ISSN 1070-4280, Russian Journal of Organic Chemistry, 2018, Vol. 54, No. 9, pp. 1406–1410. © Pleiades Publishing, Ltd., 2018.
Original Russian Text © K.Yu. Osheko, D.G. Kim, O.S. El'tsov, T.S. Shtukina, 2018, published in Zhurnal Organicheskoi Khimii, 2018, Vol. 54, No. 9, pp. 1390–1394.

Synthesis of [1,3]Thiazolo[2,3-*i*]purinium Systems

K. Yu. Osheko[a],* D. G. Kim[a], O. S. El'tsov[b], and T. S. Shtukina[b]

[a] *South Ural State University, pr. imeni Lenina 76, Chelyabinsk, 454080 Russia*
**e-mail: osheko_kseniya@mail.ru*

[b] *Yeltsin Ural Federal University, ul. Mira 19, Yekaterinburg, 620002 Russia*

Received February 28, 2018

Abstract—The alkylation of purine-6-thiol with methallyl chloride and propargyl bromide in aqueous alcohol in the presence of alkali gave 6-[methallyl(propargyl)sulfanyl]purines which reacted with iodine and bromine to afford fused [1,3]thiazolo[2,3-*i*]purinium systems.

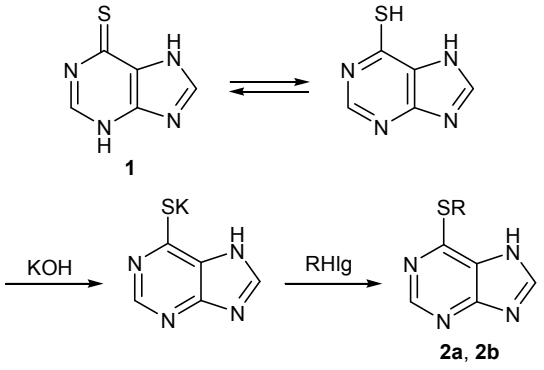
DOI: 10.1134/S1070428018090233

Derivatives of purine-6-thiol (**1**) exhibit antitumor and immunotropic activity, and they can be used for the treatment of toxoplasmosis [1–5]. There are a few published examples of synthesis of [1,3]thiazolo-[2,3-*i*]purinium systems. One method is based on heterocyclization of 6-(allylsulfanyl)purine by the action of electrophilic agents [6, 7]. Other methods for the preparation of analogous tricyclic systems include reactions of purine **1** derivatives with 1,2-dibromoethane, 2-bromocyclohexanone, and 2-(chloromethyl)-oxirane [8–10].

Herein we describe the reactions of 6-(propargylsulfanyl)purine (**2a**) and 6-(methallylsulfanyl)purine (**2b**) with halogens with the goal of obtaining new fused thiazolopurinium systems.

The alkylation of purine **1** with allyl bromide was carried out in HMPA and in water in the presence of potassium hydroxide [6, 7]. We were the first to synthesize sulfide **2a** by alkylation of purine **1** with propargyl bromide, and sulfide **2b**, by alkylation of **1** with methallyl chloride in aqueous alcohol in the presence of potassium hydroxide (Scheme 1). Compound **2a** was synthesized previously by reaction of **1** with propargyl bromide in liquid ammonia in the presence of sodium amide [11].

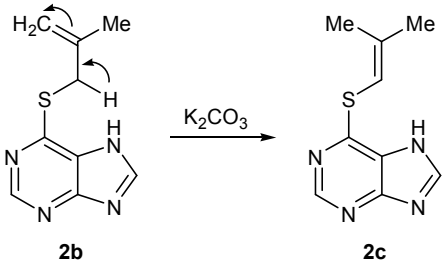
Scheme 1.



R = CH≡CCH$_2$ (**a**), CH$_2$=C(Me)CH$_2$ (**b**).

