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# Studies on Pyrazine Derivatives, XLV: Synthesis, Reactions, and Tuberculostatic Activity of *N*-Methyl-*N*′-(pyrazine-2-carbonyl)-hydrazinecarbodithioic Acid Methyl Ester

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*Methyldithiocarbonyl derivative **2** of pyrazine-2-carboxylic acid* N′*-methylhydrazide **1** was synthesized by methylation of $CS_2$ adduct. Benzylamine caused the decomposition of compound **2** to pyrazine-2-carboxylic acid benzylamide **5** and 1,3-dibenzylthiourea **6**.* N*-methyl-*N′*-(pyrazine-2-carbonyl)-hydrazinecarbodithioic acid methyl ester **2** were evidenced to cyclize to 3-methyl-5-pyrazin-2-yl-3*H*-[1,3,4]oxadiazole-2-thione **8** in the presence of triethylamine. In the reactions with secondary amines such as morpholine, pyrrolidine and phenylpiperazine pyrazinoyl derivatives (**9–11**) of thiosemicarbazide were obtained. Hydrazine, methylhydrazine, aminoalcohols, and* N*-alkylamino-substituted cyclic amines reacted with cyclization to 4-substituted 1,2,4-triazole-3-thiones **12**, **13**, and **18–22**. Synthesized compounds exhibited low tuberculostatic activity in vitro (MIC 50–100 μg/mL).*

**Keywords** 2-methyl-[1,2,4]triazole-3-thione; 3-methyl-[1,3,4]oxadiazole-2-thione; methyldithiocarbazate esters; pyrazine-2-carboxylic acid *N*′-methyl-hydrazide; thiosemicarbazides; tuberculostatic activity

## INTRODUCTION

Our previous research has shown that mono- and dithioesters of pyrazinoylcarbodithioic acid undergo reactions with amines, and the structure of products depends on the amine type and reaction conditions.

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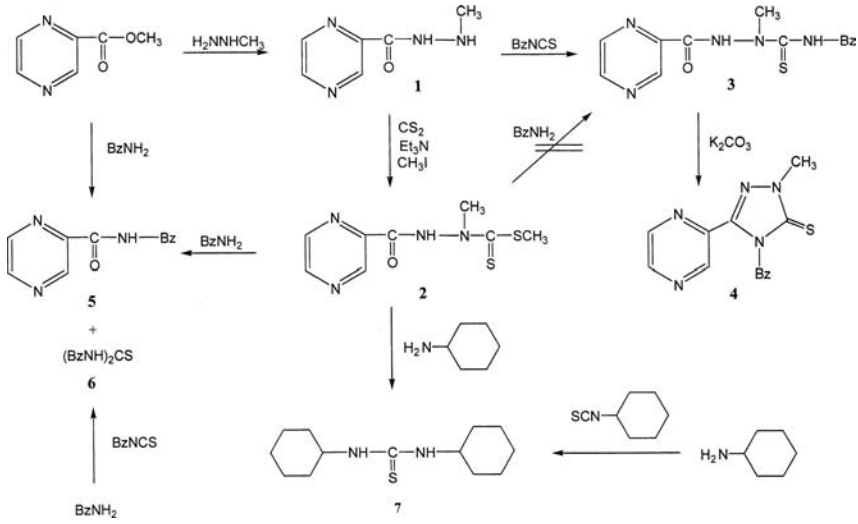
Derivatives of thiosemicarbazide as well as heterocyclic compounds such as the 1,3,4-oxadiazole,1,2,4-triazole, and triazolepyrimidine condensed structure[1–3] can be the products of reactions.

