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Synthesis and Properties of 4,6-Dimethyl-5-pentyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile and 3-Amino-4,6-dimethyl-5-pentylthieno[2,3-*b*]pyridines

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Abstract—The reaction of 3-pentylpentane-2,4-dione with cyanothioacetamide afforded 4,6-dimethyl-5-pentyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile. Alkylation of the latter led to the formation of 2-alkylsulfanyl-4,6-dimethyl-5-pentylpyridine-3-carbonitriles or 3-amino-4,6-dimethyl-5-pentylthieno[2,3-*b*]pyridines, depending on the alkylating agent and reaction conditions. The structures of the key compounds were proved by 2D NMR spectroscopy and X-ray analysis. Biological activity of the synthesized compounds was evaluated *in silico*. Some compounds were experimentally found to stimulate growth of sunflower seedlings.

Keywords: cyanothioacetamide, Thorpe–Ziegler cyclization, thieno[2,3-*b*]pyridines, lipophilicity, *in silico* biological activity, 1,3,2λ^5-diazaphosphinines

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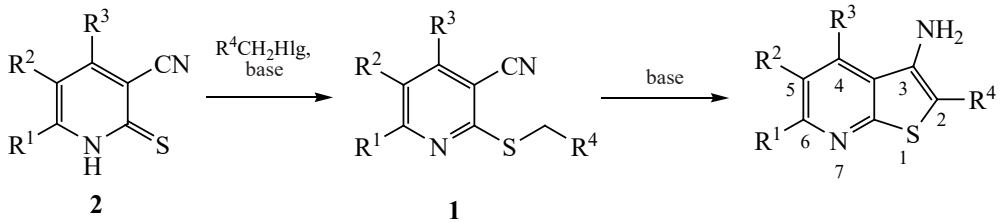
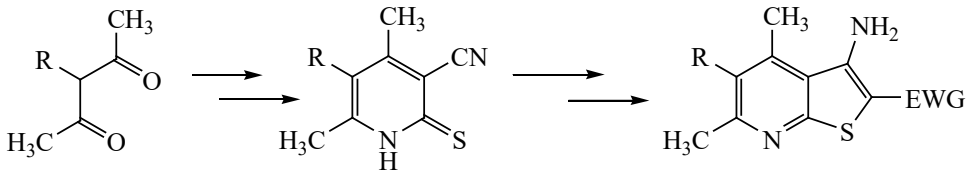
2-Thioxo-1,2-dihydropyridine-3-carbonitriles [3-cyanopyridin-2(1*H*)-thiones] is a class of readily accessible compounds which attract interest due to their diverse possible applications in fine organic synthesis [1–5]. These compounds are main precursors to 3-aminothieno[2,3-*b*]-pyridines that are promising heterocyclic compounds exhibiting a broad spectrum of biological activity [6–11]. An important factor which is necessary to be taken into account in the target-oriented synthesis of bioactive 3-aminotieno[2,3-*b*]pyridine derivatives is their lipophilicity; it characterizes their bioavailability and cell membrane permeability [12, 13]. Therefore, the synthesis of new derivatives of the 3-aminotieno[2,3-*b*] pyridine series with controlled lipophilicity seems to be an important problem.

The traditional (and most popular) synthetic approach to thieno[2,3-*b*]pyridines consists of base-catalyzed Thorpe–Ziegler cyclization of 2-(R-methylsulfanyl) pyridine-3-carbonitriles **1** prepared by alkylation of 3-cyanopyridine-2(1*H*)-thiones **2** (Scheme 1) [6–10]. In this case, the resulting thieno[2,3-*b*]pyridine molecule necessarily contains an amino group in the 3-position and

Scheme 1.



Scheme 2.



R = Me, Et, CO_2Me, CH_2Ar; EWG is an electron-withdrawing group.

a polar electron-withdrawing group (R^4) in the 2-position, and its lipophilicity can be controlled mainly by the substituents R^1–R^3 in positions *4*, *5*, and *6*.

In continuation of a series of our studies in the field of synthesis of functionalized thieno[2,3-*b*]pyridines [14–20], herein we report the synthesis and some properties of thienopyridines containing lipophilic alkyl substituents in positions *4–6*. We believed that the most rational approach to the introduction of alkyl groups into those positions is the classical pyridine ring construction by the Guareschi–Thorpe cyclization of cyanothioacetamide [21, 22] with substituted 1,3-diketones, followed by alkylation of 2-thioxo-1,2-dihydropyridine-3-carbonitriles **2** and Thorpe–Ziegler cyclization of intermediates **1**.

The synthesis of thieno[2,3-*b*]pyridines with various substituents in the 5-position starting from 3-substituted acetylacetones has been demonstrated in [23–27] on a limited number of examples (Scheme 2). This approach is advantageous primarily due to preparative convenience and accessibility of initial acetylacetone derivatives.

Preliminary estimation of the *c* log *P* values (logarithm of the octanol/water partition coefficient) for the expected products using OSIRIS Property Explorer software [28] showed that C_5–C_6 is the limiting length of the alkyl chain of the 5-substituent to meet Lipinski's rule of five [29–31] (*c* log $P \leq 5.0$) for peroral bioavailability. Therefore, it seemed reasonable to confine the maximum alkyl chain length to C_5 (*n*-pentyl).