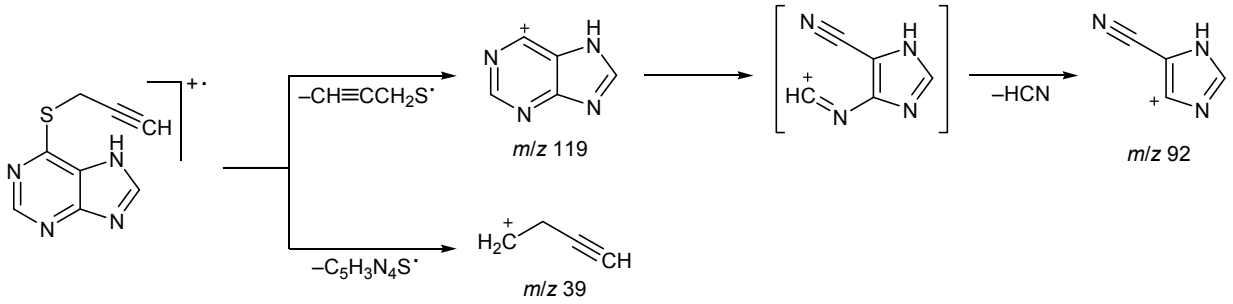
When the reaction was carried out in boiling DMF in the presence of potassium carbonate, methallyl sulfide **2b** underwent partial isomerization to 6-[(2-methylpropen-1-yl)sulfanyl]purine (**2c**) (Scheme 2). The ^{1}H NMR spectrum of **2c** displayed two methyl proton singlets at δ 1.85 and 1.95 ppm and a signal at δ 6.80 ppm due to the SCH= proton.

Scheme 2.

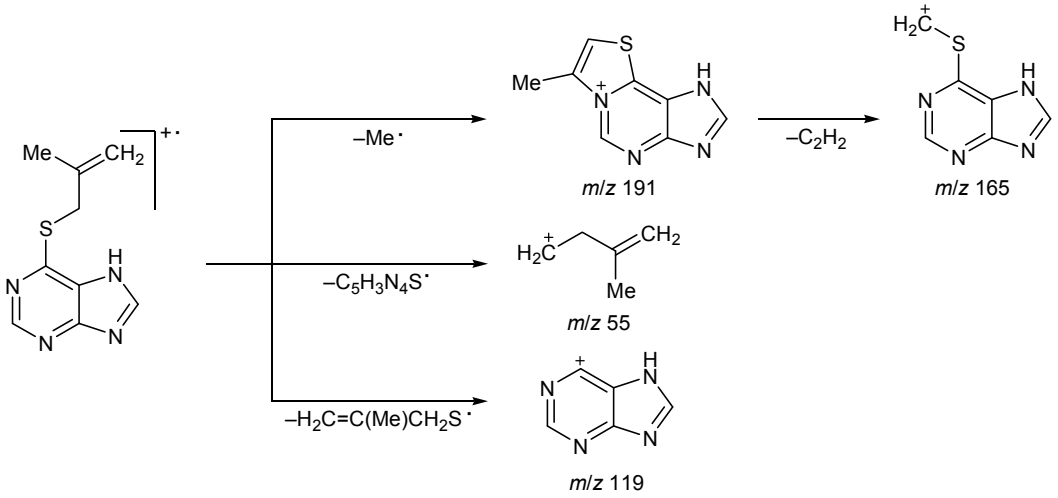


The mass spectrum of **2a** contained the molecular ion peak $[M]^+$ with a relative intensity of 17%, and the base peak was that of propargyl cation with *m*/*z* 39 (Scheme 3). In the mass spectrum of **2b**, the molecular ion peak $[M]^+$ had an intensity of 8%, while the maximum intensity peak (*m*/*z* 191) belonged to thiazolopurinium system resulting from elimination of methyl radical (Scheme 4). In addition, the ion peak with

Scheme 3.