## CHEMISTRY

In this work, we tried to investigate the possibilities of the usage of the *N*-Methyl-*N′*-(pyrazine-2-carbonyl)-hydrazinecarbodithioic acid methyl ester **2** obtained from pyrazine-2-carboxylic acid *N′*-methyl-hydrazide **1** in organic synthesis. Hydrazide was synthesized from pyrazinamide in a result of typical reaction described in the literature.[4,5] Pyrazine-2-carboxylic acid obtained by hydrolysis was estrificated with methanol in the presence of thionyl chloride. The originated ester changed into an expected pyrazine-2-carboxylic acid *N′*-methyl-hydrazide **1** under influence of hydrazine. *N*-methyl-*N′*-(pyrazine-2-carbonyl)-hydrazinecarbodithioic acid methyl ester **2** was synthesized as a product of $CS_2$ and methyl iodide treatment on compound **1** in a presence of triethylamine (Scheme 1). The reaction ran fast and with a good yield.

Next, we examined an influence of various amines on compound **2**. In our research, we used benzylamine, cyclohexylamine, triethylamine, morpholine, pyrrolidine, 1-phenylpiperazine, hydrazine and methylhydrazine, ethanolamine, 1,3-diaminopropanol,




**SCHEME 1**

1-(2-aminoethyl)pyrrolidine, 2-piperidinoethylamine, and *N*-(3-aminopropyl)imidazole. The products of the reactions were different and depended on the amine structure.

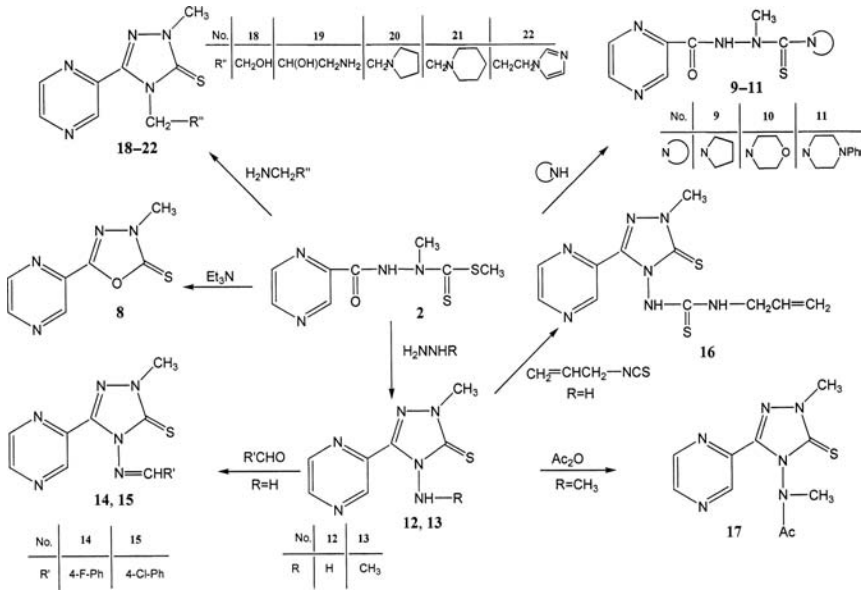
In a reaction with benzylamine we expected two products: thiosemicarbazide derivative **3** and a product of its cyclization **4**. That possibility was excluded after the synthesis of compound **3** from hydrazide **1** and benzyl isothiocyanate and compound **4** in the cyclization reaction of **3**. IR spectra exhibited a different structure of obtained products. On the basis of IR and $^1$H NMR spectra, we maintained that pyrazine-2-carboxylic acid benzylamide **5** and 1,3-dibenzylthiourea **6** were the products of a reaction between *N*-methyl-*N*′-(pyrazine-2-carbonyl)-hydrazinecarbodithioic acid methyl ester **2** and benzylamine. The structures of the obtained compounds were confirmed by control syntheses: **5** in reaction of pyrazine-2-carboxylic acid methyl ester with benzylamine and **6** from benzyl isothiocyanate and benzylamine.

In the reaction of compound **2** with cyclohexylamine, only 1,3-dicyclohexylthiourea **7** was isolated as crystalline product. That product can create as a result of methyl mercaptan elimination from compound **2** under the influence of cyclohexylamine while the thiocarbonyl carbon is attacked by another molecule of amine. Thiourea forms as a result of the C—N bond breaking. Dithiocarboxylic acid monoester without the methyl group in the hydrazine moiety demonstrated the same course of reaction with cyclohexylamine as we have described in a previous article.[5] Dicyclohexylthiourea and pyrazin-2-carboxylic acid hydrazide are the products of that reaction.