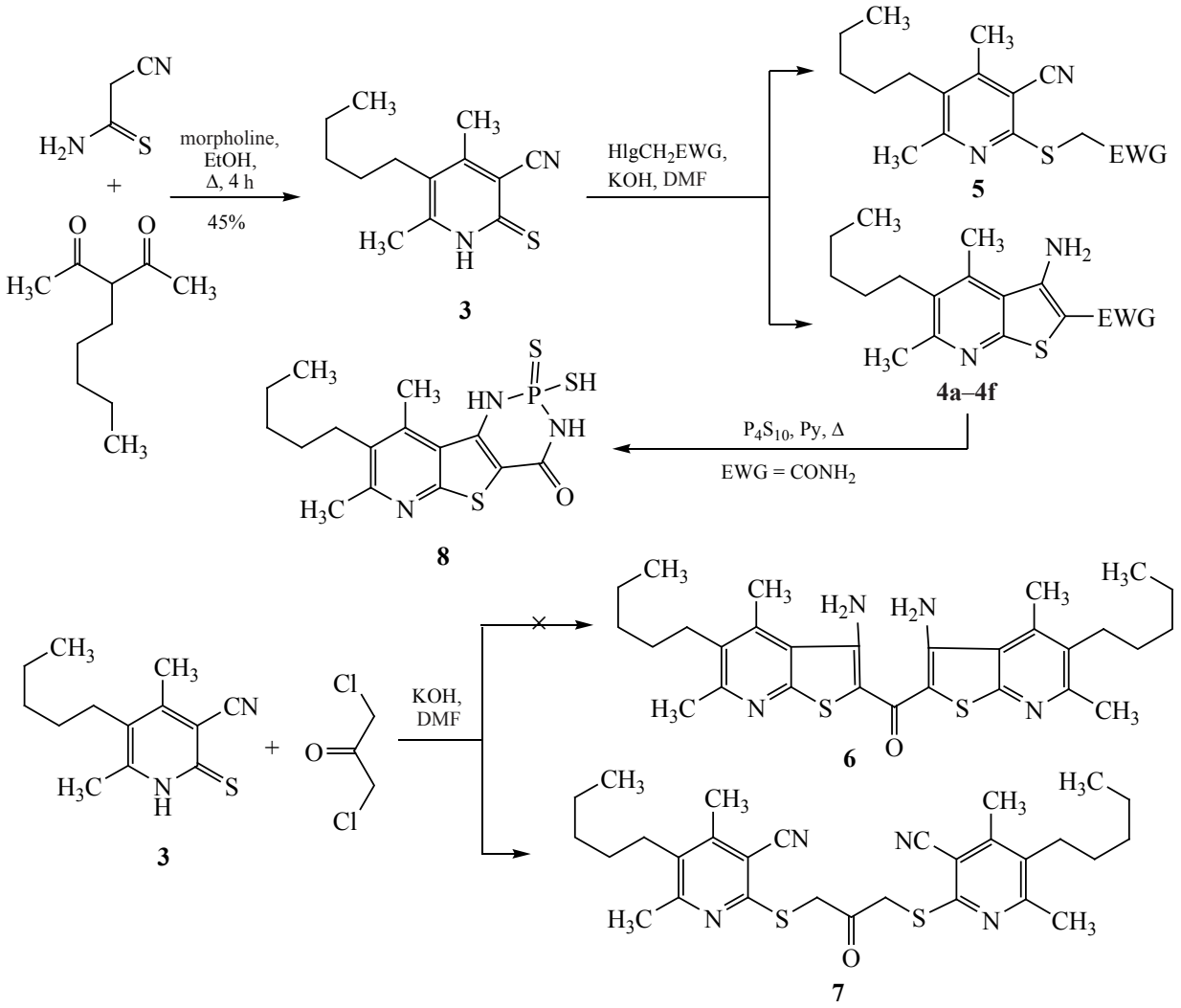
By the condensation of 3-pentylpentane-2,4-dione with cyanothioacetamide in the presence of morpholine we obtained previously unknown 4,6-dimethyl-5-pentyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile (**3**) (Scheme 3). Compound **3** could be a convenient precursor to thieno[2,3-*b*]pyridine derivatives **4** with a pentyl substituent on C^5. Treatment of **3** with alkylating agents in DMF in the presence of excess potassium hydroxide afforded thieno[2,3-*b*]pyridines **4a**–**4f**, but in the reaction of **3** with 2-chloro-*N*-(4-methylphenyl)acetanilide we isolated only uncyclized S-alkylation product **5**.

Leistner and Dumke [32] previously described an original synthesis of bis(thieno[2,3-*b*]pyridin-2-yl) ketones by reaction of 2-thioxopyridine-3-carbonitriles with 1,3-dichloroacetone. We have found that the reaction of **3** with 1,3-dichloroacetone in DMF even in the presence of excess potassium hydroxide gives no bis(thieno[2,3-*b*]pyridin-2-yl) ketone **6** and that the product is 1,3-bis(pyridin-2-ylsulfanyl)acetone **7** (Scheme 3). Inhibition of the cascade process and the formation of compounds **5** and **7** as the major products are likely to be related to the poor solubility of the latter in DMF, so that they are removed from the reaction zone.

A few examples of phosphorylation of 3-aminothieno[2,3-*b*]pyridine-2-carboxamides with the formation of fused 1,3,2λ^5-diazaphosphinine derivatives have been reported in recent years [33, 34]. It should be noted that 1,3,2-diazaphosphinines attract interest due to their diverse biological activity [35–39]. By treatment of thienopyridine **4a** (EWG = $CONH_2$) with an equimolar amount of phosphorus(V) sulfide in boiling anhydrous pyridine we obtained pyrido[3′,2′ : 4,5]thieno[3,2-*d*]-[1,3,2]diazaphosphinine **8**.

Compounds **4a**–**4f** and **8** are finely crystalline powders colored in various shades of yellow; they are readily soluble in acetone, ethyl acetate, and benzene. The product structure was proved by ^{1}H and ^{13}C NMR (DEPTQ), IR, and high-resolution mass spectra, as well as by X-ray analysis. The ^{1}H NMR spectra of all isolated compounds characteristically showed upfield signals due to pentyl and two methyl groups. The ^{1}H NMR spectrum of **8** displayed no NH_2 signal, and the most downfield signal in its ^{13}C NMR spectrum is that located at δ_C 167.0 ppm (C=O), which indicates the absence of thioamide fragment in molecule **8**. In the IR spectra of **3**, **5**, and **7** we observed an absorption band belonging to stretching vibrations of the conjugated cyano group (2216–2220 cm^{-1}), whereas no such band was present in the spectra of **4a**–**4f**. The structure of 4,6-dimethyl-5-pentyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile (**3**)

Scheme 3.



4, EWG = $CONH_2$ (**a**), CO_2Et (**b**), CN (**c**), 3-$O_2NC_6H_4NHCO$ (**d**), PhC(O) (**e**), 4-$BrC_6H_4C(O)$ (**f**); **5**, EWG = 4-MeC_6H_4NHCO.

was confirmed by two-dimensional NMR spectroscopy (^1H–^{13}C HSQC, ^1H–^{13}C HMBC, ^1H–^{15}N HMBC; Fig. 1, Table 1), and the structures of **4c** and **5** were determined by X-ray analysis (Figs. 2, 3).

Compounds **3**, **4a**–**4f**, **5**, **7**, and **8** were evaluated *in silico* for drug likeness by ADMET (absorption, distribution, metabolism, excretion, toxicity) prediction using OSIRIS Property Explorer [28] i admetSAR [40]. Their biological activity was also predicted by PASS Online [41] and Molinspiration Property Calculation Service [42]. OSIRIS Property Explorer database covers the properties of 3300 drugs and 15 000 commercially available compounds (Fluka), which can be used to estimate the lipophilicity *c* log *P*, solubility (log *S*), topological polar surface area (TPSA), toxicological parameters (i.e., risks of side effects such as mutagenic, carcinogenic, and reproductive effects), drug likeness, and general pharmacological potential of a compound [28]. OSIRIS Property Explorer provides the possibility of performing primary analysis of a structure in terms of the Lipinski rule of five (*c* log $P \le 5.0$, MW ≤ 500, TPSA ≤ 140, number of hydrogen bond acceptors ≤ 10, number of hydrogen donors ≤ 5) [29–31]. The results of calculations by OSIRIS Property Explorer are given in Table 2.

