ISSN 1070-3632, Russian Journal of General Chemistry, 2020, Vol. 90, No. 2, pp. 208–216. © Pleiades Publishing, Ltd., 2020.
Russian Text © The Author(s), 2020, published in Zhurnal Obshchei Khimii, 2020, Vol. 90, No. 2, pp. 225–235.

Synthesis and Plant Growth Stimulating Action of 2-Amino-6-methylpyrimidine-4(3*H*)-thione Derivatives

E. N. Hambardzumyan[a], A. S. Vorskanyan[a], L. V. Shahbazyan[a], and A. P. Yengoyan[a,b,*]

[a] *Research Center for Pesticide Synthesis and Plant Protection, National Agrarian University of Armenia, Yerevan, 0009 Armenia*
[b] *Russian-Armenian University, Yerevan, 0051 Armenia*
**e-mail: ayengoyan@mail.ru*

Received July 22, 2019; revised July 27, 2019; accepted July 29, 2019

Abstract—A series of new pyrimidine derivatives, including those containing an azole or azine heterocycle linked through a sulfur atom or a thiomethylene group, was synthesized based on 2-amino-6-methylpyrimidine-4(3*H*)-thione. The synthesized compounds exhibited a pronounced stimulating effect on plants growth in the range of 43–96% compared to heteroauxin.

Keywords: 2-amino-6-methylpyrimidine-4(3*H*)-thione, heterocyclization, bi(tri)heterocyclic systems, azolyl(azinyl)-thiopyrimidines, plant growth stimulating activity

DOI: 10.1134/S1070363220020073

Pyrimidine derivatives have a wide spectrum of biological activity. The pyrimidine core is a part of the natural compounds such as nucleic acids, vitamins, strong poisons (tetrodotoxin), coenzymes, as well as a number of synthetic drugs (barbiturates, sulfamides, antibiotics, antitumor agents) [1, 2]. In recent years, new pyrimidine derivatives with antitumor [3, 4], anti-inflammatory [5, 6], antimicrobial [7–9], antifungal [10–12], antiviral [13], anticonvulsant [14], antioxidant [15, 16] and anti-HIV [17, 18] activity have been synthesized. Some compounds of this series have been proposed for the treatment of cardiovascular diseases [19, 20], tuberculosis [21, 22], and malaria [23, 24]. Potential corrosion inhibitors of steel in an acidic medium were also found among compounds of this series [25].

In agriculture, the most widely used herbicides are a number of pyrimidines, which are divided into different groups according to their chemical structure [26]. At the same time, data on studies of compounds that include the pyrimidine ring and azoles or azines in the molecule are scarce, although a large number of chemical plant protectors have been synthesized [26]. Such combination of pharmacophore heterocycles can lead to the appearance of two types of pesticidal activity at the same time.

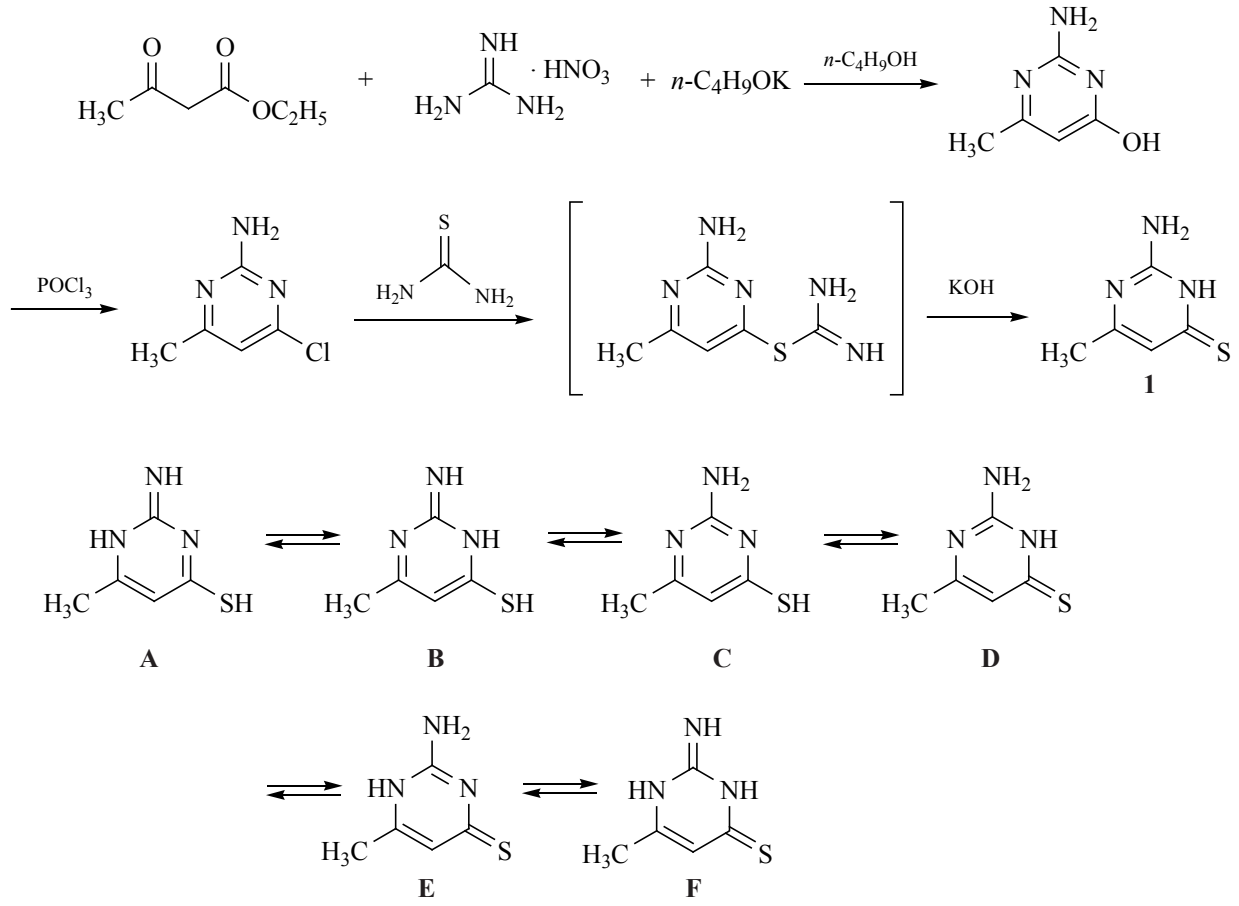
In this regard, the aim of this study was to develop available and effective methods for the synthesis of new pyrimidine derivatives, including compounds with a combination of the initial pyrimidine ring with azines or azoles, and to study their biological properties in terms of searching for new chemical protective agents or plant growth regulators.