The heating of *N*-methyl-*N*′-(pyrazine-2-carbonyl)-hydrazinecarbodithioic acid methyl ester **2** in ethanol in the presence of triethylamine led to 3-methyl-5-pyrazin-2-yl-3*H*-[1,3,4]oxadiazole-2-thione **8** (Scheme 2).

In the reactions with pyrrolidine, morpholine and 1-phenylpiperazine compound **2** gave the products of thiosemicarbazide structures **9–11**. IR spectra with a strong band at 1680 cm$^{-1}$ characteristic for the carbonyl group confirmed that kind of structure.

The reaction of compound **2** with hydrazine and methylhydrazine resulted 4-amino-[1,2,4]triazole-3-thione **12** and 4-methylamino-[1,2,4]triazole-3-thione **13**. For derivative **12** possessing a free $NH_2$ group in 4-position, condensation reactions with p-fluoro- and p-chlorobenzaldehyde were performed giving halobenzylidene compounds **14** and **15**. Both processes proceeded with very good yields when the substrates were heated in ethanol. Derivative **12** also reacted with allyl isothiocyanate and gave 1,3-disubstituted thiourea **16**. 4-methylamino-[1,2,4]triazole-3-thione **13** did not undergo that reaction,




**SCHEME 2**

and the presence of the NH group in 4-position was evidenced by the reaction with acetic anhydride, which formed acetamide **17**.

In the reactions with ethanolamine, 1,3-diaminopropanol, 1-(2-aminoethyl)pyrrolidine, 2-piperidinoethylamine, and 1-(3-aminopropyl)imidazole compound **2** gave appropriate 4-aminoalkyl-[1,2,4]triazole-3-thiones **18–22**. All products formed with good yields, especially when the reactants were liquid and the reactions could be performed with their large excess towards **2** without a solvent.

## MICROBIOLOGY

The newly synthesized derivatives were examined for their tuberculostatic activity towards the *Mycobacterium tuberculosis* $H_{37}Rv$ strain and two "wild" strains isolated from tuberculotic patients: one (Spec. 210) resistant to p-aminosalicic acid (PAS), isonicotinic acid hydrazide (INH), etambutol (ETB), and rifampicine (RFP); another (Spec. 192) fully sensitive to the administrated drugs. In vitro investigations were performed by a classical test-tube method of successive dilution with Youman's liquid medium containing 10% of bovine serum.[5] The

determined minimum concentrations (MIC) inhibiting the growth of tuberculous strains for all the tested compounds were within the limits 50–100 $\mu$g/mL, which indicates low antituberculosis activity. The defences in compound activity on particular stains have not been observed.

## EXPERIMENTAL

All materials and solvents were of analytical reagent grade. Thin-layer chromatography was performed on Merck Kieselgel $60F_{254}$ plates and visualized with UV. Silica gel 60 (70–230 mesh, Fluka) was used for column chromatography. The results of elemental analyses (% C, H, N) for all the compounds obtained were in good agreement with the data calculated. $^1$H NMR spectra in $CDCl_3$ were recorded on Varian Gemini (200 MHz) and Varian Unity Plus (500 MHz) instruments. IR Spectra (KBr) were determined as KBr pellets of the solids on a satellite FT-IR spectrophotometer. Mass spectrum for compound **18** was taken on Finingan MAT 95 (70 eV). Melting points were determined on BOETIUS apparatus and were uncorrected. Reaction yields, physical constants, and spectral data of the compounds are given in Table I.

### Pyrazine-2-carboxylic Acid *N*′-Methyl-hydrazide (1)

Pyrazine-2-carcoxylic acid methyl ester (15.3 g, 0.1 mol) was dissolved in 30 mL of ethanol, and 7.2 g (0.15 mol) of methylhydrazine were added. The reaction mixture was heated under reflux for 1.5 h. Then ethanol was evaporated in vacuum, and oily residue was treated with 20 mL of diethyl ether and 5 mL of ethanol. The precipitate (15.2 g, 68%) was filtered after cooling and recrystallized from benzene (95–96°C).

