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Synthesis and Neurotropic Activity of the Derivatives of Fused Triazolo[4,3-*c*]- and Triazolo[1,5-*c*]pyrimidines

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Abstract—The methods for preparation of fused triazolo[4,3-*c*]- and triazolo[1,5-*c*]pyrimidines were developed. The Dimroth rearrangement of these systems was studied. Pharmacological investigation of the synthesized compounds was conducted in known tests, such as antagonism with subcutaneous administration of corazole and the open-field test. The rotating rod method was used to assess the neurotoxicity. Neurotropic properties were found in many derivatives of triazolopyrimidine. They, like diazepam, prevent the occurrence of clonic twitching and corazole-induced clonic convulsions in animals. All selected compounds as well as diazepam exhibit an anxiolytic effect.

Keywords: triazolo[4,3-*c*]- and triazolo[1,5-*c*]pyrimidines, Dimroth rearrangement, neurotropic activity, anticonvulsant effect

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INTRODUCTION

Epilepsy is one of the most common diseases of the human brain, which affects more than 60 million people worldwide [1, 2]. Today, in the arsenal of neurologists there are a great number of antiepileptic drugs. The correct choice of drug can control seizures in 70–80% of patients, thereby ensuring an improvement in their quality of life. With the correct selection of anticonvulsants, most patients can be relieved of epileptic fits. However, do not forget that epilepsy is multifaceted, and each form requires special correction. Characterizing the current trend of creating a new generation of antiepileptic drugs, it should be noted that such drugs should have a wide spectrum of action, be effective both in generalized and localized seizures, not to cause unwanted side effects such as drowsiness, and reduced concentration of attention; in clinical conditions, to ensure a transition from polytherapy to monotherapy accompanied by fewer adverse effects. In addition, an antiepileptic drug should possess a general nonspecific balanced sedative-activating effect, prevent focal neurological symptoms, alleviate emotional stress, and prevent mood swings in bipolar disorders of manic-depressive states.

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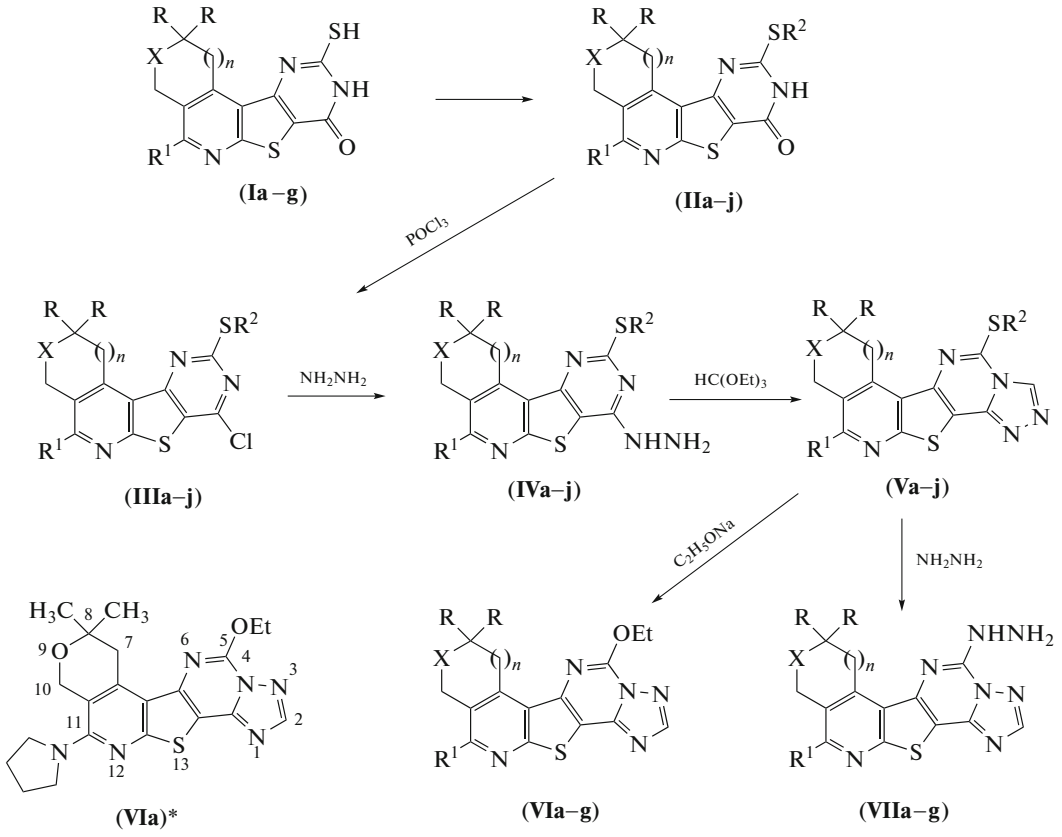
Many fused compounds with a pyrimidine fragment possess biological activities [3–5]. Derivatives of triazolopyrimidines exhibit a diverse biological effect: antitumor [5, 6], antimicrobial [7–9], anti-inflammatory [10], and anticonvulsant [11, 12].

As a continuation of studies on the synthesis and biological activity of triazolopyrimidines [13, 14], in the present work we synthesized the functionally substituted triazolo[4,3-*c*]- and triazolo[1,5-*c*]pyrimidines, studied the Dimroth rearrangement in these systems, and examined their neurotropic properties.

RESULTS AND DISCUSSION

10-Thioxo-thieno[3,2-*d*]pyrimidin-8-ones (**Ia–g**) (we described their synthesis earlier [15, 16]) were used as starting compounds for the synthesis of triazolopyrimidines (**V**)–(**VII**). The 10-thioalkyl derivatives (**IIa–j**) were obtained by the reaction of compounds (**I**) with methyl iodide and benzyl chloride (see Scheme 1) and then converted to 10-thioalkyl-8-chlorothieno[3,2-*d*]pyrimidines (**IIIa–j**) in the reaction with phosphorus oxychloride. Further, 8-hydrazino derivatives (**IVa–j**) were obtained by the reaction of compounds (**IIIa–j**) with hydrazine hydrate.



(Ia–g) (IIa–j) (IIIa–j) (IVa–j) (Va–j) (VIa)* (VIa–g) (VIIa–g)

(II–V)

(**a**) X = O, *n* = 1, R = CH_3, R^1 = pyrrolidin-1-yl, R^2 = CH_3
(**b**) X = O, *n* = 1, R = CH_3, R^1 = piperidin-1-yl, R^2 = CH_3
(**c**) X = O, *n* = 1, R = CH_3, R^1 = morpholin-4-yl, R^2 = CH_3
(**d**) X = CH_2, *n* = 1, R = H, R^1 = pyrrolidin-1-yl, R^2 = CH_3
(**e**) X = CH_2, *n* = 1, R = H, R^1 = piperidin-1-yl, R^2 = CH_3
(**f**) X = CH_2, *n* = 1, R = H, R^1 = morpholin-4-yl, R^2 = CH_3
(**g**) X = CH_2, *n* = 0, R = H, R^1 = morpholin-4-yl, R^2 = CH_3
(**h**) X = O, *n* = 1, R = CH_3, R^1 = morpholin-4-yl, R^2 = $CH_2C_6H_5$
(**i**) X = CH_2, *n* = 1, R = H, R^1 = morpholin-4-yl, R^2 = $CH_2C_6H_5$
(**j**) X = O, *n* = 1, R = CH_3, R^1 = piperidin-1-yl, R^2 = $CH_2C_6H_5$

(I, VI, VII)

(**a**) X = O, *n* = 1, R = CH_3, R^1 = pyrrolidin-1-yl
(**b**) X = O, *n* = 1, R = CH_3, R^1 = piperidin-1-yl
(**c**) X = O, *n* = 1, R = CH_3, R^1 = morpholin-4-yl
(**d**) X = CH_2, *n* = 1, R = H, R^1 = pyrrolidin-1-yl
(**e**) X = CH_2, *n* = 1, R = H, R^1 = piperidin-1-yl
(**f**) X = CH_2, *n* = 1, R = H, R^1 = morpholin-4-yl
(**g**) X = CH_2, *n* = 0, R = H, R^1 = morpholin-4-yl

* Numbering of the atoms in compound (VIa).