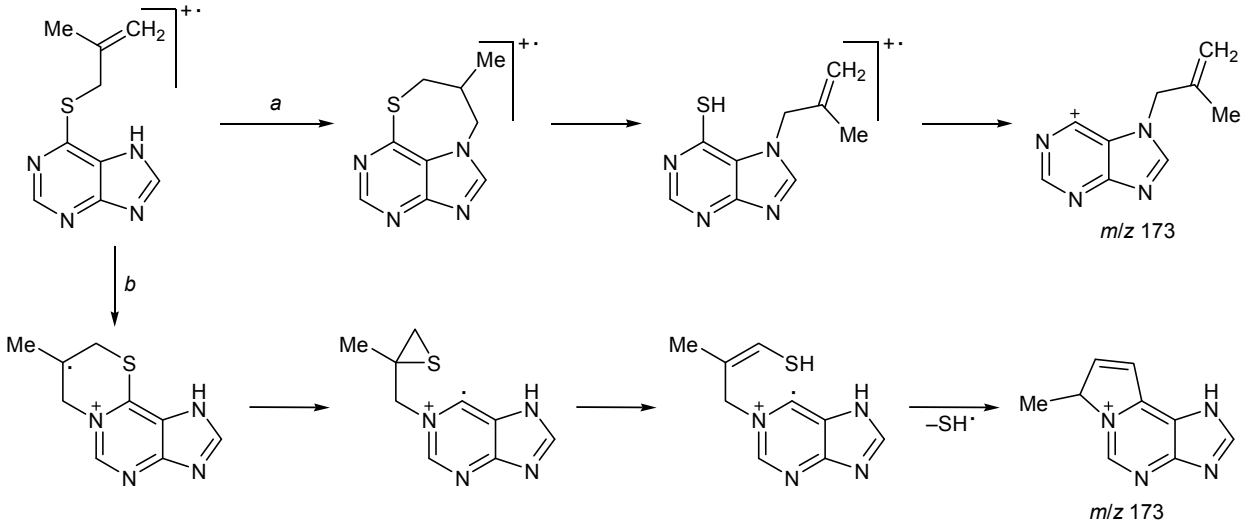
Scheme 4.



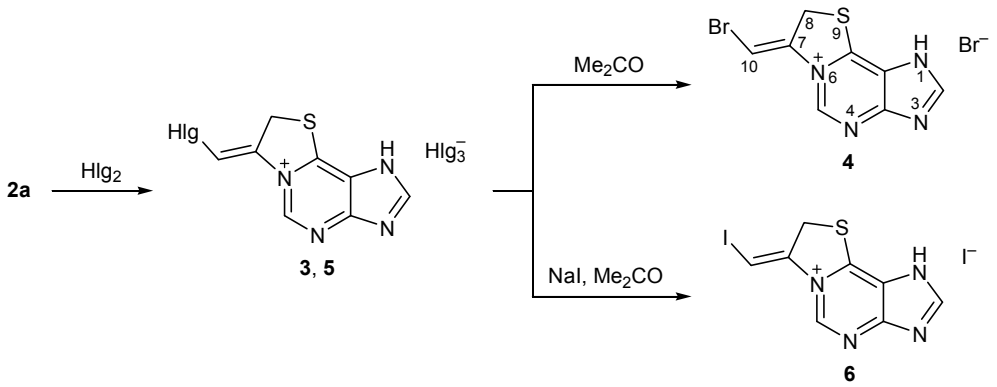
m/*z* 173 had a high intensity. This ion arises from elimination of HS· radical via allyl group migration from the sulfur atom to the N^7 atom of the purine system (pathway *a*) or through the formation of pyrrolopurinium cation (pathway *b*; Scheme 5). We believe that pathway *b* is more probable, as follows from the fairly high intensity of that peak (26%), which is typical of analogous stable systems.

The fragmentation pattern of sulfide **2c** is similar to the fragmentation of **2b**, but the peak intensities are different. For instance, the molecular ion peak of **2c** has an intensity of 90%, presumably due to higher stability

Scheme 5.



Scheme 6.



3, Hlg = Br; **5**, Hlg = I.

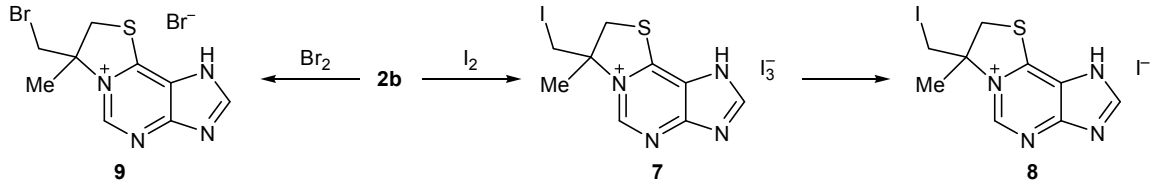
of the structure with conjugated double bond. The base peak in the mass spectrum of **2c**, as well as in the spectrum of **2b**, is that with *m*/*z* 191 $[M - CH_3]^+$. The ion peaks with *m*/*z* 119 and 92 typical of compounds **2a**–**2c** were assigned, respectively, to purinium cation resulting from cleavage of the C^6–S bond and 5-cyanoimidazolium cation resulting from elimination of hydrogen cyanide.