### *N*-Methyl-*N*′-(pyrazine-2-carbonyl)-hydrazinecarbodithioic Acid Methyl Ester (2)

A quantity of 3 g (20 mmol) of **1** was dissolved in 20 mL of methanol. Next, 3 mL (21 mmol) of triethylamine and 1.5 mL (25 mmol) of carbon disulfide were added. After 5 min of stirring, 1.5 mL (25 mmol) of methyl iodide were added. Reaction mixture was stirred for another 30 min and diluted with 100 mL of water. The crystals were filtered (2.6 g) and recrystallized.

**TABLE I Characteristics of the Newly Synthesized Compounds**

| Compound no. | Yield % | M.P. [°C] Solvent for Crystallization | Formula MW | IR [$cm^{-1}$] | $^1H$ NMR ($CDCl_3$) $\delta$ [ppm] |
|---|---|---|---|---|---|
| **2** | 68 | 146–148 ethanol | $C_8H_{10}N_4OS_2$ 242.31 | 3266 (NH); 1691 (C=O); 1135 (C=S) | 2.50 (s, 3H, $SCH_3$); 3.75 (s, 3H, $NCH_3$); 8.60, 8.85 and 9.45 (3s, 3H, pyrazine); 10.00 (s, 1H, NH) |
| **3** | 93 | 86–88 ethanol | $C_{14}H_{15}N_5O$ 269.28 | 3506, 3270 (NH); 1691 (C=O); 1144 (C=S) | 3.75 (s, 3H, $NCH_3$); 4.89 (d, 2H, $CH_2$, $J$ 4.21 Hz); 6.71 (brs, 1H, S=CN<u>H</u>$CH_2$); 7.29–7.36 (m, 5H, ArH); 8.60 (m, 2H, pyrazine); 8.88 (d, 1H, pyrazine, $J$ 2.45 Hz) 9.42 (d, 1H, pyrazine, $J$ 1.42); 9.49 (s, 1H, NH) |
| **4** | 85 | 89–90 cyclohexane | $C_{14}H_{13}N_5$ 251.28 | 1072 (C=S) | 3.99 (s, 3H, $NCH_3$); 5.98 (s, 2H, $CH_2$); 6.71; 7.22–7.31 (m, 5H, ArH); 8.63 (m, 2H, pyrazine); 9.23 (d, 1H, pyrazine, $J$ 1.30 Hz) |
| **5** | 70 | 117–118 cyclohexane | $C_{12}H_{11}N_3O$ 213.25 | 3368 (NH); 1671 (C=O) | 4.72 (d, 2H, $CH_2$, $J$ 6.14Hz); 7.30–7.41 (m, 5H, ArH); 8.18 (brs, 1H, NH), 8.54 (t, 1H, pyrazine, $J_1$ 2.32Hz, $J_2$ (1.54Hz); 8.78 (d, 1H, pyrazine, $J$ 2.40Hz); 9.48 (d, 1H, pyrazine, $J$ 1.39 Hz) |