Given the high reactivity and physiological activity of heterocyclic compounds containing amino, mercapto and alkylthio groups, we performed synthesis and functionalization of 2-amino-6-methylpyrimidine-4(3*H*)-thione **1**. The reaction of ethyl acetate and acetic acid with guanidine nitrate and potassium *n*-butanolate in *n*-butanol produces 2-amino-6-methylpyrimidin-4-ol. Chlorination of the latter with phosphorus oxychloride gave rise to the corresponding chloro derivative (Scheme 1). Further reaction with thiourea in acetone and subsequent treatment with potassium hydroxide through the intermediate thiouronium salt resulted in the formation of the target 2-amino-6-methylpyrimidine-4(3*H*)-thione **1**.

Compound **1** is easily alkylated, however, since this compound can exist in six possible tautomeric forms (**A**–**F**), depending on the position of the labile hydrogen atoms, the alkylation can occur both at exocyclic sulfur or nitrogen atoms and at the pyrimidine nitrogen atoms.

In the ^{13}C NMR spectrum of compound **1** at 181.3 ppm, a signal corresponding to the carbon atom of the C=S double bond (structures **D**–**F**) is observed. In the

Scheme 1.



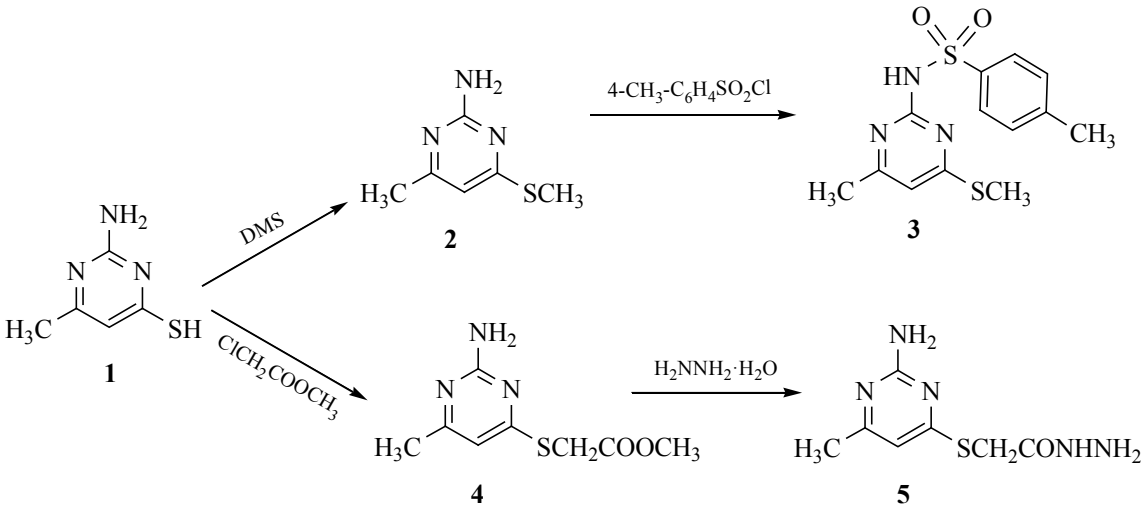
case of 4-methylthio derivative **2** obtained by methylation of **1** with dimethyl sulfate this absorption disappears (Scheme 2). So, in the spectra, signals of the S-methyl group are observed at 2.43 and 11.3 ppm, respectively. In this case, a two-proton broadened signal at 5.97 ppm, corresponding to protons of the NH_2 group, appears in the ^{1}H NMR spectrum. This data indicate that methyl derivative **2** has the structure of tautomer **C**. Subsequent reaction with tosyl chloride yielded an *N*-substitution product **3** (Scheme 2).

Alkylation of compound **1** with monochloracetic acid methyl ester resulted in an *S*-substituted product, namely methyl 2-[(2-amino-6-methylpyrimidin-4-yl)thio]acetate **4**. Hydrazinolysis of the obtained acetate was carried out using an aqueous solution of hydrazine hydrate in isopropyl alcohol (Scheme 3). The reaction of hydrazide **5** with acetylacetone furnished an acyclic condensation product **6** instead of the expected heterocyclization product.

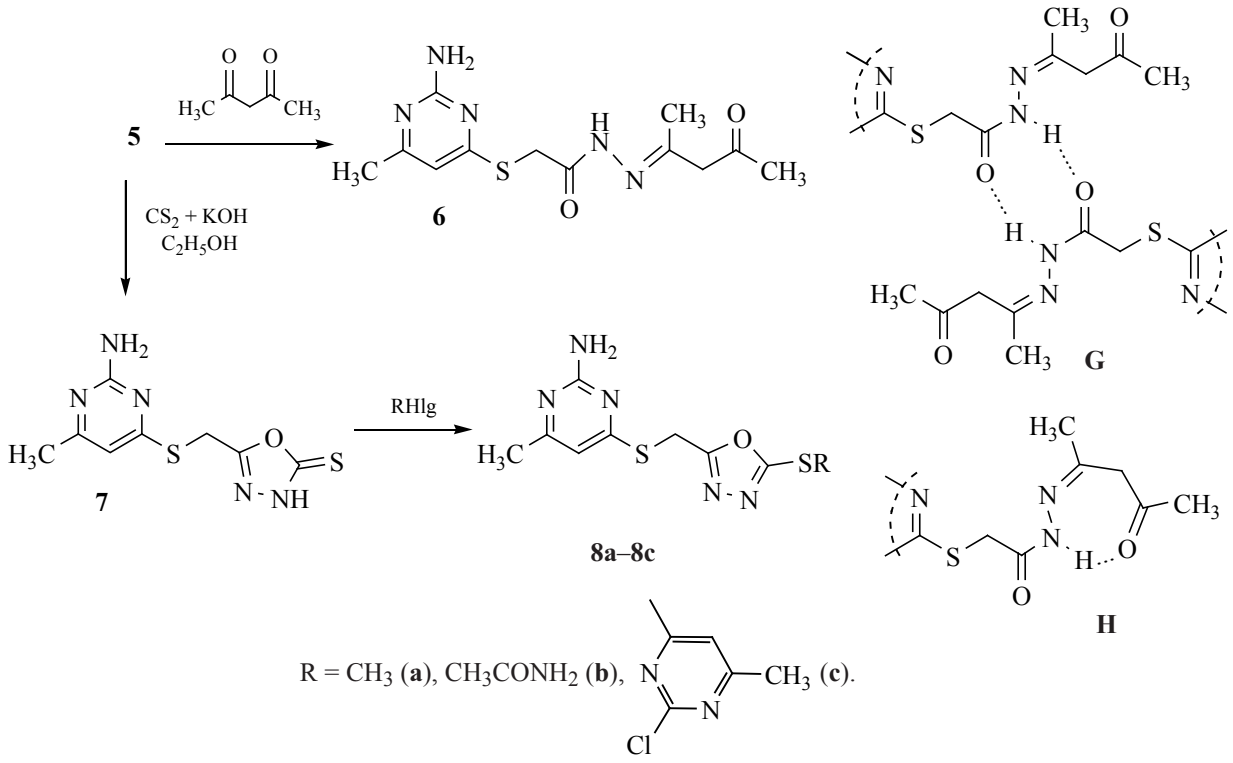
The molecule of compound **6** can exist in the form of *E*- and *Z*-isomers. However, in the ^{1}H and ^{13}C NMR spectra there is only one set of signals corresponding to the SCH_2, $N{=}CCH_3$, $N{=}CCH_2$ and $COCH_3$ groups, and only the proton of the NH group appears as two broadened signals at 6.14 and 6.29 ppm. This spectral pattern is apparently explained by the fact that the molecule has an exclusively *Z*-configuration, which can be stabilized due to the formation of dimers (**G**) or intramolecular hydrogen bond (**H**).