Propargyl sulfide **2a** reacted with 2 equiv of bromine in acetic acid to produce orange crystals of (7*E*)-7-bromomethylidene-7,8-dihydro-3*H*-[1,3]thiazolo[2,3-*i*]purin-6-ium tribromide (**3**) which was converted to colorless (7*E*)-7-bromomethylidene-7,8-dihydro-3*H*-[1,3]thiazolo[2,3-*i*]purin-6-ium bromide (**4**) by the action of acetone (Scheme 6). The reaction of **2a** with 2 equiv of iodine afforded (7*E*)-7-iodomethylidene-7,8-dihydro-3*H*-[1,3]thiazolo[2,3-*i*]purinium triiodide (**5**) as dark powder. Treatment of the latter with sodium iodide in acetone gave light yellow (7*E*)-7-iodomethylidene-7,8-dihydro-3*H*-[1,3]thiazolo-[2,3-*i*]purinium iodide (**6**). When the reactions of **2a** with iodine and bromine were carried out using equimolar amounts of the reactants, the conversion of **2a** was incomplete, and the yield of the corresponding trihalides did not exceed 50%.

Theoretically, the reactions of compound **2a** with halogens may lead to compounds with both endo- and exocyclic double bond. The ^1H and ^{13}C NMR data were insufficient for unambiguous structure determination. Therefore, we resorted to two-dimensional ^1H–^{13}C HSQC and HMBC and ^1H–^1H NOESY techniques and found that the product of the reaction of **2b** with iodine after treatment of the reaction mixture with sodium iodide in acetone was *E*-isomeric 7-iodomethylidene[1,3]thiazolo[2,3-*i*]purin-6-ium iodide (**6**) having an exocyclic double bond. Characteristic signals in the ^1H and ^{13}C NMR spectra of **6** were those of the exocyclic =CHI group: the proton signal was displaced downfield (δ 8.12 ppm), and the carbon signal appeared in a strong field (δ_C 75.47 ppm) due to effect of heavy iodine atom. The configuration of the exocyclic double bond was determined on the basis of the 2D NOESY data. The CHI proton displayed coupling with proton on C^5 of the thiazolopurine system, which is possible only for the *E* configuration of the double bond. Complete assignment of the ^1H and ^{13}C signals of **6** was done by analysis of the 2D ^1H–^{13}C HSQC and HMBC spectra. Because of overlap by the solvent signal, the CH_2 chemical shift was determined from the C–H direct coupling cross peak. The most informative cross-peaks in the 2D ^1H–^{13}C HMBC spectrum of **6** were the following: 2-H/C^{9a}, 2-H/C^{3a}, 8-H/C^{9a}, 8-H/C^7, 8-H/C^{10}, 5-H/C^{9a}, 5-H/C^{3a}, 5-H/C^7.

The reaction of **2b** with iodine at a molar ratio of 1:2 in acetic acid afforded 7-(iodomethyl)-7-methyl-7,8-dihydro-1*H*-[1,3]thiazolo[2,3-*i*]purin-6-ium triiodide (**7**) as a dark solid which separated from the reaction mixture. By treatment of **7** with sodium iodide

Scheme 7.



in acetone we obtained 7-(iodomethyl)-7-methyl-7,8-dihydro-1*H*-[1,3]thiazolo[2,3-*i*]purin-6-ium iodide (**8**) (Scheme 7). Compound **2b** reacted with an equimolar amount of bromine to give 7-(bromomethyl)-7-methyl-7,8-dihydro-1*H*-[1,3]thiazolo[2,3-*i*]purin-6-ium iodide (**9**). Compounds **8** and **9** showed in the ^{1}H NMR spectra a singlet of methyl protons at δ 2.00–2.10 ppm and a SCH_2 signal at δ 4.10–4.20 and 4.35–4.50 ppm, respectively; the SCH_2 signal of **4** and **6** was located at δ 4.70 and 4.65 ppm, respectively. In the ^{1}H NMR spectra of **4**, **6**, **8**, and **9** aromatic proton signals characteristically appeared in a weaker field due to the presence of positive charge.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on Bruker DRX-400 and Bruker Avance II spectrometers at 400 and 126 MHz, respectively, using DMSO-d_6 as solvent and tetramethylsilane as reference. The IR spectra were measured on a Bruker Tensor 27 spectrometer with Fourier transform. The mass spectra (electron impact, 70 eV) were obtained on a Shimadzu GCMS-QP2010 Ultra instrument.