Scheme 1.

We have previously shown that treatment of the hydrazino derivatives that do not contain substituents at position 5 with orthoformic ester leads to triazolo[4,3-*c*]pyrimidines; and with formic acid, to triazolo[1,5-*c*]pyrimidines [13, 14]. In this work, where the *S*-methyl and *S*-benzyl substituents are located at position 5, triazolo[4,3-*c*]pyrimidines (**Va–j**) were isolated in both reactions. This is indicated by the singlets of the triazole protons at δ 9.07–9.47 ppm, which is characteristic of triazolo[4,3-*c*]pyrimidines [13, 14].

Triazolo[1,5-*c*]pyrimidines (**VI**) and (**VII**) were synthesized using the Dimroth rearrangement under conditions of basic catalysis. We chose sodium ethoxide and hydrazine hydrate as bases. Triazolo[1,5-*c*]pyrimidines (**VIa–g**) and (**VIIa–g**) were obtained by the reaction of triazolo[4,3-*c*]pyrimidines (**Va–j**) with sodium ethoxide and hydrazine hydrate. In the ^{1}H NMR spectra, the singlet signals of CH-groups in the triazole ring were at δ 8.28–8.58 ppm. In addition, the substitution of *S*-alkyl groups with ethoxy and hydrazino groups proceeds under the reaction condi-

Table 1. Comparative anticorazole activity of compounds **(Vc)**, **(VIa–d, g)**, **(VIIa, b, d, f)**, and diazepam

Compound	Antagonism to corazole* (ED_{50}, mg/kg)
(Vc)	55.0 (39.2–77.0)
(VIa)	56.0 (43–72.8)
(VIb)	38.0 (29.2–49.4)
(VIc)	35.0 (28.0–43.75)
(VId)	40.0 (26.7–60.0)
(VIg)	50.0 (39.0–64.0)
(VIIa)	44.3 (35.44–55.38)
(VIIb)	34.0 (27.86–41.48)
(VIId)	53.0 (36.6–76.85)
(VIIf)	30.0 (21.4–42.0)
Diazepam	0.51 (0.39–0.69)

* Confidence intervals at a probability level $P = 0.05$.

tions, respectively. The mechanism of the Dimroth rearrangement was described in [17]; however, in our case, the *S*-alkyl groups instead of the base residues were leaving groups.

Neurotropic Activity

Neurotropic activity of the novel synthesized triazolopyrimidine derivatives was studied by indicators characterizing the anticonvulsant, sedative, anti-anxiety activities, and side effects. A study of 24 compounds **(V)**–**(VII)** and a reference drug diazepam was carried out in 325 white mice weighing 18–24 g and 50 male Wistar rats weighing 120–140 g.

In the study of anticonvulsant action, it was found that not all synthesized derivatives have the same anticorazole activity. Thus, compounds **(Vf, g)**, **(VIe, f)**, and **(VIIc, g)** at a dose of 50 mg/kg prevented convulsions only in 20–40% of animals, whereas compounds **(Vc)**, **(VIa–d, g)**, and **(VIIa, b, d, f)** exhibited a pronounced anticonvulsant effect: administration of these compounds starting from a dose of 25 mg/kg was accompanied by prevention of corazole seizures in mice, and ED_{50} in these animals varied from 30 to 56 mg/kg (Table 1). At these doses, coordination of movements in mice was not violated, the muscle relaxation phenomena were not observed. The most efficient compounds **(VIc, d)** and **(VIIb, f)** were investigated in the open-field model. The diazepam effective dose (ED_{50}) by anticorazole action in mice was 0.5 mg/kg (Table 1). However, diazepam already at a dose of 2 mg/kg caused central miorelaxation in mice.

In the open-field behavioral model, the number of horizontal movements was 22.8; vertical movements, 5.4; and the number of examined chambers, 1.8 in rats of the control group (Table 2). Compounds under investigation caused some changes of the behavior indicators compared to the control: a tendency to inhibition of horizontal movements (up to 14.4) of animals was observed when compound **(VId)** was injected; and other compounds did not lead to any changes in the number of both horizontal and vertical movements. However, all selected compounds increased the number of examined cells, which may be due to the manifestation of some anxiolytic activity of the compounds (Table 2). Diazepam (2 mg/kg) caused a significant increase in all the studied indicators as compared to the control, i.e., it exhibited an activating and antianxiety effect.

CONCLUSION

Thus, novel derivatives of fused triazolo[4,3-*c*]- and triazolo[1,5-*c*]pyrimidines were synthesized. The study of the Dimroth rearrangement in these systems in a basic medium showed that recyclization is accompanied by nucleophilic substitution in the pyrimidine ring. While studying the neurotropic properties of triazolopyrimidine derivatives it was found that many representatives of this series possess an anticonvulsant anticorazole effect that was not previously described. In contrast to the tranquilizer diazepam, the compounds at anticonvulsant doses did not exhibit central myorelaxant activity. With the exception of compound **(VId)** exhibiting some sedative effect, other compounds did not cause any sedative-activating effects. The behav-

Table 2. The effect of compounds **(VIc, d)**, **(VIIb, f)**, and diazepam in the open-field test

Compound	Number of (in absolute values for 5 min)*		
	horizontal movements	vertical movements	examined chambers
Control (emulsifier)	22.8 ± 3.1	5.4 ± 1.9	1.8 ± 0.3
(VIc)	20.8 ± 4.7	4.2 ± 1.2	3.2 ± 0.8
(VId)	14.4 ± 4.5	5.0 ± 2.2	3.5 ± 1.1
(VIIb)	22.5 ± 4.5	5.1 ± 2.1	4.0 ± 2.1
(VIIf)	26.8 ± 4.9	5.6 ± 1.5	3.8 ± 1.2
Diazepam	33.6 ± 3.2	8.3 ± 1.1	5.0 ± 1.3

* $P \le 0.05$.

ior-activating effect was detected in diazepam at a dose of 2 mg/kg in the open-field model. All selected compounds, like diazepam, possessed anxiolytic activity in the open-field test.

EXPERIMENTAL

In this work, we used the commercially available reagents purchased from Fluka (Germany) and Sigma-Aldrich (United States). The solvents were purified according to standard procedures. The melting points were determined on a Boetius microheater. Elemental analysis was performed on a Euro EA 3000 Elemental Analyzer (Germany). The IR spectra were recorded on a Nicolet Avatar 330 FT-IR spectrometer (United States) in mineral oil. The ^{1}H and ^{13}C NMR spectra (δ, ppm; *J*, Hz) were measured on a Mercury Vx 300 instrument (United States) at an operating frequency of 300 and 75.462 MHz, respectively, in DMSO-d_6 with tetramethylsilane as internal standard. The mass spectra were recorded on a MX-1320 instrument with a system of direct input of the sample in the ion source.

Synthesis of compounds (**Ia–g**), (**IIa–i**), and (**IIIa–i**) and their properties were described earlier [15, 16].