| **8** | 75 | 119–120 methanol | $C_7H_6N_4OS$ 178.21 | 1184 (C=S) | 3.65 (s, 3H, $NCH_3$); 8.75 (m, 2H, pyrazine); 9.25 (d, 1H, pyrazine, $J$ 1.38 Hz) |
| **9** | 29 | 137–138 ethanol | $C_{11}H_{15}N_5OS$ 265.33 | 3215 (NH); 1694 (C=O) 1171 (C=S) | 1.97 (s, 4H, $CH_2$) 3.22 (s, 3H, $NCH_3$); 3.74 (s, 4H, N $CH_2$); 8.63 (s, 1H, pyrazine); 8.84 (d, 1H, pyrazine, $J$ 2.36 Hz); 9.42 (s, 1H, pyrazine); 10.07 (s, 1H, NH) |
| **10** | 40 | 113–115 ethanol | $C_{11}H_{15}N_5O_2S$ 281.334 | 3163 (NH); 1683 (C=O); 1114 (C=S) | 3.34 (s, 3H, $NCH_3$); 3.78 (t, 4H, $NCH_2$, $J_1$ 4.47 Hz, $J_2$ 4.32 Hz); 3.93 (t, 4H, $OCH_2$,$J_1$ 4.36 Hz, $J_2$ 4.15 Hz); 8.64 (m, 1H, pyrazine); 8.84 (d, 1H, pyrazine, $J$ 2.53 Hz); 9.40 (d, 1H, pyrazine, J 1.38 Hz); 10.36 (s, 1H, NH) |
| **11** | 49 | 104–106 column chromatography | $C_{17}H_{20}N_6OS$ 356.44 | 3248 (NH); 1695 (C=O); 1158 (C=S) | 3.31–3.50 (m, 7H, 4H $NCH_3$ and 3H $SCH_3$); 4.07 (s, 4H, $NCH_2$); 6.96 (d, 3H, ArH, $J$ 7.05 Hz); 7.34 (m, 2H, ArH); 8.61 (s, 1H, pyrazine); 8.82 (s, 1H, pyrazine); 9.39 (s, 1H, pyrazine); 10.35 (s, 1H, NH) |
| **12** | 62 | 173–175 methanol | $C_7H_8N_6S$ 208.25 | 3292, 3135; 1612 ($NH_2$); 1089 (C=S) | 3.92 (s, 3H, $NCH_3$); 4.89 (s, 2H, $NH_2$); 8.71 (m, 2H, pyrazine); 9.36 (s, 1H, pyrazine) |
| **13** | 68 | 118–120 water | $C_8H_{10}N_6S$ 222.27 | 3234, 1510 (NH); 1076 (C=S) | 2.87 (s, 3H, NHC<u>H</u>$_3$); 3.82 (s, 3H, $NCH_3$); 8.75 and 9.3 (2s, 3H, pyrazine) |