Compounds 2a and 2b (*general procedure***).** Potassium hydroxide, 112 mg (2 mmol), was dissolved in 10 mL of water and 340 mg (2 mmol) of purine-6-thiol and a solution of 2 mmol of methallyl chloride or propargyl bromide in 1 mL of ethanol were added. The mixture was stirred for 2 h, and the precipitate was filtered off, washed with water, and dried.

6-(Prop-2-yn-1-ylsulfanyl)purine (2a). Yield 330 mg (87%), gray powder, mp 180–182°C (decomp.) [11]. ^{1}H NMR spectrum, δ, ppm: 3.15 t (1H, CH, J = 2.5 Hz), 4.23 d (2H, SCH_2, J = 2.7 Hz), 8.48 s (1H, 8-H), 8.74 s (1H, 2-H), 13.59 s (1H, NH). Mass spectrum, m/z (I_{rel}, %): 190 (17.0) $[M]^+$, 119 (5.0) $[M - SCH_2C{\equiv}CH]^+$, 97 (5.0), 93 (11.3), 92 (5.6) $[C_5H_3N_4]^+$, 72 (9.9), 71 (12.7), 70 (24.0), 69 (14.1), 66 (17.0), 65 (14.0), 53 (14.0), 45 (31.0), 44 (5.6), 40 (8.5), 39 (100) $[C_3H_3]^+$, 38 (52.1), 37 (18.3).

6-(2-Methylprop-2-en-1-ylsulfanyl)purine (2b). Yield 351 mg (84%), gray powder, mp 159–160°C. IR spectrum, ν, cm^{-1}: 3328, 3175, 3058, 2977, 2941, 2788, 2661, 2554, 1870, 1692, 1654, 1631, 1590, 1570, 1466, 1430, 1420, 1385 (=CH), 1326, 1263, 1242, 1230, 1158, 1128, 1054, 1014, 998, 950 (=CH), 927, 902, 882, 848, 795, 767, 716, 678, 645, 630, 599, 541, 518, 503, 422. ^{1}H NMR spectrum, δ, ppm: 1.82 s (3H, CH_3), 4.10 s (2H, SCH_2), 4.89 s and 5.08 s (2H, $=CH_2$), 8.46 s (1H, 8-H), 8.70 s (1H, 2-H). Mass spectrum, m/z (I_{rel}, %): 206 (7.7) $[M]^+$, 205 (5.5) $[M - H]^+$, 192 (11.0), 191 (100) $[M - CH_3]^+$, 173 (26.7) $[M - SH]^+$, 165 (13.2) $[M - C_3H_5]^+$, 158 (9.9), 147 (5.5), 134 (7.1), 125 (6.0), 120 (7.7), 119 (9.3) $[M - SCH_2C(CH_3){=}CH_2]$, 97 (6.0), 93 (28.0), 92 (9.3) $[C_5H_3N_4]^+$, 71 (6.6), 70 (11.5), 66 (11.0), 65 (11.0), 55 (5.6) $[C_4H_6]^+$, 53 (12.1), 45 (10.4). Found, %: C 52.45; H 4.93; N 27.14. $C_9H_{10}N_4S$. Calculated, %: C 52.41; H 4.89; N 27.16. M 206.27.

(7*E*)-7-Bromomethylidene-7,8-dihydro-3*H*-[1,3]-thiazolo[2,3-*i*]purin-6-ium bromide (4). Compound **2a**, 0.095 g (0.5 mmol), was added to a solution of 0.052 mL (1 mmol) of bromine in 5 mL of acetic acid. After 24 h, (7*E*)-7-bromomethylidene-7,8-dihydro-3*H*-[1,3]thiazolo[2,3-*i*]purin-6-ium tribromide (**3**) was filtered off and treated with acetone, and the yellow precipitate was filtered off. Yield 0.109 g (62%), mp 137–139°C (decomp.). ^{1}H NMR spectrum, δ, ppm: 4.73 d (2H, SCH_2), 8.20 t (1H, =CHBr), 9.00 s (1H, 2-H), 9.84 s (1H, 5-H). Found, %: C 27.49; H 1.75; N 16.00. $C_8H_6Br_2N_4S$. Calculated, %: C 27.45; H 1.73; N 16.01.