10-Benzylthio-2,2-dimethyl-5-piperidin-1-yl-1,4-dihydro-2*H*-pyrano[4'',3'':4',5']-pyrido[3',2':4,5]-thieno[3,2-*d*]pyrimidin-8(9*H*)-on (IIj). DMF (50 mL) and compound (**Ib**) (4.03 g, 0.01 mol) were added to a solution of potassium hydroxide (0.56 g, 0.01 mol) in water (5 mL). A solution of benzyl chloride (1.27 g, 0.01 mol) in ethanol (30 mL) was gradually added to the reaction mixture at 10°C. The reaction mixture was stirred at room temperature for 5 h. Then water (50 mL) and ethanol (50 mL) were added to the reaction mixture. The precipitate was filtered off and recrystallized from an EtOH–DMF mixture (2 : 1). Yield 91%, mp 281–282°C. Found, %: C 66.45, H 5.82, N 11.32, S 12.95. $C_{26}H_{28}N_4O_2S_2$. Calculated, %: C 63.39, H 5.79, N 11.37, S 13.02. IR (ν, cm^{-1}): 1658 (CO), 3408 (NH). ^{1}H NMR: 1.19 (s, 6 H, C(*CH*$_3$)$_2$), 1.63–1.77 (m, 6 H, 5-(*CH*$_2$)$_3$), 3.13–3.19 (m, 4 H, 5-N(*CH*$_2$)$_2$), 3.34 (s, 2 H, 1-C*H*$_2$), 4.52 (s, 2 H, SC*H*$_2$), 4.61 (s, 2 H, 4-C*H*$_2$), 7.19–7.32 (m, 3 H, 3*CH*), 7.39–7.43 (m, 2 H, 2*CH*), 12.84 (br, 1 H, N*H*).

10-Benzylthio-8-chloro-2,2-dimethyl-5-piperidin-1-yl-1,4-dihydro-2*H*-pyrano-[4'',3'':4',5']pyrido[3',2':4,5]-thieno[3,2-*d*]pyrimidine (IIIj). A mixture of compound (**IIj**) (4.93 g, 0.01 mol), phosphorus oxychloride (50 mL), and pyridine (2.5 mL) was refluxed for 2 h. An excess of phosphorus oxychloride was distilled off; ice water (100 mL) was added to the residue; and the reaction mixture was neutralized with aqueous ammonia. The precipitate was filtered off, washed with water, and recrystallized from a $CHCl_3$–EtOH mixture (4 : 1). Yield 76%, mp 203–204°C. Found, %: C 61.15, H 5.36, N 10.89, S 12.51. $C_{26}H_{27}ClN_4OS_2$. Calculated, %: C 61.10, H 5.32, N 10.96, S 12.55. ^{1}H NMR: 1.26 (s, 6 H, C(*CH*$_3$)$_2$), 1.66–1.77 (m, 6 H, 5-(*CH*$_2$)$_3$), 3.25–3.30 (m, 4 H, 5-N(*CH*$_2$)$_2$), 3.32 (s, 2 H, 1-C*H*$_2$), 4.49 (s, 2 H, SC*H*$_2$), 4.61 (s, 2 H, 4-C*H*$_2$), 7.18–7.30 (m, 3 H, 3*CH*), 7.41–7.45 (m, 2 H, 2*CH*). ^{13}C NMR: 23.9, 25.4, 26.5, 34.7, 37.1, 39.0, 50.3, 59.1, 69.0, 117.3, 118.8, 122.7, 126.5, 127.8, 128.0, 136.7, 143.6, 152.4, 158.2, 160.6, 160.8, 166.7.

Compounds (IVa–j). General procedure. Hydrazine monohydrate (5 mL) was added to a solution of compound (**IIIa–j**) (0.01 mol) in dry isopropanol (40 mL). The reaction mixture was refluxed for 5 h. After cooling, the precipitate was filtered off, washed subsequently with water and ethanol, and recrystallized from a $CHCl_3$–EtOH mixture (3 : 1). IR (ν, cm^{-1}): 3260–3410 ($NHNH_2$).

8-Hydrazino-2,2-dimethyl-10-methylthio-5-pyrrolidin-1-yl-1,4-dihydro-2*H*-pyrano-[4'',3'':4',5']pyrido-[3',2':4,5]thieno[3,2-*d*]pyrimidine (IVa). Yield 82%, mp 266–267°C. Found, %: C 54.82, H 5.78, N 20.11, S 15.46. $C_{19}H_{24}N_6OS_2$. Calculated, %: C 54.78, H 5.81, N 20.17, S 15.40. ^{1}H NMR: 1.34 (s, 6 H, C(*CH*$_3$)$_2$), 1.93–2.01 (m, 4 H, 5-(*CH*$_2$)$_2$), 2.52 (s, 3 H, SC*H*$_3$), 3.47 (s, 2 H, 1-C*H*$_2$), 3.57–3.64 (m, 4 H, 5-N(*CH*$_2$)$_2$), 4.48 (br, 2 H, N*H*$_2$), 4.76 (s, 2 H, 4-C*H*$_2$), 8.48 (br, 1 H, N*H*).

8-Hydrazino-2,2-dimethyl-10-methylthio-5-piperidin-1-yl-1,4-dihydro-2*H*-pyrano-[4'',3'':4',5']pyrido-[3',2':4,5]thieno[3,2-*d*]pyrimidine (IVb). Yield 90%, mp 275–277°C. Found, %: C 55.85, H 6.13, N 19.45, S 14.81. $C_{20}H_{26}N_6OS_2$. Calculated, %: C 55.79, H 6.09, N 19.52, S 14.89. ^{1}H NMR: 1.33 (s, 6 H, C(*CH*$_3$)$_2$), 1.62–1.80 (m, 6 H, 5-(*CH*$_2$)$_2$), 2.53 (s, 3 H, SC*H*$_3$), 3.12–3.19 (m, 4 H, 5-N(*CH*$_2$)$_2$), 3.51 (s, 2 H, 1-C*H*$_2$), 4.51 (br, 2 H, N*H*$_2$), 4.65 (s, 2 H, 4-C*H*$_2$), 8.65 (br, 1 H, N*H*).

8-Hydrazino-2,2-dimethyl-10-methylthio-5-morpholin-4-yl-1,4-dihydro-2*H*-pyrano-[4'',3'':4',5']pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine (IVc). Yield 88%, mp 261–262°C. Found, %: C 51.81, H 5.62, N 19.37, S 14.76. $C_{19}H_{24}N_6O_2S_2$. Calculated, %: C 52.76, H 5.59, N 19.43, S 14.83. ^{1}H NMR: 1.34 (s, 6 H, C(*CH*$_3$)$_2$), 2.53 (s, 3 H, SC*H*$_3$), 3.15–3.22 (m, 4 H, 5-N(*CH*$_2$)$_2$), 3.74–3.82 (m, 4 H, 5-O(*CH*$_2$)$_2$), 3.52 (s, 2 H, 1-C*H*$_2$), 4.68 (s, 2 H, 4-C*H*$_2$), 4.45 (br, 2 H, N*H*$_2$), 8.70 (br, 1 H, N*H*).

8-Hydrazino-10-methylthio-5-pyrrolidin-1-yl-1,2,3,4-tetrahydropyrimido[4',5':4,5]-thieno[2,3-*c*]-isoquinoline (IVd). Yield 82%, mp 253–255°C. Found, %: C 55.98, H 5.80, N 21.67, S 16.52. $C_{18}H_{22}N_6S_2$. Calculated, %: C 55.93, H 5.74, N 21.74, S 16.59. ^{1}H NMR: 1.70–1.79 (m, 2 H, 3-*CH*$_2$), 1.83–1.93 (m, 2 H, 2-*CH*$_2$), 1.91–2.00 (m, 4 H, 5-(*CH*$_2$)$_2$), 2.53 (s, 3 H, SC*H*$_3$), 2.70 (br. t, 2 H, *J* 5.1, 4-C*H*$_2$), 3.56 (br. t, 2 H, *J* 6.3, 1-C*H*$_2$), 3.56–3.62 (m, 4 H, 5-N(*CH*$_2$)$_2$), 4.41 (br, 2 H, N*H*$_2$), 8.41 (br, 1 H, N*H*). MS, *m/z* (I_{rel},

%): 386 $[M]^+$ (100), 366 (16), 358 (49), 356 (78), 344 (34), 335 (55).