| | | | | | |
|---|---|---|---|---|---|
| **14** | 50 | 142–144 ethanol | $C_{14}H_{11}FN_6S$ 314.34 | 1601 (C=N); 1098 (C=S) | 3.96 (s, 3H, $NCH_3$); 7.14–7.27 (m, 2H, ArH); 7.86–7.93 (m, 2H, ArH); 8.72 and 9.32 (2m, 3H, pyrazine); 10.22 (s, 1H, N=CH) |
| **15** | 70 | 177–179 methanol | $C_{14}H_{11}ClN_6S$ 330.80 | 1597 (C=N); 1088 (C=S) | 3.96 (s, 3H, $NCH_3$); 7.47 (d, 2H, ArH, *J* 8.50 Hz); 7.81 (d, 2H, ArH, *J* 8.51 Hz); 8.71–8.76 (m, 2H, pyrazine); 9.29 (d; 1H, pyrazine, *J* 1.38 Hz); 10.30 (s, 1H, N=CH) |
| **16** | 62 | 139–141 cyclohexane | $C_{11}H_{13}N_7S_2$ 307.38 | 3207 (NH); 1181, 1088 (C=S) | 3.95 (s, 3H, $NCH_3$); 4.17 (s, 2H, $NC\underline{H}_2CH$=); 5.20 (d, 2H, CH=C$\underline{H}_2$, *J* 16.65 Hz); 5.79 (brs, 1H, C$\underline{H}$=$CH_2$); 8.16 (s, 1H, NH); 8.66 (d, 2H, pyrazine, *J* 14.29); 9.24 (s, 1H, pyrazine); 10.17 (s, 1H, NH) |
| **17** | 63 | 154–156 water | $C_{10}H_{12}N_6OS$ 264.31 | 1687 (C=O); 1059 (C=S) | 1.93 (s, 3H, O=C$CH_3$); 3.29 (s, 3H, $NCH_3$); 3.93 (s, 3H, $NCH_3$); 8.58–8.73 (m, 2H, pyrazine); 9.24 (s, 1H, pyrazine) |
| **18** | 62 | 99–100 water | $C_9H_{11}N_5OS$ 237.28 | 3382 (OH); 1164 (C–O); 1074 (C= S) | 2.95 (brs, 1H, OH); 3.94 (s, 3H, $NCH_3$); 4.09 (t, 2H, $NCH_2$, *J* 5.49, J 5.09); 4.82 (t, 2H, $OCH_2$, *J* 5.05, J 5.49); 8.62 (q, 1H, pyrazine, $J_1$ 1.55 Hz, $J_2$ 1.06 Hz, $J_3$ 1.5 Hz); 8.73 (d, 1H, pyrazine, J 2.56), 9.32 (d, 1H, pyrazine, *J* 1.47) |
| **19** | 67 | 159–160 methanol | $C_{10}H_{14}N_6OS$ 266.32 | 3349 (OH); 3287 ($NH_2$); 1169 (C–O), 1076 (C=S) | 2.63 (brs, 4H, $2CH_2$); 4.91 (s, 3H, $NCH_3$); 4.5-4.8 (m, 1H, CH), 8.82 and 9.15 (2s, 3H, pyrazine) |
| **20** | 75 | 111–112 methanol | $C_{13}H_{18}N_6S$ 290.38 | 1081 (C=S) | 1.68 (s, 4H, $CH_2$); 2.57 (s, 4H, $NCH_2$); 2.88 (t, 2H, $NC\underline{H}_2CH_2$, $J_1$ 6.93 Hz, $J_2$ 7.33 Hz); 3.90 (s; 3H, $NCH_3$); 4.78 (t, 2H, $NCH_2CH_2$, $J_1$ 6.96 Hz, $J_2$ 7.32 Hz); 8.66 (s, 2H, pyrazine); 9.22 (s; 1H, pyrazine) |
| **21** | 80 | 107–109 methanol/water | $C_{14}H_{20}N_6S$ 310.46 | 1081 (C=S) | 1.30 (s, 6H, $CH_2$); 2.39 (s, 4H, $NCH_2$); 2.70 (t, 2H, $NC\underline{H}_2CH_2$, $J_1$ 6.60 Hz, $J_2$ 6.59 Hz); 3.90 (s; 3H, $NCH_3$); 4.79 (t, 2H, $NC\underline{H}_2CH_2$, $J_1$ 6.96 Hz, $J_2$ 7.32 Hz); 8.64 (m, 2H, pyrazine); 9.23 (d; 1H, pyrazine, *J* 1.39 Hz) |
| **22** | 73 | 110–112 methanol/water | $C_{12}H_{13}N_7S$ 287.33 | 1080 (C=S) | 2.40 (m, 2H, $CH_2C\underline{H}_2CH_2$); 3.90 (s; 3H, $NCH_3$); 4.17 (t, 2H, $NCH_2CH_2$, $J_1$ 6.59 Hz, $J_2$ 6.59 Hz); 4.60 (t, 2H, $NC\underline{H}_2CH_2$, $J_1$ 7.49 Hz, $J_2$ 7.89 Hz); 6.99, 7.11 and 7.73 (3s, 3H, imidazole); 8.50 (m, 1H, pyrazine); 8.64 (d, 1H, pyrazine, *J* 2.52 Hz); 9.26 (d; 1H, *J* 1.42 Hz) |