The reaction of hydrazide **5** with CS_2 in ethanol in the presence of an equimolar amount of KOH resulted in the formation of 2-[(2-amino-6-methylpyrimidin-4-yl)-thio]methyl-1,3,4-oxadiazole-2(3*H*)thione **7** (Scheme 3). Alkylation of compound **7** occurs at the sulfur atom of the oxadiazole ring to form *S*-substituted derivatives **8a**–**8c**. Structure of the obtained compounds was confirmed by NMR data. Thus, in the ^{13}C NMR spectrum of compound **7**, a signal corresponding to the carbon atom of the C=S double bond is observed at 177.8 ppm, which disappears in the ^{13}C NMR spectra of compounds **8a**–**8c**. At the same time, in the ^{1}H and ^{13}C NMR spectra, signals corresponding to *S*-alkyl groups are observed. Therefore, although the 1,3,4-oxadiazole ring is in thioxo form in tautomer

Scheme 2.



Scheme 3.

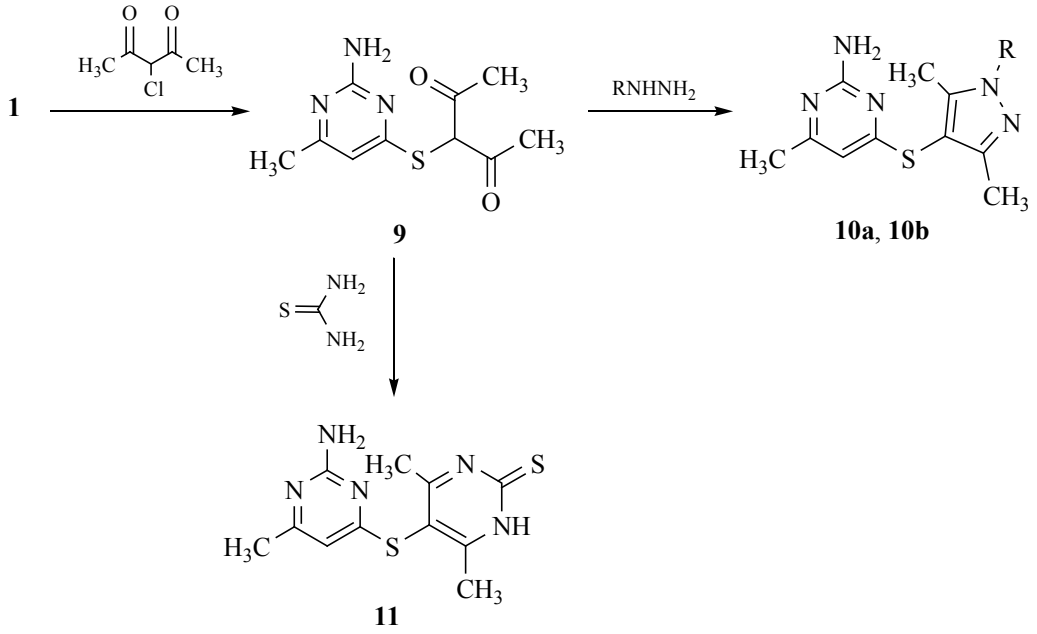


7, the alkylation proceeds at the exocyclic sulfur atom to form *S*-substituted products.

The reaction of compound **1** with 3-chloropentane-2,4-dione also proceeded at the sulfur atom, resulting in the formation of 3-[(2-amino-6-methylpyrimidin-4-yl)thio]-pentane-2,4-dione **9** (Scheme 4). According to ^{1}H NMR data, this compound exists mainly in enol form (17.30 ppm, 0.8H, OH) and undergo heterocyclization to form heterocyclic systems with a combination of a pyrazole ring with pyrimidine **10** or two pyrimidine rings **11** when reacted with hydrazine hydrate, *para*-toluenesulfohydrazide and thiourea (Scheme 4).

In the ^{13}C NMR spectrum of compound **11**, signal of the carbon atom of the double C=S bond is observed at 196.9 ppm, which indicates the thionic structure of the resulting pyrimidine ring.

Scheme 4.



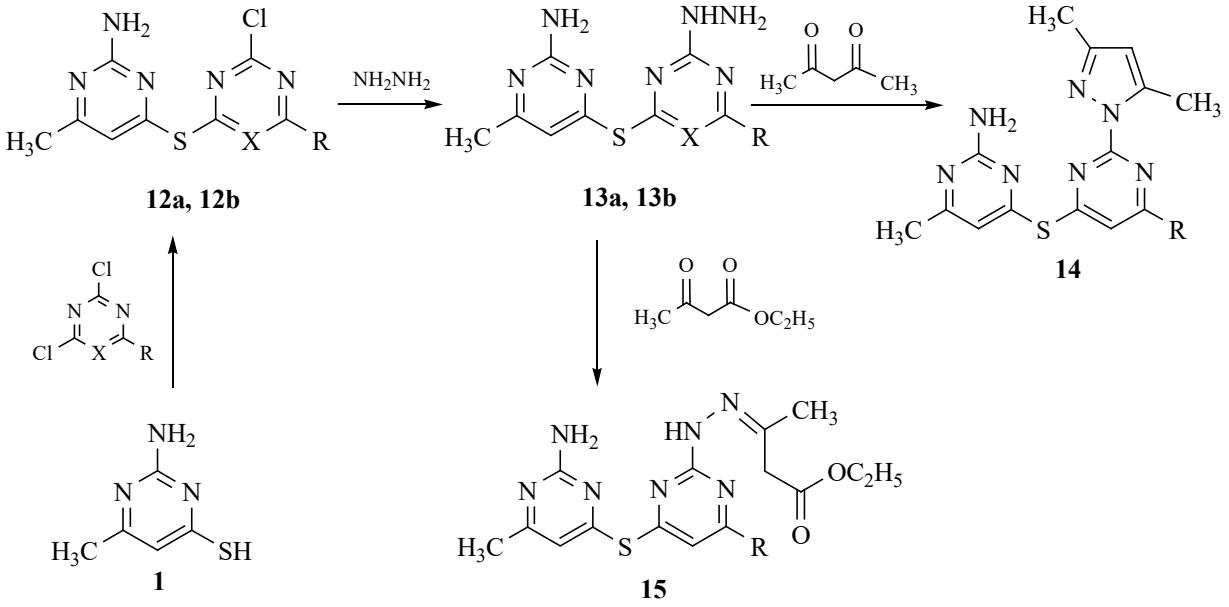
In order to synthesize compounds with two azine rings in the molecule, compound **1** was reacted with 2,4-dichloro-6-methylpyrimidine and 2,4-dichloro-6-dimethylamino-1,3,5-triazine (Scheme 5). As a result, the corresponding pyrimidinylthio- (**12a**) or triazinylthiopyrimidines (**12b**) were obtained. We previously showed that in the first case, the reaction is carried out due at the chlorine atom in the position 4 of the pyrimidine ring [27]. The reaction of the synthesized pyrimidines **12a** and **12c** with hydrazine hydrate yielded the corresponding hydrazides **13a**, **13c** (Scheme 5).

