eur. J. Med. Chem*., 2008, vol. 43, p. 135.
40. Abbasi, A., Gernmayen, S., Taheri, A.N., Shahroosvand, H., and Shabani, M., *Eur. J. Chem*., 2010, vol. 7, p. 294.