As follows from the obtained data, the lipophilicity of **3**, **4a**–**4f**, **5**, **7**, and **8** varies over a wide range, but the *c* log *P* values for thienopyridines **4** mostly do not exceed 5.0, which suggests possible good absorption

Table 1. Principal correlations in the $^{1}H–^{13}C$ and $^{1}H–^{15}N$ HSQC and HMBC spectra of 4,6-dimethyl-5-pentyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile (**3**)[a]

δ_H, ppm	K$^{1}H–^{13}C$ HSQC, δ_C, ppm	$^{1}H–^{13}C$ HMBC, δ_C, ppm	$^{1}H–^{15}N$ HSQC, δ_N, ppm	$^{1}H–^{15}N$ HMBC, δ_N, ppm
0.86 t (3H, CH_3)	14.0 (CH_3)	21.9* (CH_2) 31.3* (CH_2)	–	–
1.31–1.36 m [6H, $(CH_2)_3$]	21.9* (CH_2) 27.8* (CH_2) 31.3* (CH_2)	14.0 (CH_3) 21.9* (CH_2) 27.1* (CH_2) 27.8* (CH_2) 31.3* (CH_2)	–	–
2.38 s (3H, C^6CH_3)	17.1 (CH_3)	114.5* (C^5) 155.6* (C^6)	–	202.8 (NH)
2.39 s (3H, C^4CH_3)	18.8 (CH_3)	114.5* (C^5) 125.0* (C^3) 150.8* (C^4)	–	–
2.40–2.45 m (2H, CH_2)	27.1* (CH_2)	27.8* (CH_2) 114.5* (C^5) 150.8* (C^4) 155.6* (C^6)	–	–
13.75 уш. с (1H, NH)	–	114.5* (C^5) 125.0* (C^3)	202.8 (NH)	–

[a] Opposite phase signals in the ^{13}C DEPTQ spectrum (quaternary carbons and CH_2).

and permeability [29–31]. The molecular weights of all the examined compounds, except for 1,3-bis(pyridin-2-ylsulfanyl)propan-2-one (**7**), are not higher than 430, in keeping with the Lipinski rule of five. However, none of the above compounds showed a positive drug likeness or high drug score (>0.5). On the other hand, only compound **8** was predicted to have an appreciable toxicity due to the presence of P=S and N–P=S fragments.

The parameter log *S* characterized the solubility; as a rule, poor solubility implies low absorption and low bioavailability. It should be noted that the log *S* values calculated by OSIRIS Property Explorer [28] for 80% of commercially available drugs is higher than –4. The parameter TPSA reflects surface area of polar parts of a molecule. As a rule, increased TPSA is related to reduced cell membrane permeability; therefore, lower TPSA values are generally preferred from the viewpoint of drug likeness. TPSA, molecular weight, and lipophilicity are the key parameters responsible for transport of molecules (in particular, low-molecular-weight kinase

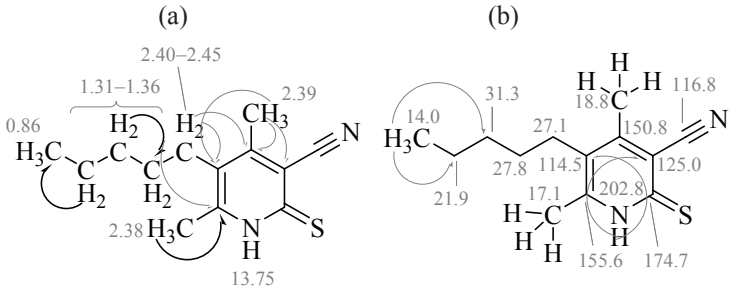


Fig. 1. Principal correlations in the $^{1}H–^{13}C$ HMBC spectrum of 4,6-dimethyl-5-pentyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile (**3**): (a) ^{1}H and (b) ^{13}C chemical shifts (δ, δ_C, ppm).

Table 2. Toxicity risks and physicochemical parameters of compounds **3**, **4a**–**4f**, **5**, **7**, and **8**, predicted by OSIRIS Property Explorer

Compound no.	Toxicity risk[a]				Physicochemical parameters					
	mutagenicity	carcinogenicity	irritation	reproductive effects	cLog*P*	log*S*	MW	TPSA	drug likeness	drug score
3	–	–	–	–	2.91	–3.9	234.0	67.91	–13.08	0.405
4a	–	–	–	–	3.05	–5.09	291.0	110.2	–8.54	0.333
4b	–	–	–	–	4.28	–5.44	320.0	93.45	–12.53	0.275
4c	–	–	–	–	3.8	–5.77	273.0	90.94	–14.88	0.282
4d	–	–	–	–	4.19	–6.97	412.0	142.0	–12.32	0.206
4e	–	–	–	–	5.09	–7.1	352.0	84.22	–8.45	0.189
4f	–	–	–	–	5.82	–7.93	430.0	84.22	–10.97	0.145
5	–	–	–	–	5.16	–5.78	381.0	91.08	–13.73	0.216
7	–	–	–	–	7.28	–7.86	522.0	141.0	–14.26	0.103
8	+	+	±	+	4.55	–3.09	385.0	162.9	–12.4	0.058

[a] "+" denotes a high risk, "±" denotes a moderate risk, and "–" denotes the absence of toxicity.

inhibitors) through the blood–brain barrier [43]. Most of the examined compounds, except for **4d**, **7**, and **8** meet the condition TPSA ≤ 140.

The results of ADMET prediction using admetSAR [40] showed (Table 3) that all compounds are characterized by a good BBB (blood–brain barrier) permeability and intestinal absorption upon peroral administration (HIA, human intestinal absorption). The examined compounds are not cytochrome P450 (CYP450) substrates but are CYP450 inhibitors to some extent, and they may affect metabolism of other drugs. The Ames tests for mutagenic activity were mainly negative. The predicted LD_{50} values in rats were comparable with those of most

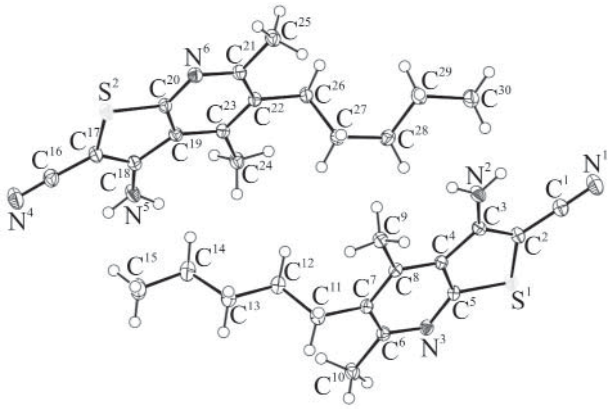


Fig. 2. Structure of the molecule of 3-amino-4,6-dimethyl-5-pentylthieno[2,3-*b*]pyridine-2-carbonitrile (**4c**) in crystal according to the X-ray diffraction data.

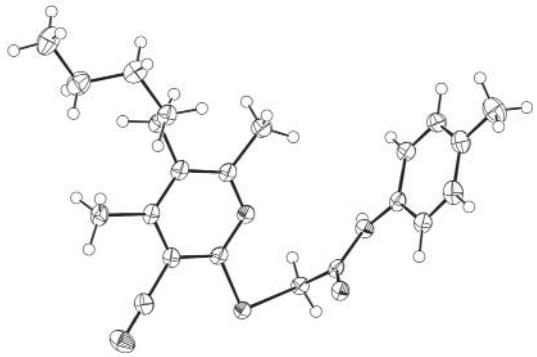


Fig. 3. Structure of the molecule of 2-[(3-cyano-4,6-dimethyl-5-pentylpyridin-2-yl)sulfanyl]-*N*-(4-methylphenyl)acetamide (**5**) in crystal according to the X-ray diffraction data.