8-Hydrazino-10-methylthio-5-piperidin-1-yl–1,2,3,4-tetrahydropyrimido[4',5':4,5]-thieno[2,3-*c*]isoquinoline (IVe). Yield 85%, mp 269–270°C. Found, %: C 57.03, H 6.08, N 20.91, S 15.95. $C_{19}H_{24}N_6S_2$. Calculated, %: C 56.97, H 6.04, N 20.98, S 16.01. ^{1}H NMR: 1.56–1.74 (m, 8 H, 3-C***H*****$_2$**, 5-(C***H*****$_2$)$_3$**), 1.81–1.91 (m, 2 H, 2-C***H*****$_2$**), 2.52 (s, 3 H, SC***H*****$_3$**), 2.68 (br. t, 2 H, *J* 5.8, 4-C***H*****$_2$**), 3.10–3.18 (m, 4 H, 5-N(C***H*****$_2$)$_2$**), 3.54 (br. t, 2 H, *J* 6.4, 1-C***H*****$_2$**), 4.79 (br, 2 H, N***H*****$_2$**), 8.89 (br, 1 H, N***H***).

8-Hydrazino-10-methylthio-5-morpholin-4-yl-1,2,3,4-tetrahydropyrimido[4',5':4,5]-thieno[2,3-*c*]-isoquinoline (IVf). Yield 83%, mp 270–272°C. Found, %: C 53.75, H 5.58, N 20.72, S 15.84. $C_{18}H_{22}N_6OS_2$. Calculated, %: C 53.71, H 5.51, N 20.88, S 15.93. ^{1}H NMR: 1.74–1.81 (m, 2 H, 3-C***H*****$_2$**), 1.86–1.95 (m, 2 H, 2-C***H*****$_2$**), 2.53 (s, 3 H, SC***H*****$_3$**), 2.67–2.74 (m, 2 H, 4-C***H*****$_2$**), 3.16–3.24 (m, 4 H, 5-N(C***H*****$_2$)$_2$**), 3.57–3.63 (m, 2 H, 1-C***H*****$_2$**), 3.74–3.80 (m, 4 H, 5-O(C***H*****$_2$)$_2$**), 4.60 (br, 2 H, N***H*****$_2$**), 8.68 (br, 1 H, N***H***).

7-Hydrazino-9-methylthio-4-morpholin-4-yl-2,3-dihydro-1*H*-cyclopenta[4',5']pyrido-[3',2':4,5]thieno[3,2-*d*]-pyrimidine (IVg). Yield 86%, mp 271–272°C. Found, %: C 52.64, H 5.25, N 21.55, S 16.42. $C_{17}H_{20}N_6OS_2$. Calculated, %: C 52.55, H 5.19, N 21.63, S 16.51. ^{1}H NMR: 1.90–1.98 (m, 2 H, 2-C***H*****$_2$**), 2.57 (s, 3 H, SC***H*****$_3$**), 2.87–2.98 (m, 2 H, 3-C***H*****$_2$**), 3.51–3.57 (m, 2 H, 1-C***H*****$_2$**), 3.56–3.61 (m, 4 H, 4-N(C***H*****$_2$)$_2$**), 3.74–3.83 (m, 4 H, 4-O(C***H*****$_2$)$_2$**), 4.51 (s, 2 H, N***H*****$_2$**), 8.29 (s, 1 H, N***H***).

10-Benzylthio-8-hydrazino-2,2-dimethyl-5-morpholin-4-yl-1,4-dihydro-2*H*-pyrano-[4'',3'':4',5']pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine (IVh). Yield 85%, mp 247–248°C. Found, %: C 59.10, H 5.63, N 16.44, S 12.55. $C_{25}H_{28}N_6O_2S_2$. Calculated, %: C 59.03, H 5.55, N 16.52, S 12.61. ^{1}H NMR: 1.21 (s, 6 H, C(C***H*****$_3$)$_2$**), 2.96 (br, 2 H, N***H*****$_2$**), 3.16–3.22 (m, 4 H, 5-N(C***H*****$_2$)$_2$**), 3.74–3.81 (m, 4 H, 5-O(C***H*****$_2$)$_2$**), 3.43 (s, 2 H, 1-C***H*****$_2$**), 4.44 (s, 2 H, SC***H*****$_2$**), 4.65 (s, 2 H, 4-C***H*****$_2$**), 7.14–7.28 (m, 3 H, 3C***H***), 7.38–7.44 (m, 2 H, 2C***H***), 8.82 (br, 1 H, N***H***).

10-Benzylthio-8-hydrazino-5-morpholin-4-yl-1,2,3,4-tetrahydropyrimido-[4',5':4,5]-thieno[2,3-*c*]isoquinoline (IVi). Yield 87%, mp 272–273°C. Found, %: C 60.28, H 5.56, N 17.47, S 13.28. $C_{24}H_{26}N_6OS_2$. Calculated, %: C 60.22, H 5.48, N 17.56, S 13.40. ^{1}H NMR: 1.72–1.80 (m, 2 H, 3-C***H*****$_2$**), 1.87–1.98 (m, 2 H, 2-C***H*****$_2$**), 2.68–2.74 (m, 2 H, 4-C***H*****$_2$**), 3.21–3.35 (m, 4 H, 5-N(C***H*****$_2$)$_2$**), 3.48–3.56 (m, 2 H, 1-C***H*****$_2$**), 3.75–3.81 (m, 4 H, 5-O(C***H*****$_2$)$_2$**), 4.51 (s, 2 H, N***H*****$_2$**), 4.55 (s, 2 H, SC***H*****$_2$**), 7.18–7.27 (m, 3 H, 3C***H***), 7.36–7.45 (m, 2 H, 2C***H***), 8.72 (s, 1 H, N***H***).

10-Benzylthio-8-hydrazino-2,2-dimethyl-5-piperidin-1-yl-1,4-dihydro-2*H*-pyrano-[4'',3'':4',5']pyrido-[3',2':4,5]thieno[3,2-*d*]pyrimidine (IVj). Yield 64%, mp 271–272°C. Found, %: C 61.71, H 5.92, N 16.67, S 12.59. $C_{26}H_{30}N_6OS_2$. Calculated, %: C 61.63, H 5.97, N 16.59, S 12.66. ^{1}H NMR: 1.21 (s, 6 H, C(C***H*****$_3$)$_2$**), 1.63–1.77 (m, 6 H, 5-(C***H*****$_2$)$_3$**), 3.11–3.17 (m, 4 H, 5-N(C***H*****$_2$)$_2$**), 3.41 (s, 2 H, 1-C***H*****$_2$**), 4.44 (s, 2 H, SC***H*****$_2$**), 4.57 (br, 2 H, N***H*****$_2$**), 4.62 (s, 2 H, 4-C***H*****$_2$**), 7.14–7.28 (m, 3 H, 3C***H***), 7.39–7.43 (m, 2 H, 2C***H***), 8.80 (br, 1 H, N***H***).

Compounds (Va–j). General procedure. A mixture of compound **(IVa–j)** (0.01 mol) and triethyl orthoformate (50 ML) was refluxed for 15 h. The reaction mixture was cooled; the precipitate was filtered off, washed with water and recrystallized from a $CHCl_3$–EtOH mixture (2 : 1). IR (ν, cm^{-1}): 1610–1615 (C=N).