Some transformations of the obtained hydrazinopyrimidinylpyrimidine **13a** were performed. Thus, the reaction with acetylacetate in an acetic acid medium in the presence of catalytic amounts of DMF provided a cyclic product, pyrazolylpyrimidinylpyrimidine **14**, whereas the reaction with acetoacetic acid ethyl ester led to the formation of an acyclic condensation product **15** (Scheme 5).

The synthesized compounds were subjected to preliminary laboratory vegetation tests to determine their herbicidal, fungicidal and growth-regulating properties. Almost all of the studied compounds showed a stimulating effect on plant growth. The experiments were carried out on the seeds and seedlings of common beans (*Phaseolus vulgaris* L.). The effect of aqueous suspensions of compounds **1–15** at concentrations of 25 and 50 mg/L on seed viability, germination and seedling growth was studied. These data were compared with a similar effect of heteroauxin solutions of the same concentrations. The activity of the compounds ranged from 43–96% compared to heteroauxin (Table 1). Biological screening data reflect an interesting fact, when in some cases the stimulating effect of solutions with a lower concentration turned out to be higher than more concentrated solutions. Substances exhibiting in the experiment activity above 80% (**5**, **6**, **8b**, **8c**, **10a**, **12a**, **13b**, **14**, **15**) were selected for more in-depth study and further field testing using solutions of synthesized compounds at concentrations <25 mg/L.

In conclusion, we developed effective methods for the synthesis of 2-*N*- and 4-*S*-substituted derivatives of 2-amino-6-methylpyrimidine-4(3H)-thione, including compounds with a combination of pyrimidine ring with various pharmacophore five-membered and six-membered heterocycles. During preliminary biological screening, the synthesized compounds showed a pronounced stimulating effect on plant growth. The results of the study indicate the promise of a further search for new plant growth stimulants in the series of derivatives studied.

Scheme 5.



X = CH, R = CH_3 (**a**); X = N, R = $(CH_3)_2N$ (**b**).

EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded at 30°C on a Varian Mercury-300 NMR spectrometer (300 and 75 MHz, respectively) in DMSO-d_6–CCl_4 (3 : 1) solutions using a standard pulse sequence; TMS was used as the internal standard. The reaction progress and the purity of the obtained compounds were monitored by TLC on Silufol UV-254 plates; an acetone–hexane mixture (2 : 1) was used as an eluent. Elemental analysis was performed on an Eurovector EA3000 CHNS analyzer. Melting points were determined by capillary method without correction.

2-Amino-6-methylpyrimidine-4(3*H*)-thione (1). To a solution of 0.42 g (0.0055 mol) of thiourea in 30 mL of acetone was added 0.1 mL of conc. HCl, then 7.2 g (0.0055 mol) of 2-amino-4-chloro-6-methylpyrimidine. The mixture was boiled for 4–5 h, and then cooled. The precipitate was filtered off and washed with diethyl ether. The obtained thiuronium salt (12 g) was dissolved in 10 mL of water and neutralized with 2.4 g of Na_2CO_3 dissolved in 8–10 mL of water. The resulting precipitate was filtered off, washed with water and dried. Yield 0.9 g (98%), mp > 280°C. ^1H NMR spectrum, δ, ppm: 2.07 s (3H, CH_3-pyrimidine), 6.29 s (1H, CH-pyrimidine), 6.60 br. s (2H, NH_2), 11.80 br. s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 23.1, 114.0, 154.5, 163.2, 181.3. Found, %: C 42.44; H 4.89; N 29.55. $C_5H_7N_3S$. Calculated, %: C 42.53; H 5.00; N 29.76.

2-Amino-4-methylthio-6-methylpyrimidine (2). To a solution of 0.35 g (0.005 mol) of KOH in 2 mL of water was added 0.7 g (0.005 mol) of compound **1**. The mixture was stirred for 5–10 min, and then 0.5 mL (0.005 mol) of dimethyl sulfate was added under cooling with ice water. The resulting mixture was stirred and left overnight. The precipitate was filtered off, washed with a diluted KOH solution, then with water. Yield 0.7 g (93.5%), mp 155–156°C. ^1H NMR spectrum, δ, ppm: 2.17 s (3H, CH_3-pyrimidine), 2.43 s (3H, SCH_3), 5.97 br. s (2H, NH_2), 6.25 s (1H, CH-pyrimidine). ^{13}C NMR spectrum, δ_C, ppm: 11.3, 22.9, 105.7, 162.0, 164.5, 169.1. Found, %: C 46.54; H 5.78; N 27.30. $C_6H_9N_3S$. Calculated, %: C 46.43; H 5.84; N 27.07.

2-(Tosylamino)-4-(methylthio)-6-methylpyrimidine (3). A mixture of 0.8 g (0.005 mol) of compound **2** and 0.95 g (0.005 mol) of *para*-toluenesulfonyl chloride in 2 mL of pyrimidine was stirred, then kept at room temperature for 24 h. After treatment with diethyl ether and water, the precipitate was filtered off and dried. Yield 0.55 g (61.3%), mp 175–177°C. ^1H NMR spectrum, δ, ppm: 2.36 s (3H, CH_3-pyrimidine), 2.37 s (3H, CH_3), 2.58 s (3H, SCH_3), 6.66 s (1H, CH-pyrimidine), 7.12–7.63 m (4H, C_6H_4), 12.5–13.5 br. s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 12.3, 17.8, 20.7, 106.2, 125.3, 127.9, 138.5, 142.9, 153.7, 154.3, 179.2. Found, %: C 50.59; H 4.95; N 13.72. $C_{13}H_{15}N_3O_2S_2$. Calculated, %: C 50.47; H 4.89; N 13.58.