Table 3. ADMET parameters and possible biological activity of compounds **3**, **4a**–**4f**, **5**, **7**, and **8** predicted by admetSAR

Compound no.	HIA[a]	BBB[a]	Metabolism		Ames' toxicity[a]	LD_{50} in rats, mol/kg
			CYP450 inhibitor	CYP450 substrate		
3	+ (0.9280)	+ (0.9622)	+	–	– (0.7131)	2.4633
4a	+ (0.9004)	+ (0.9406)	+	–	– (0.6693)	2.6092
4б	+ (0.9755)	+ (0.9679)	+	–	– (0.6874)	2.5456
4в	+ (0.9640)	+ (0.9503)	+	–	+ (0.6247)	2.7938
4г	+ (0.9860)	+ (0.8080)	+	–	+ (0.6620)	2.7431
4д	+ (0.9844)	+ (0.9714)	+	–	+ (0.5440)	2.7324
4e	+ (0.9809)	+ (0.9479)	+	–	– (0.5242)	2.7086
5	+ (0.9025)	+ (0.9615)	+	–	– (0.7356)	2.4791
7	+ (0.9434)	+ (0.9686)	+	–	– (0.7494)	2.5677
8	+ (0.5290)	+ (0.8432)	+	–	– (0.6342)	2.7179

[a] "+" denotes the occurrence of effect, and "–" denotes the absence of effect; the probability is given in parentheses in fractions of unity.

Table 4. Growth-regulating activity of compounds **4b** and **4d**[a]

Comp. no.	Organ	Control (L_c)	Concentration, %							
			10^{-2}		10^{-3}		10^{-4}		10^{-5}	
			L_t	A	L_t	A	L_t	A	L_t	A
4b	Stem	67	75	112[b]	71	106	77	115[b]	80	119[b]
	Root	102	109	107	119	117[b]	117	115[b]	124	122[b]
4d	Stem	67	81	120[b]	82	122[b]	74	105	85	127[b]
	Root	102	112	110[b]	116	113[b]	122	120[b]	122	120[b]

[a] L_c is the length (mm) of an organ in the control group of seedlings; L_t is the length (mm) of an organ in the treated group of seedlings; $A = (L_t/L_c) \times 100\%$ is the growth-regulating effect.
[b] The differences are reliable at $p = 0.95$.

drugs; compounds **3** and **5** were predicted to be most toxic. According to the results of prediction of possible biological activity using PASS Online software, compound **3** is a Cyp2c12 substrate of cytochrome P450 with a probability of 0.814, and compound **8** is expected to inhibit dihydroorotase with a probability of 0.964. Molinspiration Property Calculation Service predicted possible kinase inhibitory activity of thienopyridines **4a** and **4c**–**4f** (Molinspiration bioactivity score 0.08, –0.05, –0.09, –0.03, and –0.07, respectively; the higher the score, the greater the probability of biological activity).

The prospects of using the synthesized compounds in agrochemistry was studied at the All-Russian Research Institute of Biological Plant Protection (Krasnodar). The growth-regulating activity of compounds **4a**–**4f** was evaluated by laboratory experiments on *Flagman* sunflower seedlings (Table 4). Sunflower seeds were treated with a solution of a test compound at different concentrations (10^{-2} to 10^{-5}). Each experiment was carried out in triplicate with 100 seeds. The effect was evaluated by the elongation of the stem and root of treated seedlings in comparison to control (untreated seeds). The results

were statistically processed using Student's t-test at p = 0.95. Table 4 contains data for those compounds which showed a growth-stimulating effect. Compounds **4b** and **4d** favored stem elongation by 12–27% relative to control and stimulated root growth by 10–20%, depending on the concentration.

In summary, we have proposed a procedure for the synthesis of 4,6-dimethyl-5-pentyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile by the Guareschi–Thorpe cyclization and used it as starting material to obtain a number of new 5-pentylpyridine-3-carbonitrile, 3-amino-4,6-dimethyl-5-pentylthieno[2,3-*b*]pyridine, and pyrido[3′,2′ : 4,5]thieno[3,2-*d*][1,3,2]diazaphosphinine derivatives. The structure of the obtained compounds was confirmed by 2D NMR techniques and X-ray analysis. The presence of a pentyl substituent in their molecules endows them with high lipophilicity in comparison to previously reported structural analogs. *In silico* analysis of molecular parameters responsible for biological activity and pharmacological potential indicated prospects of further studies in this line. A moderate growth-stimulating activity has been revealed for two 3-amino-4,6-dimethyl-5-pentylthieno[2,3-*b*]pyridines in laboratory tests on sunflower seeds.

EXPERIMENTAL

The NMR spectra were recorded on a Bruker Avance III HD 400 spectrometer at 400.17 (^{1}H), 100.63 (^{13}C), and 40.55 MHz (^{15}N) from solutions in DMSO-d_6; the chemical shifts were measured relative to the residual proton and carbon signals of the solvent (^{1}H and ^{13}C) or nitromethane (external standard, ^{15}N). The IR spectra were recorded on Bruker Vertex 70 spectrometer with Fourier transform equipped with a diamond ATR accessory; spectral resolution ±4 cm^{-1}. The high-resolution mass spectra were obtained on a Bruker maXis TOF mass spectrometer (electrospray ionization) using acetonitrile as solvent and HCO_2Na–HCO_2H calibration. The elemental compositions (C, H, N) were determined with a Carlo Erba 1106 analyzer. The purity of the isolated compounds was checked by TLC on Sorbfil-A plates (eluent acetone–hexane, 1 : 1); spots were visualized by treatment with iodine vapor or under UV light.

Cyanothioacetamide was synthesized by passing gaseous hydrogen sulfide through a solution of malononitrile in ethanol in the presence of triethylamine [44].

3-Pentylpentane-2,4-dione was prepared by analogy with the patented procedure for the synthesis of 3-methylpentane-2,4-dione [45]. A mixture of 33.0 g (0.33 mol) of freshly distilled acetylacetone, 49.5 mL (60.4 g, 0.4 mol) of freshly distilled 1-bromopentane, 42.0 g (0.3 mol) of potassium carbonate, 6.6 g (0.04 mol) of potassium iodide, and 70 mL of anhydrous acetone was refluxed for 17 h (GC/MS monitoring). The precipitate of potassium bromide was filtered off and washed with acetone. Additional amounts of K_2CO_3 (8.4 g) and KI (1.3 g) were added to the filtrate, and the mixture was refluxed for 6.5 h more. The precipitate of KBr was filtered off, acetone was distilled off under reduced pressure, and the residue was distilled in a vacuum (10–12 mmHg) to collect a fraction boiling in the range from 96 to 102°C. The product was a colorless oil which was pure according to the GC/MS data. Yield 73%.

4,6-Dimethyl-5-pentyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile (3). A mixture of 8.4 g (0.049 mol) of 3-pentylpentane-2,4-dione, 5.01 g (0.05 mol) of cyanothioacetamide, 0.43 mL (0.005 mol) of morpholine, and 20 mL of 96% ethanol was refluxed for 4 h. The mixture was cooled, 30 drops of glacial acetic acid were added, and the precipitate was filtered off, washed with 50% aqueous propan-2-ol and petroleum ether, and recrystallized from propan-2-ol. Yield 45%, yellow finely crystalline powder. IR spectrum, ν, cm^{-1}: 3180 (N–H), 3059, 2955, 2910, 2876, 2804 (C–H), 2218 (C≡N), 1610, 1572 (C=C), 1229 (C=S). ^{1}H NMR spectrum, δ, ppm: 0.86 t (3H, CH_3, ^3J = 6.8 Hz), 1.31–1.36 m [6H, $(CH_2)_3$], 2.38 s (3H, 6-CH_3), 2.39 s (3H, 4-CH_3), 2.40–2.45 m (2H, CH_2), 13.75 br.s (1H, NH). ^{13}C NMR spectrum (DEPTQ), δ_C, ppm: 14.0 (CH_3), 17.1 (CH_3), 18.8 (CH_3), 21.9 (CH_2), 27.1 (CH_2), 27.8 (CH_2), 31.3 (CH_2), 114.5 (C^5), 116.8 (C≡N), 125.0 (C^3), 150.8 (C^4), 155.6 (C^6), 174.7 (C=S). Mass spectrum: *m*/*z*: 257.1083 $[M + Na]^+$; calculated for $C_{13}H_{18}N_2NaS$: 257.1089.