8,8-Dimethyl-5-methylthio-11-pyrrolidin-1-yl-7,10-dihydro-8*H*-pyrano[4'',3'':4',5']-pyrido[3',2':4,5]-thieno[2,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine (Va). Yield 92%, mp 269–270°C. Found, %: C 56.39, H 5.24, N 19.58, S 14.95. $C_{20}H_{22}N_6OS_2$. Calculated, %: C 56.31, H 5.20, N 19.70, S 15.03. ^{1}H NMR: 1.35 (s, 6 H, C(C***H*****$_3$)$_2$**), 1.96–2.04 (m, 4 H, 11-(C***H*****$_2$)$_2$**), 2.84 (s, 3 H, SC***H*****$_3$**), 3.34 (s, 2 H, 7-C***H*****$_2$**), 3.58–3.68 (m, 4 H, 11-N(C***H*****$_2$)$_2$**), 4.79 (s, 2 H, 10-C***H*****$_2$**), 9.07 (s, 1 H, 3-C***H***).

8,8-Dimethyl-5-methylthio-11-piperidin-1-yl-7,10-dihydro-8*H*-pyrano[4'',3'':4',5']-pyrido[3',2':4,5]-thieno[2,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine (Vb). Yield 81%, mp 312–314°C. Found, %: C 57.31, H 5.56, N 19.16, S 14.47. $C_{21}H_{24}N_6OS_2$. Calculated, %: C 57.25, H 5.49, N 19.07, S 14.56. ^{1}H NMR: 0.69 (s, 6 H, C(C***H*****$_3$)$_2$**), 1.52–1.64 (m, 6 H, 11-(C***H*****$_2$)$_3$**), 2.86 (s, 3 H, SC***H*****$_3$**), 3.02–3.08 (m, 6 H, 7-C***H*****$_2$**, 11-N(C***H*****$_2$)$_2$**), 4.45 (s, 2 H, 10-C***H*****$_2$**), 8.58 (s, 1 H, 3-C***H***).

8,8-Dimethyl-5-methylthio-11-morpholin-4-yl-7,10-dihydro-8*H*-pyrano[4',3'':4',5']-pyrido[3',2':4,5]-thieno[2,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine (Vc). Yield 85%, mp 294–295°C. Found, %: C 54.35, H 5.06, N 18.87, S 14.40. $C_{20}H_{22}N_6O_2S_2$. Calculated, %: C 54.28, H 5.01, N 18.99, S 14.49. ^{1}H NMR: 1.37 (s, 6 H, C(C***H*****$_3$)$_2$**), 3.01 (s, 3 H, SC***H*****$_3$**), 3.21 (t, 4 H, J 5.1, 11-N(C***H*****$_2$)$_2$**), 3.50 (s, 2 H, 7-C***H*****$_2$**), 3.80 (t, 4 H, *J* 4.6, 11-O(C***H*****$_2$)$_2$**), 4.71 (s, 2 H, 10-C***H*****$_2$**), 8.61 (s, 1 H, 3-C***H***).

5-Methylthio-11-pyrrolidin-1-yl-7,8,9,10-tetrahydro[1,2,4]triazolo[4'',3'':1',6']-pyrimido[4',5':4,5]-thieno[2,3-*c*]isoquinoline (Vd). Yield 89%, mp 318–320°C. Found, %: C 57.63, H 5.04, N 21.27, S 16.06. $C_{19}H_{20}N_6S_2$. Calculated, %: C 57.55, H 5.08, N 21.19, S 16.17. ^{1}H NMR: 1.73–1.82 (m, 2 H, 9-C***H*****$_2$**), 1.90–1.98 (m, 2 H, 8-C***H*****$_2$**), 2.12–2.24 (m, 4 H, 11-(C***H*****$_2$)$_2$**), 2.68–2.77 (m, 2 H, 10-C***H*****$_2$**), 2.85 (s, 3 H, SC***H*****$_3$**), 3.18–3.25 (m, 4 H, 5-N(C***H*****$_2$)$_2$**), 3.52–3.60 (m, 2 H, 7-C***H*****$_2$**), 9.28 (s, 1 H, 3-C***H***). MS, *m/z* (I_{rel}, %): 396

$[M]^+$ (24), 381 (28), 355 (48), 254 (43), 212 (34), 185 (28), 184 (100).

5-Methylthio-11-piperidin-1-yl-7,8,9,10-tetrahydro-[1,2,4]triazolo[4",3":1',6']-pyrimido[4',5':4,5]thieno-[2,3-*c*]isoquinoline (Ve). Yield 90%, mp 300–302°C. Found, %: C 58.57, H 5.46, N 20.38, S 15.51. $C_{20}H_{22}N_6S_2$. Calculated, %: C 58.51, H 5.40, N 20.47, S 15.62. ^{1}H NMR: 1.71–1.86 (m, 8 H, 9-C***H*****$_2$**, 11-(C***H*****$_2$)$_3$**), 1.90–1.97 (m, 2 H, 8-C***H*****$_2$**), 2.72–2.79 (m, 2 H, 10-C***H*****$_2$**), 2.86 (s, 3 H, SC***H*****$_3$**), 3.20–3.28 (m, 4 H, 11-N(C***H*****$_2$)$_2$**), 3.55–3.64 (m, 2 H, 7-C***H*****$_2$**), 9.23 (s, 1 H, 3-C***H***).

5-Methylthio-11-morpholin-4-yl-7,8,9,10-tetrahydro[1,2,4]triazolo[4",3":1',6']-pyrimido[4',5':4,5]-thieno[2,3-*c*]isoquinoline (Vf). Yield 81%, mp 286–288°C. Found, %: C 55.37, H 4.82, N 20.26, S 15.48. $C_{19}H_{20}N_6OS_2$. Calculated, %: C 55.32, H 4.89, N 20.37, S 15.55. ^{1}H NMR: 1.74–1.84 (m, 2 H, 9-C***H*****$_2$**), 1.91–2.00 (m, 2 H, 8-C***H*****$_2$**), 2.71–2.78 (m, 2 H, 10-C***H*****$_2$**), 2.88 (s, 3 H, SC***H*****$_3$**), 3.22–3.27 (m, 4 H, 11-N(C***H*****$_2$)$_2$**), 3.55–3.62 (m, 2 H, 7-C***H*****$_2$**), 3.77–3.83 (m, 4 H, 11-O(C***H*****$_2$)$_2$**), 9.30 (s, 1 H, 3-C***H***).

5-Methylthio-10-morpholin-4-yl-8,9-dihydro-7*H*-cyclopenta[4',5']pyrido[3',2':4,5]-thieno[2,3-*e*] [1, 2, 4]triazolo[4,3-*c*]pyrimidine (Vg). Yield 90%, mp 304–306°C. Found, %: C 54.32, H 4.58, N 20.98, S 16.01. $C_{18}H_{18}N_6OS_2$. Calculated, %: C 54.25, H 4.55, N 21.09, S 16.09. ^{1}H NMR: 2.12–2.23 (m, 2 H, 8-C***H*****$_2$**), 2.86 (s, 3 H, SC***H*****$_3$**), 2.98 (t, 2 H, *J* 7.2, 9-C***H*****$_2$**), 3.42 (t, 2 H, *J* 7.7, 7-C***H*****$_2$**), 3.48–3.55 (m, 4 H, 10-N(C***H*****$_2$)$_2$**), 3.72–3.80 (m, 2 H, 10-C***H*****$_2$**), 9.47 (s, 1 H, 3-C***H***).