### Pyrazine-2-carboxylic Acid *N′*-Methyl-*N′*-(benzylamine-4-carbothioyl)-hydrazide (3)

Compound **1** (1.5 g, 10 mmol) and benzyl isothiocyanate (1.3 mL, 10 mmol) were refluxed in 10 mL of ethanol for 1 h. The resulting solid was filtered after cooling and recrystallized. Yield: 2.8 g.

### 4-Benzyl-2-methyl-5-pyrazin-2-yl-2,4-dihydro-[1,2,4]triazole-3-Thione (4)

A quantity of 0.3 g (1 mmol) of **3** was suspended in a solution of potassium carbonate (1 g) in water (10 mL). The mixture was heated under reflux for 30 min and then cooled, yielding crystals (0.24 g), which were filtered and recrystallized.

### Pyrazine-2-carboxylic Acid Benzylamide (5)

#### *A.*

Pyrazine-2-carboxylic acid methyl ester (1.38 g, 10 mmol) was refluxed with 2 mL (18 mmol) of benzylamine for 2 h. Then the mixture was cooled and treated with 5 mL of diethyl ether and 20 mL of cyclohexane. The precipitate (1.5 g) was filtered and recrystallized.

#### *B.*

The synthesis was carried out as described in Method A from 0.5 g (3 mmol) of **2** and 1.5 mL (14 mmol) of benzylamine. $^{1}$H NMR and IR spectra and m.p. determined for the product obtained by both methods were the same as measured for the compound synthesized by heating **2** with benzylamine.

### 1,3-Dicyclohexyl-thiourea (7)

Compound **2** (0.5 g, 2 mmol) was refluxed with 2 mL (17 mmol) of cyclohexylamine for 4.5 h. Then the mixture was cooled and treated with diethyl ether and then with petroleum ether until the product precipitated completely. Yield: 0.42 g. IR spectrum determined for the product was identical as for dicyclohexylthiourea obtained from cyclohexylamine and benzyl isothiocyanate.

### 3-Methyl-5-pyrazin-2-yl-3*H*-[1,3,4]oxadiazole-2-thione (8)

A quantity of 0.56 g (2.5 mmol) of **2**, 10 mL of ethanol, and 0.5 mL (3.6 mmol) of triethylamine was refluxed for 30 min, and then the

reaction mixture was concentrated. Next, 2 mL of ethanol was added, and 0.45 g of precipitate was filtered.

### Pyrazine-2-carboxylic Acid *N*′-Methyl-*N*′-(pyrrolidine-4-carbothioyl)-hydrazide (9)

Compound **2** (1 g, 4 mmol) was suspended in 3.5 mL of pyrrolidine. The mixture was refluxed for 4 h and then poured on 50 g of ice, the the water solution was extracted with chloroform and dried with magnesium sulfate. Chloroform was evaporated and the residue was extracted with hot cyclohexane. The solid (0.31 g) was filtered after cooling and recrystallized.

### Pyrazine-2-carboxylic Acid *N*′-Methyl-*N*′-(morpholine-4-carbothioyl)-hydrazide (10)

The synthesis was performed as described for **9** from compound **2** (1 g, 4 mmol) and 3 mL of morpholine. Yield: 0.37 g.

### Pyrazine-2-carboxylic Acid *N*′-Methyl-*N*′-[(4-phenyl)-piperazine-4-carbothioyl]-hydrazide (11)

A quantity of 1 g (4 mmol) of 2 and 3 mL of 1-phenyl-piperazine was heated at 150°C with stirring for 3 h. Then, the mixture was cooled, and the product was isolated by column chromatography with benzene/acetone system 50:1 as a liquid phase. Yield: 0.70 g.

### 4-Amino-2-methyl-5-pyrazin-2-yl-2,4-dihydro-[1,2,4]triazole-3-thione (12)

Compound **2** (1.13 g, 5 mmol) was added to the solution consisting of 3 mL of dioxane, 2 mL of ethanol, and 0.5 mL of 100% hydrazine hydrate. The mixture was heated under reflux for 2 h. Then, the solution was cooled, and the precipitate in the amount of 0.6 g was filtered and recrystallized.

### 2-Methyl-4-methylamino-5-pyrazin-2-yl-2,4-dihydro-[1,2,4]triazole-3-thione (13)

A quantity of **2** (4.52 g, 20 mmol), 15 mL of dioxane, and 1.6 mL (30 mmol) of methylhydrazine were refluxed for 2 h, and then the solvent was evaporated. Next, 10 mL of water was added to the residue. The solid (2.82 g) was filtered and recrystallized.

### 4-[(4-Fluoro-benzylidene)-amino]-2-methyl-5-pyrazin-2-yl-2,4-dihydro-[1,2,4]triazole-3-thione (14)

Equimolecular amounts (2.5 mmol) of compound **8** and p-fluorobenzaldehyde were heated under reflux in 10 ml of ethanol for 30 min. The yellow crystals (0.35 g) were filtered after cooling.