3-Amino-4,6-dimethyl-5-pentylthieno[2,3-*b*]-pyridines 4a–4f and pyridine-3-carbonitrile 5 (*general procedure*). 4,6-Dimethyl-5-pentyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile (**3**), 300 mg (1.28 mmol), was dissolved in 2 mL of DMF, and 0.7 mL of 10% aqueous potassium hydroxide (d = 1.09 g/mL, 1.36 mmol) was added with stirring on heating. The corresponding alkylating agent (chloroacetamide, ethyl bromoacetate, chloroacetonitrile, substituted chloroacetanilide, or bromoacetophenone), 1.3 mmol, was then added to the resulting solution of potassium pyridine-2-thiolate, the mixture was stirred for 20 min at 50–60°C, an additional 0.7 mL of 10% aqueous potassium hydroxide was added, and

the mixture was stirred for 10–15 min at room temperature. Aqueous ethanol (1 : 1), 5 mL, was added, and the precipitate was filtered off, washed with water, aqueous ethanol, and hexane, and dried in air at 60°C.

3-Amino-4,6-dimethyl-5-pentylthieno[2,3-*b*]pyridine-2-carboxamide (4a). Yield 45%, yellow powder. ^{1}H NMR spectrum, δ, ppm: 0.88 t (3H, CH_3, ^3J = 6.8 Hz), 1.33–1.39 m [6N, $(CH_2)_3$], 2.53 s (3H, CH_3), 2.64–2.67 m (5H, CH_3, 5-CH_2), 6.87 br.s (2H, NH_2), 7.11 br.s [2H, C(O)NH_2]. ^{13}C NMR spectrum (DEPTQ), δ_C, ppm: 14.0 (CH_3), 15.1 (CH_3), 22.0 (CH_2), 23.3 (CH_3), 27.9 (CH_2), 28.8 (CH_2), 31.5 (CH_2), 97.6 (C^2), 123.9 (C^{3a}), 130.7 (C^5), 142.3, 148.5, 155.8, 157.4, 167.5 (C=O). Found, %: C 61.77; H 7.37; N 14.40. $C_{15}H_{21}N_3OS$. Calculated, %: C 61.82; H 7.26; N 14.42.

Ethyl 3-amino-4,6-dimethyl-5-pentylthieno[2,3-*b*]-pyridine-2-carboxylate (4b). Yield 52%, yellow powder, mp 170°C. IR spectrum, ν, cm^{-1}: 3433, 3331 (N–H), 2972, 2953, 2922, 2872, 2854 (C–H), 1668 (C=O). ^{1}H NMR spectrum, δ, ppm: 0.88 t (3H, CH_3, ^3J = 6.9 Hz), 1.27 t (3H, $OCH_2C\mathbf{H}_3$, ^3J = 7.1 Hz), 1.32–1.43 m [6H, $(CH_2)_3$], 2.55 s (3H, CH_3), 2.65–2.71 m (5H, CH_3, 5-CH_2), 4.24 q (2H, OCH_2, ^3J = 7.1 Hz), 6.86 br.s (2H, NH_2). Mass spectrum: *m*/*z* 321.1637 [*M* + H]$^+$; calculated for $C_{17}H_{25}N_2O_2S$: 321.1631.

3-Amino-4,6-dimethyl-5-pentylthieno[2,3-*b*]-pyridine-2-carbonitrile (4c). Yield 67%, yellow crystals. IR spectrum, ν, cm^{-1}: 3344, 3230 (N–H), 2957, 2924, 2872, 2858 (C–H), 2193 (C≡N). ^{1}H NMR spectrum, δ, ppm: 0.87 t (3H, CH_3, ^3J = 6.8 Hz), 1.32–1.40 m [6H, $(CH_2)_3$], 2.53 s (3H, CH_3), 2.63–2.69 m (5H, CH_3, 5-CH_2), 6.46 br.s (2H, NH_2). ^{13}C NMR spectrum (DEPTQ), δ_C, ppm: 13.9 (CH_3), 15.3 (CH_3), 21.9 (CH_2), 23.3 (CH_3), 27.8 (CH_2), 28.6 (CH_2), 31.5 (CH_2), 72.9 (C^2), 116.0 (C≡N), 121.7 (C^{3a}), 131.4 (C^5), 142.8, 152.3, 157.2, 158.7. Mass spectrum: *m*/*z* 296.1193 [*M* + Na]$^+$; calculated for $C_{15}H_{19}N_3NaS$: 296.1192.

3-Amino-4,6-dimethyl-*N*-(3-nitrophenyl)-5-pentylthieno[2,3-*b*]pyridine-2-carboxamide (4d). Yield 96%, yellow powder. IR spectrum, ν, cm^{-1}: 3464, 3408, 3317 (N–H), 2955, 2927, 2870 (C–H), 1651 (C=O), 1524 (NO_2, asym.), 1342 (NO_2, sym.). ^{1}H NMR spectrum, δ, ppm: 0.86 t (3H, CH_3, ^3J = 6.8 Hz), 1.29–1.38 m [6H, $(CH_2)_3$], 2.54 s (3H, CH_3), 2.62–2.65 m (3H, CH_2), 2.68 s (3H, CH_3), 7.15 br.s (2H, NH_2), 7.55–7.59 m (1H, 5′-H), 7.88 d.d (1H, 4′-H, ^3J = 8.1, ^4J = 2.0 Hz), 8.12 d (1H, 6′-H, ^3J = 8.3 Hz), 8.72 d (1H, 2′-H, ^4J = 2.0 Hz), 9.79 br.s (CONH). ^{13}C NMR spectrum (DEPTQ), δ_C, ppm: 13.9 (CH_3), 15.3 (CH_3), 21.9 (CH_2), 23.3 (CH_3), 27.9 (CH_2), 28.7 (CH_2), 31.5 (CH_2), 95.9 (C^2), 114.9 (CH_{arom}), 117.6 (CH_{arom}), 123.2 (C^{3a}), 126.7 (CH_{arom}), 129.7 (CH_{arom}), 131.0 (C^5), 140.4 ($C^{1'}$), 142.6, 147.8 ($C^{3'}$), 150.6, 156.3, 158.3, 164.7 (C=O). Found, %: C 61.17; H 5.97; N 13.54. $C_{21}H_{24}N_4O_3S$. Calculated, %: C 61.14; H 5.86; N 13.58.