5-Benzylthio-8,8-dimethyl-11-morpholin-4-yl-7,10-dihydro-8*H*-pyrano[4",3":4',5']-pyrido[3',2':4,5]thieno-[2,3-*e*] [1, 2, 4]triazolo[4,3-*c*]pyrimidine (Vh). Yiled, 83%, mp 236–237°C. Found, %: C 60.27, H 5.09, N 16.12, S 12.31. $C_{26}H_{26}N_6O_2S_2$. Calculated, %: C 60.21, H 5.05, N 16.20, S 12.37. ^{1}H NMR: 1.23 (s, 6 H, C(C***H*****$_3$)$_2$**), 3.20–3.25 (m, 4 H, 11-N(C***H*****$_2$)$_2$**), 3.40 (s, 2 H, 7-C***H*****$_2$**), 3.77–3.82 (m, 4 H, 11-O(C***H*****$_2$)$_2$**), 4.69 (s, 2 H, 10-C***H*****$_2$**), 4.80 (s, 2 H, SC***H*****$_2$**), 7.24–7.36 (m, 3 H, 3C***H***), 7.47–7.52 (m, 2 H, 2C***H***), 9.23 (s, 1 H, 3-C***H***).

5-Benzylthio-11-morpholin-4-yl-7,8,9,10-tetrahydro-[1,2,4]triazolo[4",3":1',6']-pyrimido[4',5':4,5]thieno-[2,3-*c*]isoquinoline (Vi). Yield 93%, mp 274–275°C. Found, %: C 61.52, H 4.98, N 17.28, S 12.04. $C_{25}H_{24}N_6OS_2$. Calculated, %: C 61.45, H 4.95, N 17.20, S 13.12. ^{1}H NMR: 1.73–1.93 (m, 4 H, 9-C***H*****$_2$**, 8-C***H*****$_2$**), 2.71–2.75 (m, 2 H, 10-C***H*****$_2$**), 3.22–3.27 (m, 4 H, 11-N(C***H*****$_2$)$_2$**), 3.77–3.81 (m, 4 H, 11-O(C***H*****$_2$)$_2$**), 3.46–3.52 (m, 2 H, 7-C***H*****$_2$**), 4.82 (s, 2 H, SC***H*****$_2$**), 7.25–7.37 (m, 3 H, 3C***H***), 7.46–7.52 (m, 2 H, 2C***H***), 9.20 (s, 1 H, 3-C***H***). ^{13}C NMR: 21.3, 21.7, 25.7, 26.8, 34.9, 49.7, 65.9, 122.6, 127.4, 128.3, 128.4, 134.4, 125.3, 142.1, 144.6, 144.9, 145.5, 156.1, 160.7.

5-Benzylthio-8,8-dimethyl-11-piperidin-1-yl-7,10-dihydro-8*H*-pyrano[4",3":4',5']-pyrido[3',2':4,5]-thieno[2,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine (Vj). Yield 83%, mp 239–240°C. Found, %: C 62.84, H 5.51, N 16.19, S 12.28. $C_{27}H_{28}N_6OS_2$. Calculated, %: C 62.76, H 5.46, N 16.27, S 12.41. ^{1}H NMR: 1.23 (s, 6 H, C(C***H*****$_3$)$_2$**), 1.64–1.78 (m, 6 H, 11-(C***H*****$_2$)$_3$**), 3.16–3.21 (m, 4 H, 11-N(C***H*****$_2$)$_2$**), 3.39 (s, 2 H, 7-C***H*****$_2$**), 4.66 (s, 2 H, 10-C***H*****$_2$**), 4.81 (s, 2 H, SC***H*****$_2$**), 7.24–7.36 (m, 3 H, 3C***H***), 7.47–7.51 (m, 2 H, 2C***H***), 9.20 (s, 1 H, 3-C***H***). ^{13}C NMR: 23.9, 25.5, 26.4, 34.7, 37.1, 38.7, 50.7, 59.1, 68.9, 110.8, 119.1, 119.5, 127.2, 128.0, 128.1, 128.2, 133.6, 134.8, 135.2, 137.6, 141.1, 141.9, 144.7, 145.4, 157.6, 159.2.

Compounds (VIa–g). General procedure. Compound (**Va–j**) (0.01 mol) was added to a solution of sodium ethylate obtained from sodium (0.23 g, 0.01 mol) and absolute ethanol. The reaction mixture was refluxed for 0.5 h and kept at room temperature for 12 h. The precipitate was filtered off, washed with water, dried, and recrystallized from EtOH. IR (ν, cm^{-1}): 1623–1628 (C=N).

5-Ethoxy-8,8-dimethyl-11-pyrrolidin-1-yl-7,10-dihydro-8*H*-pyrano[4",3":4',5']pyrido-[3',2':4,5]thieno-[2,3-*e*] [1, 2, 4]triazolo[1,5-*c*]pyrimidine (VIa). Yield 68%, mp 218–219°C. Found, %: C 59.48, H 5.75, N 19.71, S 7.46. $C_{21}H_{24}N_6O_2S$. Calculated, %: C 59.41, H 5.70, N 19.80, S 7.55. ^{1}H NMR: 1.37 (s, 6 H, C(C***H*****$_3$)$_2$**), 1.65 (t, 3 H, *J* 7.0, 5-C***H*****$_3$**), 1.95–2.03 (m, 4 H, 11-(C***H*****$_2$)$_2$**), 3.43 (s, 2 H, 7-C***H*****$_2$**), 3.60–3.68 (m, 4 H, 11-N(C***H*****$_2$)$_2$**), 4.79 (q, 2 H, *J* 7.0, 5-OC***H*****$_2$**), 4.80 (s, 2 H, 10-C***H*****$_2$**), 8.29 (s, 1 H, 2-C***H***).

5-Ethoxy-8,8-dimethyl-11-piperidin-1-yl-7,10-dihydro-8*H*-pyrano[4",3":4',5']pyrido-[3',2':4,5]thieno-[2,3-*e*] [1, 2, 4]triazolo[1,5-*c*]pyrimidine (VIb). Yield 70%, mp 213–214°C. Found, %: C 60.32, H 6.02, N 19.25, S 7.24. $C_{22}H_{26}N_6O_2S$. Calculated, %: C 60.25, H 5.98, N 19.16, S 7.31. ^{1}H NMR: 1.37 (s, 6 H, C(C***H*****$_3$)$_2$**), 1.66 (t, 3 H, *J* 7.1, 5-C***H*****$_3$**), 1.69–1.80 (m, 46 H, 11-(C***H*****$_2$)$_3$**), 3.18–3.23 (m, 4 H, 11-N(C***H*****$_2$)$_2$**), 3.48 (s, 2 H, 7-C***H*****$_2$**), 4.68 (s, 2 H, 10-C***H*****$_2$**), 4.81 (q, 2 H, *J* 7.1, 5-OC***H*****$_2$**), 8.35 (s, 1 H, 2-C***H***). ^{13}C NMR: 13.7, 24.0, 25.5, 26.6, 36.8, 50.7, 59.2, 65.0, 69.0, 109.5, 119.0, 119.2, 141.4, 143.7, 146.9, 149.6, 153.6, 158.6, 159.3.

5-Ethoxy-8,8-dimethyl-11-morpholin-4-yl-7,10-dihydro-8*H*-pyrano[4",3":4',5']pyrido-[3',2':4,5]thieno-[2,3-*e*] [1, 2, 4]triazolo[1,5-*c*]pyrimidine (VIc). Yield 64%, mp 245–246°C. Found, %: C 57.34, H 5.52, N 18.96, S 7.17. $C_{21}H_{24}N_6O_3S$. Calculated, %: C 57.26, H 5.49, N 19.08, S 7.28. ^{1}H NMR: 1.37 (s, 6 H, C(C***H*****$_3$)$_2$**), 1.65 (t, 3 H, *J* 7.0, 5-C***H*****$_3$**), 3.20–3.28 (m, 4 H, 11-N(C***H*****$_2$)$_2$**), 3.48 (s, 2 H, 7-C***H*****$_2$**), 3.77–3.84 (m, 4 H, 11-O(C***H*****$_2$)$_2$**), 4.70 (s, 2 H, 10-C***H*****$_2$**), 4.80 (q, 2 H, *J* 7.0, 5-OC***H*****$_2$**), 8.37 (s, 1 H, 2-C***H***). ^{13}C NMR: 13.7,

26.6, 36.9, 49.9, 59.1, 65.1, 65.9, 69.0, 109.8, 119.2, 119.5, 141.8, 143.6, 147.0, 149.6, 153.7, 158.2, 158.4.