Table 1. Plant growth stimulating activity of compounds **2–15**

Compound	*c*, mg/L	Activity relative to heteroauxin, %	Compound	*c*, mg/L	Activity relative to heteroauxin, %
Heteroauxin	25	100.0	**9**	25	63.7
	50	100.0		50	–
2	25	54.3	**10a**	25	82.2
	50	–		50	74.0
3	25	77.4	**10b**	25	58.8
	50	68.9		50	63.7
4	25	76.3	**12a**	25	83.0
	50	61.3		50	–
5	25	82.6	**12b**	25	61.4
	50	67.3		50	64.4
6	25	67.4	**13a**	25	63.1
	50	95.9		50	43.3
7	25	65.1	**13b**	25	70.8
	50	43.3		50	83.7
8a	25	79.1	**13**	25	84.7
	50	65.5		50	56.2
8b	25	95.0	**15**	25	90.5
	50	85.1		50	–
8c	25	86.3			
	50	83.4			

Methyl 2-[(2-amino-6-methylpyrimidin-4-yl)thio]-acetate (4). To a solution of 0.2 g (0.005 mol) of NaOH in 3–4 mL of water was added 0.7 g (0.005 mol) of compound **1**. The mixture was stirred until the reagents were completely dissolved, then 0.9 mL (0.005 mol) of $NaI \cdot 2H_2O$ and 0.55 g (0.005 mol) of methyl chloroacetate were added. The resulting mixture was stirred at room temperature, then at 35–40°C for 3 h and left overnight. The next day, 4–5 mL of cold water was added, the precipitate was filtered off and dried. Yield 0.9 g (85%), mp 108–110°C. ^{1}H NMR spectrum, δ, ppm: 2.19 s (3H, CH_3-pyrimidine), 3.70 s (3H, OCH_3), 3.91 s (2H, SCH_2), 6.02 br. s (2H, NH_2), 6.30 s (1H, CH-pyrimidine). ^{13}C NMR spectrum, δ_C, ppm: 22.9, 29.9, 51.7, 105.9, 162.0, 165.2, 166.5, 168.5. Found, %: C 44.91; H 5.12; N 19.51. $C_8H_{11}N_3O_2S$. Calculated, %: C 45.06; H 5.20; N 19.70.

2-[(2-Amino-6-methylpyrimidin-4-yl)thio]acetohydrazide (5). To a mixture of 1.07 g (0.005 mol) of compound **4** in 5–6 mL of propan-2-ol, 0.5 mL (0.007 mol) of 70% hydrazine hydrate was added under cooling with ice water. The resulting mixture was stirred for 0.5 h at room temperature and at 35°C for 1–2 h, then 5–8 mL of cold water was added. The precipitate was filtered off and dried. Yield 0.85 g (85%), mp 200–202°C. ^{1}H NMR spectrum, δ, ppm: 2.17 s (3H, CH_3-pyrimidine), 3.66 s (2H, SCH_2), 4.12 br. s (2H, NH–**NH_2**), 6.31 s (1H, CH-pyrimidine), 6.35 br. s (2H, NH_2), 8.99 br. s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 23.0, 30.0, 105.6, 162.2, 165.2, 167.1, 167.3. Found, %: C 39.33; H 5.16; N 32.67. $C_7H_{11}N_5OS$. Calculated, %: C 39.42; H 5.20; N 32.84.

(*Z*)-2-[(2-Amino-6-methylpyrimidin-4-yl)thio]-*N*'-(4-oxopentan-2-ylidene)acetohydrazide (6). A mixture of 0.8 g (0.0038 mol) of compound 5, 0.65 mL (0.007 mol) of acetylacetone in 4–5 mL of dioxane was stirred at 60–70°C for 3–4 h. After removal of the solvent, the residue was treated with water and filtered, washed with a diluted HCl solution, then with water. Yield 0.6 g (60%), mp 275–276°C. ^{1}H NMR spectrum, δ, ppm:

1.79 s (3H, N=CCH$_3$), 2.02 s (3H, COCH$_3$), 2.17 s (3H, CH$_3$-pyrimidine), 2.82 d and 2.85 d (2H, N=CCH$_2$, J = 18.9 Hz), 4.09 d and 4.24 d (2H, SCH$_2$, J = 15.4 Hz), 6.01 br. s (2H, NH$_2$), 6.14 s and 6.29 s (1H, NH), 6.32 s (1H, CH-pyrimidine). ^{13}C NMR spectrum, δ_C, ppm: 15.7, 23.0, 25.9, 32.1, 51.9, 90.4, 105.9, 153.5, 162.0, 164.9, 165.0, 168.2. Found, %: C 48.92; H 5.88; N 23.94. $C_{12}H_{17}N_5O_2S$. Calculated, %: C 48.80; H 5.80; N 23.71.

2-Amino-4-[(2-thioxo-1,3,4-oxadiazol-5-yl)methyl]-thio-6-methylpyrimidine (7). To a 84% solution of 0.2 g (0.005 mol) KOH in 3–4 mL of absolute alcohol was added 0.53 g (0.0025 mol) of compound **5**, and then 0.4 g (0.005 mol) of CS_2. The resulting mixture was boiled for 5–6 h, then the solvent was removed and 5–6 mL of water was added. The resulting solution was acidified with AcOH. The precipitate was filtered off, washed with water and dried. Yield 0.5 g (83%), mp 213–215°C. ^{1}H NMR spectrum, δ, ppm: 2.20 s (3H, CH$_3$-pyrimidine), 3.20–3.80 br. s (1H, NH + H_2O), 4.48 s (2H, SCH$_2$), 6.20 br. s (2H, NH$_2$), 6.32 s (1H, CH-pyrimidine). ^{13}C NMR spectrum, δ_C, ppm: 21.1, 23.0, 106.0, 160.2, 162.0, 165.0, 165.7, 177.8. Found, %: C 37.64; H 3.55; N 27.43. $C_8H_9N_5OS_2$. Calculated, %: C 37.64; H 3.55; N 27.43.

General procedure for the synthesis of compounds 8a, 8b. To a solution of 0.14 g (0.002 mol) of KOH in 3 mL of water was added 0.5 g (0.002 mol) of compound **7**. The mixture was stirred for 10–15 min, then 0.002 mol of dimethyl sulfate or chloroacetamide was added with cooling. The resulting mixture was stirred for 0.5–1 h and left overnight. The precipitate was filtered off and dried.