(3-Amino-4,6-dimethyl-5-pentylthieno[2,3-*b*]pyridin-2-yl)(phenyl)methanone (4e). Yield 60%, yellow crystals, mp 180–181°C. IR spectrum, ν, cm^{-1}: 3499, 3271 (N–H), 2960, 2949, 2920, 2895, 2864 (C–H), 1688 (C=O). ^{1}H NMR spectrum, δ, ppm: 0.89 t (3H, CH_3, ^3J = 6.8 Hz), 1.32–1.41 m [6H, $(CH_2)_3$], 2.55 s (3H, CH_3), 2.66–2.69 m (3H, CH_2), 2.71 s (3H, CH_3), 7.50–7.58 m (3H, *m*-H, *p*-H), 7.72 d (2H, *o*-H, ^3J = 7.8 Hz), 8.17 br.s (2H, NH_2). ^{13}C NMR spectrum (DEPTQ), δ_C, ppm: 14.0 (CH_3), 15.7 (CH_3), 21.9 (CH_2), 23.5 (CH_3), 27.9 (CH_2), 28.7 (CH_2), 31.5 (CH_2), 102.6 (C^2), 122.2 (C^{3a}), 127.3 (CH_{arom}), 128.4 (CH_{arom}), 131.0 (CH_{arom}), 131.1 (C^5), 141.1 ($C^{1'}$), 143.8, 153.3, 158.8, 159.8, 189.0 (C=O). Mass spectrum: *m*/*z*: 353.1684 [*M* + H]$^+$; calculated for $C_{21}H_{25}N_2OS$: 353.1692.

(3-Amino-4,6-dimethyl-5-pentylthieno[2,3-*b*]pyridin-2-yl)(4-bromophenyl)methanone (4f). Yield 54%, yellow–orange finely crystalline powder, mp 163–164°C. IR spectrum, ν, cm^{-1}: 3495, 3292 (N–H), 2954, 2926, 2870 (C–H), 1682 (C=O). ^{1}H NMR spectrum, δ, ppm: 0.89 t (3H, CH_3, ^3J = 6.8 Hz), 1.32–1.44 m [6H, $(CH_2)_3$], 2.55 s (3H, CH_3), 2.66–2.75 m (5H, CH_2, CH_3), 7.67 d (2H, *m*-H, ^3J = 7.8 Hz), 7.72 d (2H, *o*-H, ^3J = 7.8 Hz), 8.22 br.s (2H, NH_2). ^{13}C NMR spectrum (DEPTQ), δ_C, ppm: 13.9 (CH_3), 15.7 (CH_3), 21.9 (CH_2), 23.5 (CH_3), 27.8 (CH_2), 28.7 (CH_2), 31.5 (CH_2), 102.2 (C^2), 122.1 (C^{3a}), 124.5 ($C^{4'}$), 129.4 (CH_{arom}), 131.2 (C^5), 131.5 (CH_{arom}), 140.0 ($C^{1'}$), 143.9, 153.6, 158.8, 160.0, 187.6 (C=O). Found, %: C 58.45; H 5.50; N 6.44. $C_{21}H_{23}BrN_2OS$. Calculated, %: C 58.47; H 5.37; N 6.49.

2-[(3-Cyano-4,6-dimethyl-5-pentylpyridin-2-yl)-sulfanyl]-*N*-(4-methylphenyl)acetamide (5). Yield 96%, beige powder. IR spectrum, ν, cm^{-1}: 3280, 3254, 3194, 3122 (N–H), 2957, 2914, 2868, 2845 (C–H), 2216 (C≡N), 1660 (C=O). ^{1}H NMR spectrum, δ, ppm: 0.86 t (3H, CH_3, ^3J = 6.7 Hz), 1.30–1.40 m [6H, $(CH_2)_3$], 2.23 s (3H, 4′-CH_3), 2.41 s (3H, CH_3), 2.45 s (3H, CH_3), 2.52–2.56 m (2H, CH_2), 4.10 s (2H, SCH_2), 7.09 d (2H, H_{arom}, ^3J = 8.2 Hz), 7.44 d (2H, H_{arom}, ^3J = 8.2 Hz), 10.18 br.s (2H, NH). ^{13}C NMR spectrum (DEPTQ), δ_C, ppm: 13.9 (CH_3), 17.5 (4-CH_3), 20.5 (4′-CH_3), 21.8 (CH_2), 22.8 (6-CH_3), 27.8 (CH_2), 27.9 (CH_2), 31.5 (CH_2), 34.7

(SCH_2), 104.7 (C^3), 115.5 (C≡N), 119.1 (C^o), 129.1 (C^m), 131.1 (C^5), 132.2 ($C^{4'}$), 136.5 ($C^{1'}$), 150.1 (C^4), 156.8 (C^2), 159.9 (C^6), 165.9 (C=O). Mass spectrum: *m*/*z*: 404.1770 $[M + Na]^+$; calculated for $C_{22}H_{27}N_3NaOS$: 404.1767.

1,3-Bis[(3-cyano-4,6-dimethyl-5-pentylpyridin-2-yl)sulfanyl]propan-2-one (7). Pyridine-2(1*H*)-thione **3**, 600 mg (2.56 mmol), was dissolved in 2 mL of DMF, 1.3 mL of 10% aqueous potassium hydroxide (*d* = 1.09 g/mL, 2.56 mmol) was added with stirring on heating, and 160 mg (1.26 mmol) of 1,3-dichloropropan-2-one and 1.3 mL of 10% KOH were added. A beige solid precipitated. Aqueous ethanol (1 : 1), 5 mL, was added to the resulting suspension, and the precipitate was filtered off, washed with water, recrystallized from DMF, and dried at 60°C. Yield 18%, beige powder, mp 110°C. IR spectrum, ν, cm^{-1}: 2957, 2920, 2872, 2856 (C–H), 2220 (C≡N), 1740 (C=O), 1548 (C=C). ^{1}H NMR spectrum, δ, ppm: 0.86 t (6H, CH_3, ^3J = 6.7 Hz), 1.30–1.37 m [12H, $(CH_2)_3$], 2.40 s (6H, CH_3), 2.43 s (6H, CH_3), 2.52–2.55 m (4H, CH_2), 4.37 s (4H, SCH_2). ^{13}C NMR spectrum (DEPTQ), δ_C, ppm: 13.9 (CH_3), 17.5 (4-CH_3), 21.8 (CH_2), 22.6 (6-CH_3), 27.8 (CH_2), 27.9 (CH_2), 31.4 (CH_2), 38.7 (SCH_2), 104.8 (C^3), 115.4 (C≡N), 131.2 (C^5), 150.2 (C^4), 156.0 (C^2), 159.9 (C^6), 198.6 (C=O). Mass spectrum: *m*/*z*: 545.2372 $[M + Na]^+$; calculated for $C_{29}H_{38}N_4NaOS_2$: 545.2379.

7,9-Dimethyl-8-pentyl-2-mercapto-2-thioxo-2,3-dihydropyrido[3′,2′:4,5]thieno[3,2-*d*]-[1,3,2λ^5]diazaphosphinin-4(1*H*)-one (8). Crystalline 3-amino-4,6-dimethyl-5-pentylthieno[2,3-*b*]pyridine-2-carboxamide (**4a**), 300 mg (1.03 mmol), was ground in a porcelain mortar to obtain a fine powder which was dissolved on heating in 4 mL of anhydrous pyridine. Diphosphorus decasulfide, 114 mg (0.257 mmol), was added in one portion to the resulting solution, and the mixture was refluxed for 1 h (TLC monitoring). The mixture was cooled, poured into 15 mL of cold ethanol, carefully acidified with aqueous HCl to pH 3, and stirred for 3 h. The yellow solid was filtered off and washed with ethanol and petroleum ether. Yield 65%, yellow powder, mp 218–220°C. IR spectrum, ν, cm^{-1}: 3396, 3325, 3256, 3211 (N–H), 2951, 2924, 2866, 2852 (C–H), 1661 (C=O). ^{1}H NMR spectrum, δ, ppm: 0.88 t (3H, CH_3, ^3J = 6.8 Hz), 1.31–1.44 m [6H, $(CH_2)_3$], 2.63 s (3H, CH_3), 2.67–2.71 m (2H, CH_2), 2.75 s (3H, CH_3), 7.20–7.32 br.s (1H, NH, partially H–D exchangeable); no SH and C(O)NH signals were observed; presumably, because of H–D exchange. ^{13}C NMR spectrum (DEPTQ), δ_C, ppm: 13.9 (CH_3), 15.7 (CH_3), 21.5 (CH_3), 21.9 (CH_2), 27.7 (CH_2), 28.4 (CH_2), 31.4 (CH_2), 98.4 (C^{4a}), 125.3 (C^{9a}), 131.7 (S^8), 147.9 (C^{9b}), 155.5 (C^9), 157.6 (C^7), 167.0 (C=O). Found, %: C 48.70; H 5.58; N 11.40. $C_{15}H_{20}N_3PS_3$. Calculated, %: C 48.76; H 5.46; N 11.37.