5-Ethoxy-11-pyrrolidin-1-yl-7,8,9,10-tetrahydro-[1,2,4]triazolo[1",5":1',6']pyrimido-[4',5':4,5]thieno-[2,3-*c*]isoquinoline (VId). Yield 71%, mp 239–240°C. Found, %: C 60.97, H 5.68, N 21.18, S 8.04. $C_{20}H_{20}N_6OS$. Calculated, %: C 60.89, H 5.62, N 21.30, S 8.13. ^{1}H NMR: 1.65 (t, 3 H, *J* 7.0, 5-C***H*$_3$**), 1.72–1.82 (m, 2 H, 11-C***H*$_2$**), 1.86–1.96 (m, 2 H, 11-C***H*$_2$**), 1.96–2.04 (m, 4 H, 9-C***H*$_2$**, 8-C***H*$_2$**), 2.72 (br. t, 2 H, *J* 5.6, 10-C***H*$_2$**), 3.49 (br. t, 2 H, *J* 6.2, 7-C***H*$_2$**), 3.60–3.68 (m, 4 H, 11-N(C***H*$_2$**)$_2$), 4.78 (q, 2 H, *J* 7.1, 5-OC***H*$_2$**), 8.28 (s, 1 H, 2-C***H***).

5-Ethoxy-11-piperidin-1-ил-7,8,9,10-tetrahydro-[1,2,4]triazolo[1",5":1',6']pyrimido-[4',5':4,5]thieno-[2,3-*c*]isoquinoline (VIe). Yield 85%, mp 239–240°C. Found, %: C 61.79, H 5.88, N 20.48, S 7.76. $C_{21}H_{24}N_6OS$. Calculated, %: C 61.74, H 5.92, N 20.57, S 7.85. ^{1}H NMR: 1.65 (t, 3 H, *J* 7.1, 5-C***H*$_3$**), 1.62–1.84 (m, 8 H, 11-(C***H*$_2$**)$_3$, 9-C***H*$_2$**), 1.91–2.01 (m, 2 H, 8-C***H*$_2$**), 2.73 (br. t, 2 H, *J* 5.8, 10-C***H*$_2$**), 3.17–3.25 (m, 4 H, 11-N(C***H*$_2$**)$_2$), 3.57 (br. t, 2 H, *J* 6.5, 7-C***H*$_2$**), 4.80 (q, 2 H, *J* 7.1, 5-OC***H*$_2$**), 8.32 (s, 1 H, 2-C***H***).

5-Ethoxy-11-morpholin-4-yl-7,8,9,10-tetrahydro-[1,2,4]triazolo[1",5":1',6']pyrimido-[4',5':4,5]thieno-[2,3-*c*]isoquinoline (VIf). Yield 71%, mp 271–272°C. Found, %: C 58.59, H 5.46, N 20.35, S 7.74. $C_{20}H_{22}N_6O_2S$. Calculated, %: C 58.52, H 5.40, N 20.47, S 7.81. ^{1}H NMR: 1.65 (t, 3 H, *J* 7.0, 5-C***H*$_3$**), 1.76–1.82 (m, 2 H, 9-C***H*$_2$**), 1.92–2.02 (m, 2 H, 8-C***H*$_2$**), 2.69–2.77 (m, 2 H, 10-C***H*$_2$**), 3.20–3.30 (m, 4 H, 11-N(C***H*$_2$**)$_2$), 3.53–3.61 (m, 2 H, 7-C***H*$_2$**), 3.75–3.85 (m, 4 H, 11-O(C***H*$_2$**)$_2$), 4.80 (q, 2 H, *J* 7.0, 5-OC***H*$_2$**), 8.35 (s, 1 H, 2-C***H***).

5-Ethoxy-10-morpholin-4-yl-8,9-dihydro-7*H*-cyclopenta[4',5']pyrido[3',2':4,5]thieno-[2,3-*e*][1, 2, 4]triazolo[1,5-*c*]pyrimidine (VIg). Yield 65%, mp 273–274°C. Found, %: C 57.62, H 5.05, N 21.13, S 7.98. $C_{19}H_{20}N_6O_2S$. Calculated, %: C 57.56, H 5.08, N 21.20, S 8.09. ^{1}H NMR: 1.61 (t, 3 H, *J* 7.0, 5-C***H*$_3$**), 2.15–2.26 (m, 2 H, 8-C***H*$_2$**), 2.96 (t, 2 H, *J* 7.0, 9-C***H*$_2$**), 3.42 (t, 2 H, *J* 7.4, 8-C***H*$_2$**), 3.49–3.58 (m, 4 H, 10-N(C***H*$_2$**)$_2$), 3.73–3.83 (m, 4 H, 10-O(C***H*$_2$**)$_2$), 4.79 (q, 2 H, *J* 7.0, 5-OC***H*$_2$**), 8.41 (s, 1 H, 2-C***H***).

Compounds (VIIa–j). General procedure. A mixture of compound (**Va–j**) (0.01 mol), hydrazine monohydrate (20 mL), and DMSO (40 mL) was refluxed for 6 h. The precipitate was filtered off, washed with water, and recrystallized form DMSO.

5-Hydrazino-8,8-dimethyl-11-pyrrolidin-1-yl-7,10-dihydro-8*H*-pyrano[4",3":4',5']-pyrido[3',2':4,5]thieno-[2,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (VIIa). Yield 72%, mp 285–287°C. Found, %: C 55.65, H 5.47, N 21.19, S 7.75. $C_{19}H_{22}N_8OS$. Calculated, %: C 55.59, H 5.40, N 27.30, S 7.81. IR (ν, cm^{-1}): 1620 (C=N), 3312, 3270 (NHNH$_2$). ^{1}H NMR: 1.37 (s, 6 H, C(C***H*$_3$**)$_2$), 1.91–2.01 (m, 4 H, 11-(C***H*$_2$**)$_2$), 3.58 (s, 2 H, 7-C***H*$_2$**), 3.57–3.65 (m, 4 H, 11-N(C***H*$_2$**)$_2$), 4.62 (br, 2 H, N***H*$_2$**), 4.79 (s, 2 H, 10-C***H*$_2$**), 8.36 (s, 1 H, 2-C***H***), 8.99 (br, 1 H, N***H***).

5-Hydrazino-8,8-dimethyl-11-piperidin-1-yl-7,10-dihydro-8*H*-pyrano[4",3":4',5']-pyrido[3',2':4,5]thieno-[2,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (VIIb). Yield 85%, mp 321–323°C. Found, %: C 56.65, H 5.76, N 26.31, S 7.47. $C_{20}H_{24}N_8OS$. Calculated, %: C 56.58, H 5.70, N 26.40, S 7.55. IR (ν, cm^{-1}): 1623 (C=N), 3315, 3268 (NHNH$_2$). ^{1}H NMR: 1.34 (s, 6 H, C(C***H*$_3$**)$_2$), 1.57–1.72 (m, 6 H, 11-(C***H*$_2$**)$_3$), 3.11–3.16 (m, 4 H, 11-N(C***H*$_2$**)$_2$), 3.63 (s, 2 H, 7-C***H*$_2$**), 4.67 (s, 2 H, 10-C***H*$_2$**), 4.71 (br, 2 H, N***H*$_2$**), 8.57 (s, 1 H, 2-C***H***), 9.34 (br, 1 H, N***H***).