2-Amino-4-({[5-(methylthio)-1,3,4-oxadiazol-2-yl]-methyl}thio)-6-methylpyrimidine (8a). Yield 0.4 g (80%), mp 119–20°C. ^{1}H NMR spectrum, δ, ppm: 2.20 s (3H, CH$_3$-pyrimidine), 2.69 s (3H, SCH$_3$), 4.60 s (2H, SCH$_2$), 6.17 br. s (2H, NH$_2$), 6.33 s (1H, CH-pyrimidine). ^{13}C NMR spectrum, δ_C, ppm: 13.9, 20.9, 23.0, 105.9, 162.0, 164.2, 165.2, 165.7. Found, %: C 40.02; H 4.07; N 26.13. $C_9H_{11}N_5OS_2$. Calculated, %: C 40.13; H 4.12; N 26.00.

2-[(5-{[(2-Amino-6-methylpyrimidin-4-yl)thio]-methyl}-1,3,4-oxadiazol-2-yl)thio]acetamide (8b). Yield 0.5 g (83%), mp 179–181°C. ^{1}H NMR spectrum, δ, ppm: 2.20 s (3H, CH$_3$-pyrimidine), 3.95 s (2H, SCH$_2$CO), 4.59 s (2H, SCH$_2$), 6.22 br. s (2H, NH$_2$), 6.34 s (1H, CH-pyrimidine), 7.09 s and 7.56 s (2H, NH$_2$-amide). ^{13}C NMR spectrum, δ_C, ppm: 20.9, 23.0, 105.9, 162.1, 163.6, 164.4, 165.2, 165.7, 167.3. Found, %: C 38.31; H 3.78; N 26.75. $C_{10}H_{12}N_6O_2S_2$. Calculated, %: C 38.45; H 3.87; N 26.90.

2-Amino-4-{[({5-[(2-chloro-6-methylpyrimidin-4-yl)thio]methyl}-1,3,4-oxadiazol-2-yl)methyl]thio}-6-methylpyrimidine (8c). To a solution of 0.6 g (0.002 mol) of the potassium salt of compound **7** obtained by evaporation of a solution of 0.51 g (0.002 mol) of compound **1** and 0.14 g (0.002 mol) of KOH in 5 mL of water, 0.37 g (0.002 mol) of 4-dichloro-6-methylpyrimidine **2** was added in 3 mL of DMF. The resulting mixture was heated for 5–6 h at 40–50°C. DMF was removed at low pressure. The residue was treated with water, filtered, washed with a diluted NaOH solution, then with water and dried. Yield 0.45 g (60%), mp 148–50°C. ^{1}H NMR spectrum, δ, ppm: 2.20 s (3H, CH$_3$-pyrimidine), 2.45 s (3H, CH$_3$-pyrimidine), 4.70 s (2H, SCH$_2$), 6.20 br. s (2H, NH$_2$), 6.35 s (1H, CH-pyrimidine), 7.37 s (1H, CH-pyrimidine). Found, %: C 40.74; H 3.02; N 25.55. $C_{13}H_{12}ClN_7OS_2$. Calculated, %: C 40.89; H 3.17; N 25.68.

3-[(2-Amino-6-methylpyrimidin-4-yl)thio]pentane-2,4-dione (9). To a solution of 0.7 g (0.01 mol) of 84% KOH in 4 mL of water was added 1.4 g (0.01 mol) of compound **1**. The resulting mixture was stirred for 10–15 min, and then 1.47 g (0.011 mol) of 3-chloropentane-2,4-dione was added in portions with cooling. The mixture was stirred at room temperature for 1–2 h, and then left overnight. Next, 2–3 mL of water was added to the mixture, the precipitate was filtered off and dried. Yield 1.8 g (78%), mp 180–181°C. ^{1}H NMR spectrum, δ, ppm: 2.19 s (3H, CH$_3$-pyrimidine), 2.29 s (6H, CH$_3$), 6.12 br. s (2H, NH$_2$), 6.13 s (1H, CH-pyrimidine), 17.30 s (0.8H, OH-enol). ^{13}C NMR spectrum, δ_C, ppm: 23.2, 23.7, 98.7, 103.7, 162.4, 166.1, 168.9, 196.9. Found, %: C 50.27; H 5.60; N 17.71. $C_{10}H_{13}N_3O_2S$. Calculated, %: C 50.19; H 5.48; N 17.56.

General procedure for the synthesis of compounds 10a, 10b. A mixture of 0.48 g (0.002 mol) of compound **9**, 0.2 mL of a 70% aqueous solution of hydrazine hydrate (or 0.4 g, 0.002 mol of *para*-toluenesulfohydrazide) and 3 mL of acetic acid was stirred at room temperature for 2 days. After removing the solvent, the residue was treated with water. The precipitate was filtered off and dried.

2-Amino-4-[(3,5-dimethyl-1*H*-pyrazol-4-yl)thio]-6-methylpyrimidine (10a). Yield 0.45 g (98%), mp 123–125°C. ^{1}H NMR spectrum, δ, ppm: 2.09 s and 2.16 s (6H, CH$_3$-pyrazole), 2.16 s (3H, CH$_3$-pyrimidine), 5.67 s (1H, CH-pyrimidine), 6.02 br. s (2H, NH$_2$), 11.76 br. s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 10.3, 20.4, 23.2, 99.0, 103.0, 146.9, 162.0, 165.6, 171.1, 171.6. Found, %: C 51.04; H 5.57; N 29.76. $C_{10}H_{13}N_5S$. Calculated, %: C 51.04; H 5.57; N 29.76.

2-Amino-4-[(3,5-dimethyl-1-tosyl-1*H*-pyrazol-4-yl)thio]-6-methylpyrimidine (10b). Yield 0.6 g (77%), mp 129–130°C. ^{1}H NMR spectrum, δ, ppm: 2.08 s and 2.45 s (6H, CH_3-pyrazole), 2.20 s (3H, CH_3-pyrimidine), 2.55 s (3H, $CH_3C_6H_4$), 5.77 s (1H, CH-pyrimidine), 6.20 br. s (2H, NH_2), 7.40–7.89 m (4H, C_6H_4). Found, %: C 52.33; H 4.85; N 17.77. $C_{17}H_{19}N_5O_2S_2$. Calculated, %: C 52.42; H 4.92; N 17.98.

5-[(2-Amino-6-methylpyrimidin-4-yl)thio]-4,6-dimethylpyrimidine-2(1*H*)-thione (11). To a solution of 0.3 g (0.004 mol) of thiourea in 4–5 mL of absolute ethanol was added 0.48 g (0.002 mol) of compound **9**, and then 0.7 mL of conc. HCl. The resulting mixture was boiled for 2 h, then left overnight. After removal of the solvent, the residue was dissolved in water, neutralized with $NaHCO_3$ and filtered off. Yield 0.44 g (60%), mp 175–176°C. ^{1}H NMR spectrum, δ, ppm: 2.19 s (3H, CH_3-pyrimidine), 2.27 s (6H, CH_3-pyrimidine), 6.08 br. s (2H, NH_2), 6.13 s (1H, CH-pyrimidine), 17.28 br. s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 23.2, 23.7, 98.7, 103.6, 162.4, 166.1, 168.9, 196.9. Found, %: C 47.29; H 4.69; N 25.07. $C_{11}H_{13}N_5S_2$. Calculated, %: C 47.29; H 4.69; N 25.07.