X-Ray analysis of a single crystal of compound **4c** ($C_{15}H_{19}N_3S$) was performed on an Agilent SuperNova automated four-circle diffractometer (Dual, Cu at zero, Atlas S2 CCD detector) at 100.00(10) K. The structure was solved by the direct method implemented in Olex2 [46] and ShelXD [47] and was refined against F^2 by the full-matrix least-squares method in anisotropic approximation for non-hydrogen atoms using SHELXL [48]. Triclinic crystal system, space group *P*-1, *M* 273.39; unit cell parameters: *a* = 7.7903(2), *b* = 12.1422(3), *c* = 15.2460(4) Å; α = 95.790(2)°, β = 92.145(2)°, γ = 102.757(2)°; *V* = 1396.71(6) Å^3; *Z* = 4; d_{calc} 1.300 g/cm^3; μ(Cu K_α) = 1.962 mm^{-1}; *F*(000) = 584.0; 7.512° ≤ θ ≤ 152.492°; –9 ≤ *h* ≤ 9, –15 ≤ *k* ≤ 14, –19 ≤ *l* ≤ 19. Total of 28 431 reflection intensities were measured, including 5803 independent reflections (R_{int} = 0.0399, R_σ = 0.0242) and 5803 reflections with $I > 2\sigma(I)$; number of variables 365; final divergence factors: R_1 = 0.0350, wR_2 = 0.0963 for reflections with $I > 2\sigma(I)$; R_1 = 0.0373, wR_2 = 0.0985 for all independent reflections; goodness of fit with respect to F^2 1.053; $\Delta\rho_{max}/\Delta\rho_{min}$ = 0.32/–0.31 *e* Å^{-3}. The X-ray diffraction data for compound **4c** were deposited to the Cambridge Crystallographic Data Centre (CCDC entry no. 1 900 576).

A single crystal of **5** ($C_{22}H_{27}N_3OS$) for X-ray analysis was obtained by recrystallization from DMSO; the X-ray diffraction data were obtained using the same instrument as for compound **4c** at 99.98(15) K. The structure was solved by the direct method implemented in Olex2 [47] and ShelXD [48] and was refined against F^2 by the full-matrix least-squares method in anisotropic approximation for non-hydrogen atoms using SHELXL [49]. Monoclinic crystal system, space group $P2_1/n$, *M* 381.52; unit cell parameters: *a* = 9.1298(2), *b* = 19.3640(3), *c* = 23.3341(4); β = 95.378(2)°; *V* = 4107.06(13) Å^3; *Z* = 8; d_{calc} = 1.234 g/cm^3; μ(Cu K_α) = 1.517 mm^{-1}; *F*(000) = 1632.0, 7.61 ≤ θ ≤ 136.498°; –10 ≤ *h* ≤ 9, –23 ≤ *k* ≤ 23, –28 ≤ *l* ≤ 28. Total of 117 536 reflection intensities were measured, including 7284 independent reflections (R_{int} = 0.1391, R_σ = 0.0411) and 7284 reflections with $I > 2\sigma(I)$; number of variables 499; final divergence factors: R_1 = 0.0732, wR_2 = 0.1906 for reflections with $I > 2\sigma(I)$; R_1 = 0.0857, wR_2 = 0.2041 for all independent reflections;

goodness of fit 1.027 (with respect to F^2); $\Delta\rho_{max}/\Delta\rho_{min}$ = 1.09/–0.44 *e* Å^{-3}. The X-ray diffraction data for compound **5** were deposited to the Cambridge Crystallographic Data Centre (CCDC entry no. 1 900 583).

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CONFLICT OF INTERESTS

No conflict of interest was declared by the authors.