### 4-[(4-Chloro-benzylidene)-amino]-2-methyl-5-pyrazin-2-yl-2,4-dihydro-[1,2,4]triazole-3-thione (15)

The synthesis was performed as described for compound **14** from 2.5 mmol of **8** and p-chlorobenzaldehyde, yielding 0.6 g of the product.

### 1-Allyl-3-(1-methyl-3-pyrazin-2-yl-thixo-1,5-dihydro-[1,2,4]triazol-4-yl)-thiourea (16)

Compound **12** (0.5 g, 2.6 mmol) was dissolved in 5 mL of ethanol, and 0.53 mL (5.2 mmol) of allyl isothiocyanate was added. The mixture was heated under reflux for 4 h, and then the solvent was evaporated. The oily residue was extracted with hot cyclohexane, yielding the solid after cooling. Yield: 0.47 g.

### *N*-Methyl-*N*-(1-methyl-3-pyrazin-2-yl-5-thioxo-1,5-dihydro-[1,2,4]triazol-4-yl)-acetamide (17)

Compound **13** (0.54 g, 2.6 mmol) was dissolved in 2.5 mL of acetic anhydride. The solution was refluxed for 2 h and then poured into 10 mL of water. After 15 min of stirring, the solution was neutralized with solid potassium carbonate. The precipitate (0.41 g) was filtered and recrystallized.

### 4-(2-Hydroxy-ethyl)-2-methyl-5-pyrazin-2-yl-2,4-dihydro-[1,2,4]triazole-3-thione (18)

A quantity of 3.4 g (15 mmol) of **2** in 2 mL of ethanolamine was refluxed for 3 h. Then, 50 mL of water was added, and the solution was extracted with chloroform and dried with magnesium sulfate. The solvent was evaporated and 2.08 g of the residual was recrystallized. MS, m/e (%): 72.3 (20.27); 79.1 (33.82); 106 (40.51), 194 (100), $M^+$ 237 (7.28).

### 4-(3-Amino-2-hydroxy-propyl)-2-methyl-5-pyrazin-2-yl-2,4-dihydro-[1,2,4]triazole-3-thione (19)

Compound **2** (1.13 g, 5 mmol) and 1,3-diamino-2-propanol (0.6 g, 6.5 mmol) were heated under reflux in combination of 10 mL of dioxane

and 3 mL of ethanol for 5 h. The mixture was cooled, and the solution was separated from the lower oily layer and treated with 80 mL of petroleum ether. The precipitate (1.2 g) was filtered and recrystallized.

### 2-Methyl-5-pyrazin-2-yl-4-(2-pyrrolidin-1-yl-ethyl)-2,4-dihydro-[1,2,4]triazole-3-thione (20)

Quantities of 0.75 g (3 mmol) of **2** and 1.5 mL of 1-(2-aminoethyl)pyrrolidine were heated at 120°C with stirring for 1.5 h. Then, the reaction mixture was cooled and diluted with 25 mL of water. The precipitate (0.65 g) was filtered and recrystallized.

### 2-Methyl-5-pyrazin-2-yl-4-(2-pyridin-1-yl-ethyl)-2,4-dihydro-[1,2,4]triazole-3-thione (21)

The synthesis was carried out as described for compound **20** from 1 g (4 mmol) of 2 and 2 mL of 2-piperidinoethylamine. Yield: 0.98 g.

### 4-(2-Imidazol-1-yl-ethyl)-2-methyl-5-pyrazin-2-yl-2,4-dihydro-[1,2,4]triazole-3-thione (22)

A quantity of 0.75 g (3 mmol) of **2** in 1.4 mL of *N*-(3-aminopropyl)imidazole was heated at 120°C with stirring for 1.5 h. Then, the reaction mixture was cooled and diluted with 25 mL of water. The solution was extracted with chloroform and dried with magnesium sulfate. The solvent was evaporated, and the residue was treated with diethyl ether, yielding 0.66 g of the solid.

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