General procedure for the synthesis of compounds 12a, 12b. To a mixture of 1.8 g (0.01 mol) of the potassium salt of compound **1** in 5 mL of DMF, 1.6 g (0.01 mol) of 2,4-dichloro-6-methylpyrimidine (or 1.9 g 0.01 mol of 2,4-dichloro-6-dimethylamino-1,3,5-triazine) was added with cooling. The mixture was stirred at room temperature for 0.5–1 h, and then heated for 5–6 h at 40–50°C. After cooling, the residue was treated with cold water; the precipitate was filtered off and dried.

2-Amino-4-[(2-chloro-6-methylpyrimidin-4-yl)-thio]-6-methylpyrimidine (12a). Yield 1.4 g (67%), mp 158–160°C. ^{1}H NMR spectrum, δ, ppm: 2.24 s (3H, CH_3-pyrimidine), 2.49 s (3H, CH_3-pyrimidine), 6.50 br. s (2H, NH_2), 6.59 s (1H, CH-pyrimidine), 7.77 s (1H, CH-pyrimidine). Found, %: C 44.95; H 3.81; N 26.38. Calculated, %: C 44.86; H 3.76; N 26.16.

2-Amino-4-[(2-*N,N*-dimethylamino-6-chloro-1,3,5-triazin-4-yl)thio]-6-methylpyrimidine (12b). Yield 2.5 g (84%), mp 198–200°C. ^{1}H NMR spectrum, δ, ppm: 2.28 s (3H, CH_3-pyrimidine), 3.13 s and 3.19 s [6H, $N(CH_3)_2$], 6.33 br. s (2H, NH_2), 7.05 s (1H, CH-pyrimidine). ^{13}C NMR spectrum, δ_C, ppm: 23.3, 35.9, 36.0, 111.7, 162.1, 162.5, 162.8, 166.9, 167.7, 178.7. Found, %: C 40.30; H 4.10; N 32.72. $C_{10}H_{12}ClN_7S$. Calculated, %: C 40.34; H 4.06; N 32.93.

General procedure for the synthesis of compounds 13a, 13b. To a solution of 1.35 g (0.005 mol) of compound **12** in 5 mL of dioxane was added 1 mL (0.014 mol) of a 70% aqueous solution of hydrazine hydrate. The mixture was kept at room temperature for 24 h. After removal of dioxane, 8–10 mL of water was added to the residue. The precipitate was filtered off and dried.

2-Amino-4-[(2-hydrazinyl-6-methylpyrimidin-4-yl)thio]-6-methylpyrimidine (13a). Yield 1.0 g (73%), mp 185–187°C. ^{1}H NMR spectrum, δ, ppm: 2.25 s (3H, CH_3-pyrimidine), 2.28 s (3H, CH_3-pyrimidine), 4.01 br. s (2H, NH–**NH_2**), 6.30 br. s (2H, NH_2), 6.64 s (1H, CH-pyrimidine), 6.68 s (1H, CH-pyrimidine), 7.90 br. s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 23.3, 23.4, 109.3, 109,5, 162.5, 163.3, 164.6, 165.3, 166.6, 166.9. Found, %: C 45.49; H 4.87; N 37.05. $C_{10}H_{13}N_7S$. Calculated, %: C 45.61; H 4.98; N 37.24.

2-Amino-4-[(2-hydrazinyl-6-*N,N*-dimethylamino-1,3,5-triazin-4-yl)thio]-6-methylpyrimidine (13b). Yield 1.0 g (69%), mp 204–206°C. ^{1}H NMR spectrum, δ, ppm: 2.25 s (3H, CH_3-pyrimidine), 3.13 s and 3.18 s [6H, $N(CH_3)_2$], 2.90–3.20 br. s [$NHNH_2$ + $N(CH_3)_2$ + H_2O], 6.20 br. s (2H, NH_2), 7.32 s (1H, CH-pyrimidine), 8.38 br. s (1H, NH). Found, %: C 40.80; H 5.04; N 42.75. $C_{10}H_{15}N_9S$. Calculated, %: C 40.94; H 5.15; N 42.97.

2-Amino-4-{[2-(3,5-dimethyl-1*H*-pyrazol-1-yl)-6-methylpyrimidin-4-yl]thio}-6-methylpyrimidine (14). A mixture of 0.53 g (0.0025 mol) of compound **13a**, 1 mL of acetylacetone and 1–2 drops of DMF in 5 mL of glacial acetic acid was stirred for 10–15 min and kept at room temperature for 24 h. After removing the solvent, the residue was treated with water; the precipitate was filtered off, washed with diluted HCl solution and dried. Yield 0.65 g (81%), mp 209–210°C. ^{1}H NMR spectrum, δ, ppm: 2.24 s and 2.41 s (6H, CH_3-pyrazole), 2.54 s and 2.55 s (6H, CH_3-pyrimidine), 5.98 s (1H, CH-pyrazole), 7.22 s (1H, CH-pyrimidine), 7.36 br. s (2H, NH_2), 7.54 s (1H, CH-pyrimidine). ^{13}C NMR spectrum, δ_C, ppm: 13.2, 14.4, 21.1, 23.5, 109.2, 109.4, 117.1, 141.8, 149.4, 155.7, 159.1, 162.7, 164.0, 165.4, 168.1. Found, %: C 55.03; H 5.23; N 29.95. $C_{15}H_{17}N_7S$. Calculated, %: C 55.03; H 5.23; N 29.95.

Ethyl 3-(2-{4-[(2-amino-6-methylpyrimidin-4-yl)-thio]-6-methylpyrimidin-2-yl}hydrazono)butanoate (15). A mixture of 0.4 g (0.0015 mol) of compound **13a**, 0.75 mL of acetoacetic acid ester and 1–2 drops of DMF in 0.8 mL of acetic acid was kept at room temperature for 24 h. After removal of the solvent, the residue was

treated with water; the precipitate was filtered off, washed with diluted HCl solution and dried. Yield 0.4 g (71%), mp 120–121°C. ^{1}H NMR spectrum, δ, ppm: 1.28 t (3H, $OCH_2\mathbf{CH}_3$, J = 7.1 Hz), 2.00 s (3H, N=CCH_3), 2.25 s and 2.34 s (6H, CH_3-pyrimidine), 3.32 s (2H, $COCH_2$), 4.13 q (2H, $O\mathbf{CH}_2CH_3$, J = 7.1 Hz), 6.33 br. s (2H, NH_2), 6.83 s and 6.86 s (2H, CH-pyrimidine), 9.62 br. s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 13.8, 15.7, 20.5, 23.3, 43.8, 59.8, 109.4, 111.3, 144.8, 159.4, 162.4, 164.6, 166.8, 166.9, 169.1, 171.0. Found, %: C 51.19; H 5.64; N 26.11. $C_{16}H_{21}N_7O_2S$. Calculated, %: C 51.19; H 5.64; N 26.11.

CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

REFERENCES

1. Mashkovskii, M.D., *Lekarstvennye sredstva* (Drugs), Moscow: Novaya Volna, 2002.
2. Koroleva, E.V., Gusak, K.N., and Ignatovich, Zh.V., *Russ. Chem. Rev.*, 2010, vol. 79, p. 655. https://doi.org/10.1070/RC2010v079n08ABEH004116
3. Kraljević, T.G., Ilić, N., Stepanić, V., Sappe, L., Petranović, J., Pavelić, S.K., and Raić-Malić, S., *Bioorg. Med. Chem. Lett.*, 2014, vol. 24, p. 2913. https://doi.org/10.1016/j.bmcl.2014.04.079
4. Ghorab, M.M., Ragab, F.A., Alqasoumi, S.I., Alafeefy, A.M., and Aboulmagd, S.A., *Eur. J. Med. Chem.*, 2010, vol. 45, p. 171. https://doi.org/10.1016/j.ejmech.2009.09.039
5. Goudar, V., Rashmi, P., Shantharam, U., Hazra, K., and Nargund, L.G., *J. Chem. Pharm. Res.*, 2012, vol. 4, p. 3100.
6. Kumaresan, S., Chandrasekaran, S., Sakthivel, K.M., Guruvayoorappan, C., and Enoch, I.V.M., *J. Chem. Pharm. Res.*, 2014, vol. 6, p. 593.
7. Kaur, N., Aggarwal, A.K., Sharma, N., and Choudhary, B., *Int. J. Pharm. Sci. Drug Res.*, 2012, vol. 4, p. 199.
8. Patel, D.H., Chikhalia, K.H., Shah, N.K., Patel, D.P., Kaswala, P.B., and Buha, V.M., *Pharm. Chem. J.*, 2010, vol. 44, p. 94. https://doi.org/10.1007/s11094-010-0406-9
9. Moustafa, A.H., Saad, H., Shehab, W., and El-Mobayed, M.M., *Phosphorus, Sulfur, Silicon, Relat. Elem.*, 2007, vol. 183, p. 115. https://doi.org/10.1080/10426500701557286
10. Ingarsal, N., Saravanan, G., Amutha, P., and Nagarajan, S., *Eur. J. Med. Chem.*, 2007, vol. 42, p. 517. https://doi.org/10.1016/j.ejmech.2006.09.012
11. Kanagarajan, V., Thanusu, J., and Gopalakrishnan, M.A., *J. Korean Chem. Soc.*, 2009, vol. 53, p. 731. https://doi.org/10.5012/jkcs.2009.53.6.731
12. Wang, S.C., Gao, J.-G., Zhang, S., Liu, S., and Jiang, L., *Phosphorus, Sulfur, Silicon, Relat. Elem.*, 2018, vol. 193, p. 245. https://doi.org/10.1080/10426507.2017.1395439
13. Holy, A., Votruba, I., Masojìdkova, M., Andrei, G., Snoeck, R., Naesens, L., De Clercq, E., and Balzarini, J., *J. Med. Chem.*, 2002, vol. 45, p. 1918. https://doi.org/10.1021/jm011095y
14. Dalkara, S., Karakurt, A., *Curr. Top. Med. Chem.*, 2012, vol. 12, p. 1033. doi 10.2174/156802612800229215
15. Abu-Hashem, A.A., Youssef, M.M., and Hussein, H.A.R., *J. Chin. Chem. Soc.*, 2011, vol. 58, p. 41. https://doi.org/10.1002/jccs.201190056
16. Abu-Hashem, A.A., El-Shehry, M.F., and Badria, F.A., *Act. Pharm.*, 2010, vol. 60, p. 311. doi 10.2478/v10007-010-0027-6
17. Sakakibara, N., Hamasaki, T., Baba, M., Demizu, Y., Kurihara, M., Irie, K., Iwai, M., Asada, E., Kato, Y., and Maruyama, T., *Bioorg. Med. Chem.*, 2013, vol. 21, p. 5900. https://doi.org/10.1016/j.bmc.2013.06.061
18. Tang, J., Maddali, K., Dries, C.D., Sham, Y.Y., Vince, R., Pommier, Y., and Wang, Zh., *Bioorg. Med. Chem. Lett.*, 2011, vol. 21, p. 2400. https://doi.org/10.1016/j.bmcl.2011.02.069
19. Rana, K., Kaur, B., and Kumar, B., *Ind. J. Chem. (B)*, 2004, vol. 43, p. 1553.
20. Kumar, B., Kaur, B., Kaur, J., Parmar, A., Anand, R.D., and Kumar, H., *Ind. J. Chem. (B)*, 2002, vol. 41, p. 1526.
21. Virsodia, V., Pissurlenkar, R.R.S., Manvar, D., Dholakia, Ch., Adlakha, P., Shah, A., and Coutinhio, E.C., *Eur. J. Med. Chem.*, 2008, vol. 43, p. 2103. https://doi.org/10.1016/j.ejmech.2007.08.004
22. Srivastav, N.C., Rai, D., Tse, C., Agrawal, B., Kunimoto, D.Y., and Kumar, R., *J. Med. Chem.*, 2010, vol. 53, p. 6180. https://doi.org/10.1021/jm100568q
23. Agarwal, A., Srivastava, K., Puri, S.K., and Chauhan, P.M.S., *Bioorg. Med. Chem.*, 2005, vol. 13, p. 4645. https://doi.org/10.1016/j.bmc.2005.04.061
24. Singh, K., Kaur, H., Chibale, K., and Balzarini, J., *Eur. J. Med. Chem.*, 2013, vol. 66, p. 314. https://doi.org/10.1016/j.ejmech.2013.05.046
25. Rasheeda, K., Alva, V.D.P., Krishnaprasad, P.A., and Samshuddin, S., *Int. J. Corros. Scale Inhib.*, 2018, vol. 7, p. 48. https://doi.org/10.17675/2305-6894-2018-7-1-5
26. Classified Lists of Pesticides. http://www.alanwood.net/pesticides/class_pesticides.html.
27. Grigoryan, A.A., *Vestn. RAU. Ser. Fiz.-Mat. Estestv. Nauk*, 2014, no. 2, p. 46.