REFERENCES

1. Litvinov, V.P., Rodinovskaya, L.A., Sharanin, Yu.A., Shestopalov, A.M., and Senning, A., *J. Sulfur Chem*., 1992, vol. 13, no. 1, p. 1. doi 10.1080/01961779208048951
2. Litvinov, V.P., *Phosphorus, Sulfur Silicon Relat. Elem*., 1993, vol. 74, no. 1, p. 139. doi 10.1080/10426509308038105
3. Litvinov, V.P., *Russ. Chem. Bull*., 1998, vol. 47, no. 11, p. 2053. doi https://doi.org/10.1007/BF02494257
4. Litvinov, V.P., Krivokolysko, S.G., and Dyachenko, V.D., *Chem. Heterocycl. Compd*., 1999, vol. 35, no. 5, p. 509. doi 10.1007/BF02324634
5. Litvinov, V.P., *Russ. Chem. Rev*., 2006, vol. 75, no. 7, p. 577. doi 10.1070/RC2006v075n07ABEH003619
6. Bakhite, E.A.-G., *Phosphorus, Sulfur Silicon Relat. Elem*., 2003, vol. 178, p. 929. doi 10.1080/10426500390208820
7. Litvinov, V.P., Dotsenko, V.V., and Krivokolysko, S.G., *Russ. Chem. Bull., Int. Ed*., 2005, vol. 54, no. 4, p. 864. doi 10.1007/s11172-005-0333-1
8. Litvinov, V.P., Dotsenko, V.V., and Krivokolysko, S.G., *Adv. Heterocycl. Chem*., 2007, vol. 93, p. 117. doi 10.1016/S0065-2725(06)93003-7
9. Litvinov, V.P., Dotsenko, V.V., and Krivokolysko, S.G., *Khimiya tienopiridinov i rodstvennykh sistem* (Chemistry of Thienopyridines and Related Systems), Moscow: Nauka, 2006, p. 6.
10. El-Sayed, H.A., *J. Iran. Chem. Soc*., 2014, vol. 11, no. 1, p. 131. doi 10.1007/s13738-013-0283-8
11. Eurtivong, C., Semenov, V., Semenova, M., Konyushkin, L., Atamanenko, O., Reynisson, J., and Kiselyov, A., *Bioorg. Med. Chem*., 2017, vol. 25, no. 2, p. 658. doi 10.1016/j.bmc.2016.11.041
12. Krauze, A., Grinberga, S., Krasnova, L., Adlere, I., Sokolova, E., Domracheva, I., Shestakova, I., Andzans, Z., and Duburs, G., *Bioorg. Med. Chem*., 2014, vol. 22, p. 5860. doi 10.1016/j.bmc.2014.09.023
13. Wang, N.Y., Zuo, W.Q., Xu, Y., Gao, C., Zeng, X.X., Zhang, L.D., You, X.Y,, Peng, C.T., Shen, Y., Yang, S.Y., and Wei, Y.Q., *Bioorg. Med. Chem. Lett*., 2014, vol. 24, no. 6, p. 1581. doi 10.1016/j.bmcl.2014.01.075
14. Dotsenko, V.V., Krivokolysko, S.G., Krivokolysko, B.S., and Frolov, K.A., *Russ. J. Gen. Chem*., 2018, vol. 88, no. 4, p. 682. doi 10.1134/S1070363218040114
15. Dotsenko, V.V., Krivokolysko, S.G., and Litvinov, V.P., *Mendeleev Commun*., 2003, vol. 13, no. 6, p. 267. doi 10.1070/MC2003v013n06ABEH001851
16. Dotsenko, V.V., Krivokolysko, S.G., and Litvinov, V.P., *Mendeleev Commun*., 2004, vol. 14, no. 1, p. 30. doi 10.1070/MC2004v014n01ABEH001882
17. Dotsenko, V.V., Krivokolysko, S.G., Chernega, A.N., and Litvinov, V.P., *Russ. Chem. Bull., Int. Ed*., 2002, vol. 51, no. 8, p. 1556. doi 10.1023/A:1020939712830
18. Dotsenko, V.V., Krivokolysko, S.G., Litvinov, V.P., and Chernega, A.N., *Russ. Chem. Bull., Int. Ed*., 2002, vol. 51, no. 2, p. 362. doi 10.1023/A:1015436500899
19. Dotsenko, V.V., Chigorina, E.A., and Krivokolysko, S.G., *Chem. Heterocycl. Compd*., 2017, vol. 53, no. 5, p. 626. doi 10.1007/s10593-017-2103-z
20. Dotsenko, V.V., Krivokolysko, S.G., and Litvinov, V.P., *Monatsh. Chem*., 2008, vol. 139, no. 3, p. 271. doi 10.1007/s00706-007-0784-1
21. Litvinov, V.P., *Russ. Chem. Rev*., 1999, vol. 68, no. 9, p. 737. doi 10.1070/RC1999v068n09ABEH000533
22. Dyachenko, V.D., Dyachenko, I.V., and Nenajdenko, V.G., *Russ. Chem. Rev*., 2018, vol. 87, no. 1, p. 1. doi 10.1070/RCR4760
23. Elgemeie, G.E.H., Ali, H.A., and Eid, M.M., *J. Chem. Res., Synop*., 1993, no. 7, p 256.
24. Wagner, G., Vieweg, H., Leistner, S., Böhm, N., Krasselt, U., Hanfeld, V., Prantz, J., and Grupe, R., *Pharmazie*, 1990, vol. 45, p. 102.
25. Frolova, N.G., Zav'yalova, V.K., and Litvinov, V.P., *Russ. Chem. Bull*., 1996, vol. 45, no. 11, p. 2578. doi 10.1007/BF01431119
26. Reichelt, C., Ludwig, A., Schulze, A., Daghish, M., and Leistner, S., WO Patent no. 2006 010 568, 2006.

27. Shuttleworth, S.J., Quimpere, M., Lee, N., and DeLuca, J., *Mol. Diversity*, 1998, vol. 4, no. 3, p. 183. doi 10.1023/A:1009633311699
28. Sander, T., OSIRIS Property Explorer. http://www.organic-chemistry.org/prog/peo/
29. Lipinski, C.A., Lombardo, F., Dominy, B.W., and Feeney, P.J., *Adv. Drug. Delivery Rev*., 1997, vol. 23, nos. 1–3, p. 4. doi 10.1016/S0169-409X(96)00423-1
30. Lipinski, C.A., *Drug Discovery Today: Technol*., 2004, vol. 1, no. 4, p. 337. doi 10.1016/j.ddtec.2004.11.007
31. Lipinski, C.A., Lombardo, F., Dominy, B.W., and Feeney, P.J., *Adv. Drug Delivery Rev*., 2012, vol. 64, suppl., p. 4. doi 10.1016/j.addr.2012.09.019
32. Leistner, S. and Dumke, S., *Arch. Pharm*., 1993, vol. 326, no. 12, p. 959. doi 10.1002/ardp.19933261209
33. Red'kin, V.M., Stroganova, T.A., Vasilin, V.K., and Krapivin, G.D., *Chem. Heterocycl. Compd*., 2012, vol. 48, no. 11, p. 1701. doi 10.1007/s10593-013-1196-2
34. Dotsenko, V.V. and Krivokolysko, S.G., *Chem. Heterocycl. Compd*., 2012, vol. 48, no. 12, p. 1863. doi 10.1007/s10593-013-1220-6
35. Frank, E. and Wölfling, J., *Curr. Org. Chem*., 2007, vol. 11, no. 18, p. 1610. doi 10.2174/138527207783221228
36. Gholivand, K., Ghaziani, F., Shariatinia, Z., Dorosti, N., Mirshahi, M., and Sarikhani, S., *Med. Chem. Res*., 2012, vol. 21, no. 9, p. 2185. doi 10.1007/s00044-011-9737-7
37. Huang, J. and Chen, R., *Heteroatom Chem*., 2001, vol. 12, no. 2, p. 97. doi 10.1002/hc.6
38. Nilov, D.B., Solov'eva, N.P., Nikolaeva, I.S., Peters, V.V., Krylova, L.Yu., Gus'kova, T.A., and Granik, V.G., *Pharm. Chem. J*., 1998, vol. 32, no. 7, p. 358. doi 10.1007/BF02645992
39. Bull, E.O.J. and Naidu, M.S.R., *Phosphorus, Sulfur Silicon Relat. Elem*., 2000, vol. 162, no. 1, p. 231. doi 10.1080/10426500008045223
40. Cheng, F., Li, W., Zhou, Y., Shen, J., Wu, Z., Liu, G., Lee, P.W., and Tang, Y., *J. Chem. Inf. Model*., 2012, vol. 52, no. 11, p. 3099. doi 10.1021/ci300367a
41. PASS Online. Laboratory for Structure-Function Based Drug Design, Institute of Biomedical Chemistry (IBMC), Moscow, Russia. http://www.pharmaexpert.ru/passonline/predict.php.
42. Molinspiration Property Calculation Service. Molinspiration Cheminformatics, Slovak Republic, 2002. www.molinspiration.com
43. Chico, L.K., Van Eldik, L.J., and Watterson, D.M., *Nat. Rev. Drug Discovery*, 2009, vol. 8, no. 11, p. 892. doi 10.1038/nrd2999
44. Dotsenko, V.V., Krivokolysko, S.G., Polovinko, V.V., and Litvinov, V.P., *Chem. Heterocycl. Compd*., 2012, vol. 48, no. 2, p. 309. doi 10.1007/s10593-012-0991-5
45. Odo, N., Otsuka K., and Maruyama, T., JPN Patent no. 60-146 873, 1984; *Ref. Zh., Khim*., 1986, no. 12 O 97 P.
46. Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K., and Puschmann, H., *J. Appl. Crystallogr*., 2009, vol. 42, p. 339. doi 10.1107/S0021889808042726
47. Sheldrick, G.M., *Acta Crystallogr., Sect. A*, 2008, vol. 64, p. 112. doi 10.1107/S0108767307043930
48. Sheldrick, G.M., *Acta Crystallogr., Sect. C*, 2015, vol. 71, p. 3. doi 10.1107/S2053229614024218