5-Hydrazino-8,8-dimethyl-11-morpholin-4-yl-7,10-dihydro-8*H*-pyrano[4",3":4',5']-pyrido[3',2':4,5]thieno-[2,3-*e*] [1, 2, 4]triazolo[1,5-*c*]pyrimidine (VIIc). Yield 78%, mp 299–300°C. Found, %: C 53.58, H 5.24, N 26.18, S 7.44. $C_{19}H_{22}N_8O_2S$. Calculated, %: C 53.51, H 5.20, N 26.27, S 7.52. IR (ν, cm^{-1}): 1626 (C=N), 3316, 3273 (NHNH$_2$). ^{1}H NMR: 1.35 (s, 6 H, C(C***H*$_3$**)$_2$), 3.15–3.21 (m, 4 H, 11-N(C***H*$_2$**)$_2$), 3.66 (s, 2 H, 7-C***H*$_2$**), 3.74–3.79 (m, 4 H, 11-O(C***H*$_2$**)$_2$), 4.72 (s, 2 H, 10-C***H*$_2$**), 4.74 (br, 2 H, N***H*$_2$**), 8.58 (s, 1 H, 2-C***H***), 9.35 (br, 1 H, N***H***).

5-Hydrazino-11-pyrrolidin-1-yl-7,8,9,10-tetrahydro[1,2,4]triazolo[1",5":1',6']-pyrimido[4',5':4,5]-thieno[2,3-*c*]isoquinoline (VIId). Yield 79%, mp 280–282°C. Found, %: C 56.86, H 5.27, N 29.34, S 8.36. $C_{18}H_{20}N_8S$. Calculated, %: C 56.82, H 5.30, N 29.45, S 8.43. IR (ν, cm^{-1}): 1622 (C=N), 3314, 3271 (NHNH$_2$). ^{1}H NMR: 1.71–1.81 (m, 2 H, 9-C***H*$_2$**), 1.87–2.01 (m, 6 H, 11-(C***H*$_2$**)$_2$, 8-C***H*$_2$**), 2.74 (br. t, 2 H, *J* 5.7, 7-C***H*$_2$**), 3.56–3.63 (m, 4 H, 11-N(C***H*$_2$**)$_2$), 3.67 (br. t, 2 H, *J* 6.4, 10-C***H*$_2$**), 4.50 (br, 2 H, N***H*$_2$**), 8.34 (s, 1 H, 2-C***H***), 8.90 (br, 1 H, N***H***).

5-Hydrazino-11-piperidin-1-yl-7,8,9,10-tetrahydro-[1,2,4]triazolo[1",5":1',6']-pyrimido[4',5':4,5]thieno-[2,3-*c*]isoquinoline (VIIe). Yield 92%, mp 298–300°C. Found, %: C 57.91, H 5.66, N 28.31, S 8.04. $C_{19}H_{22}N_8S$. Calculated, %: C 57.85, H 5.62, N 28.40, S 8.13. IR (ν, cm^{-1}): 1625 (C=N), 3310, 3267 (NHNH$_2$). ^{1}H NMR: 1.63–1.83 (m, 8 H, 9-C***H*$_2$**, 11-(C***H*$_2$**)$_3$), 1.92–2.00 (m, 2 H, 8-C***H*$_2$**), 2.73 (t, 2 H, *J* 5.9, 10-C***H*$_2$**), 3.15–3.23 (m, 4 H, 11-N(C***H*$_2$**)$_2$), 3.69 (t, 2 H, *J* 6.5, 7-C***H*$_2$**), 4.48 (br, 2 H, N***H*$_2$**), 8.31 (s, 1 H, 2-C***H***), 8.75 (br, 1 H, N***H***).

5-Hydrazino-11-morpholin-4-yl-7,8,9,10-tetrahydro[1,2,4]triazolo[1",5":1',6']-pyrimido[4',5':4,5]-thieno[2,3-*c*]isoquinoline (VIIf). Yield 84%, mp 287–288°C. Found, %: C 54.58, H 5.12, N 28.19, S 7.98. $C_{18}H_{20}N_8OS$. Calculated, %: C 54.53, H 5.08, N 28.26, S 8.09. IR (ν, cm^{-1}): 1623 (C=N), 3316, 3272

($NHNH_2$). ^1H NMR: 1.69–1.78 (m, 2 H, 9-CH_2), 2.85–2.94 (m, 2 H, 8-CH_2), 2.70–2.75 (m, 2 H, 10-CH_2), 3.17–3.22 (m, 4 H, 11-N(CH_2)$_2$), 3.74–3.80 (m, 4 H, 11-O(CH_2)$_2$), 3.67–3.73 (m, 2 H, 7-CH_2), 4.69 (br, 2 H, NH_2), 8.58 (s, 1 H, 2-C*H*), 9.29 (br, 1 H, N*H*).

5-Hydrazino-10-morpholin-4-yl-8,9-dihydro-7*H*-cyclopenta[4',5']pyrido[3',2':4,5]-thieno[2,3-*e*] [1, 2, 4]triazolo[1,5-*c*]pyrimidine (VIIg). Yield 79%, mp 289–290°C. Found, %: C 53.45, H 4.78, N 29.21, S 8.29. $C_{17}H_{18}N_8OS$. Calculated, %: C 53.39, H 4.74, N 29.30, S 8.38. IR (ν, cm^{-1}): 1623 (C=N), 3328, 3279 ($NHNH_2$). ^1H NMR: 2.10–2.20 (m, 2 H, 8-CH_2), 2.97 (t, 2 H, *J* 7.2, 9-CH_2), 3.46–3.51 (m, 4 H, 10-N(CH_2)$_2$), 3.72–3.78 (m, 4 H, 10-O(CH_2)$_2$), 3.53 (t, 2 H, *J* 7.7, 7-CH_2), 4.67 (br, 2 H, NH_2), 8.54 (s, 1 H, 2-C*H*), 9.27 (br, 1 H, N*H*).

Biological Tests

Anticonvulsant activity of the compounds was assessed by the prevention of the seizure clonic component induced by subcutaneous injection of corazole (90 mg/kg) to mice [18–22]. Unwanted side effects in these animals, namely the central myorelaxant effect and impaired motor coordination were examined by the rotating rod method [18, 23, 24]. The compounds under investigation were injected in a dose range of 12.5, 25, 50, and 100 mg/kg; reference drug diazepam (Polfa, Poland), at doses of 0.1–0.3, 1.0, and 2.0 mg/kg intraperitoneally 45 min before injection of corazole (Acros Organics, United States) in the form of a suspension with carboxymethyl cellulose (Viadi-Ingredienti, Russia) and Tween 80 (Ferak Berlin, Germany). An emulsifier was administered to control animals. A 50% effective dose (ED_{50}) of the tested compounds was determined by the Litchfield and Wilcoxon method [25].

Sedative, activating, and anxiolytic effects of the selected most active compounds were examined in rats in the open field test while studying the motor and orienting-exploratory activity [26–28]. Experiments were carried out during the daytime under natural lighting. Recording of spontaneous behavior in each individual animal was continued for 5 min. The presence of sedative and activating effects was assessed by the number of horizontal (intersection of squares) and vertical (rising on hind legs) movements; the anxiolytic effect was evaluated by the number of chambers examined by animals of experimental and control groups. In this model, the number of animals was eight for each tested compound, control, and diazepam. The tested compounds were injected to rats in the most effective dose of 50 mg/kg intraperitoneally in a suspension of carboxymethyl cellulose and Tween 80. The compounds were injected to mice 45 min before the animals were placed in the open field. Diazepam, the known tranquilizer, served as a reference drug; it was injected intraperitoneally in a dose of 2 mg/kg. An emulsifier was injected to control animals. The results were statistically processed at a probability level of $P \leq 0.05$ [25].

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