(7*E*)-7-Iodomethylidene-7,8-dihydro-3*H*-[1,3]-thiazolo[2,3-*i*]purin-6-ium iodide (6). Compound **2a**, 0.095 g (0.5 mmol), was added to a solution of 0.254 g (1 mmol) of iodine in 5 mL of acetic acid. After 24 h, (7*E*)-7-iodomethylidene-7,8-dihydro-3*H*-[1,3]thiazolo-[2,3-*i*]purin-6-ium triiodide (**5**) was filtered off and dissolved in acetone, sodium iodide was added, and the light yellow precipitate of iodide **6** was filtered off. Yield 0.133 g (60%), mp 250–254°C (decomp.). ^{1}H NMR spectrum, δ, ppm: 4.64 s (2H, SCH_2), 8.12 s (1H, CHI), 8.97 s (1H, 2-H), 9.73 s (1H, 5-H). ^{13}C NMR spectrum, δ_C, ppm: 39.73 (SCH_2), 75.47 (CHI), 126.67 (C^{9b}), 141.28 (C^7), 142.58 (C^5), 149.79 (C^2), 151.22 (C^{3a}), 159.27 (C^{9a}). Found, %: C 21.61; H 1.38; N 12.65. $C_8H_6I_2N_4S$. Calculated, %: C 21.64; H 1.36; N 12.62.

7-(Iodomethyl)-7-methyl-7,8-dihydro-1*H*-[1,3]-thiazolo[2,3-*i*]purin-6-ium iodide (8). Compound **2b**, 0.103 g (0.5 mmol), was added to a solution of 0.254 g (1 mmol) of iodine in 5 mL of acetic acid. After 24 h, the solvent was evaporated, the residue was dissolved in acetone, sodium iodide was added, and the precipitate was filtered off. Yield 0.111 g (48%), mp 139–140°C. ^{1}H NMR spectrum, δ, ppm: 2.04 s (3H, CH_3), 3.99 s (2H, SCH_2), 4.14 d (2H, CH_2Br, J = 11.3 Hz), 8.78 s (1H, 2-H), 9.32 s (1H, 5-H). ^{13}C NMR spectrum, δ_C, ppm: 13.96 (CH_3), 25.62 (CH_2I), 31.29

(SCH_2), 43.10 (C^7), 128.17 (C^{9b}), 143.71 (C^5), 155.26 (C^2), 155.90 (C^{3a}), 172.47 (C^{9a}). Found, %: C 23.47; H 2.17; N 12.21. $C_9H_{10}I_2N_4S$. Calculated, %: C 23.50; H 2.19; N 12.18.

7-(Bromomethyl)-7-methyl-7,8-dihydro-1*H*-[1,3]-thiazolo[2,3-*i*]purin-6-ium bromide (9). Compound **2b**, 0.103 g (0.5 mmol), was added to a solution of 0.026 mL (0.5 mmol) of bromine in 5 mL of acetic acid. After 24 h, the white crystals were filtered off. Yield 0.119 g (65%), mp 230–233°C (decomp.). ^{1}H NMR spectrum, δ, ppm: 2.06 s (3H, CH_3), 4.05 d and 4.14 d (1H each, SCH_2, J = 12.3 Hz), 4.37 d and 4.48 d (1H each, CH_2Br, J = 11.4 Hz), 9.02 s (1H, 2-H), 9.59 s (1H, 5-H). Found, %: C 23.51; H 2.21; N 12.16. $C_9H_{10}I_2N_4S$. Calculated, %: C 23.50; H 2.19; N 12.18.

This study was performed under financial support by the Government of the Russian Federation (resolution no. 211, March 16, 2013; contract no. 02.A03.21.0011) in the framework of state assignment no 4.9665.2017/8.9.

REFERENCES

1. Drawbaugh, R., Bouffard, C., and Strauss, M., *J. Med. Chem*., 1976, vol. 19, no. 11, p. 1342.
2. Zercher, C.K. and Fedor, L.R., *Carbohydr. Res*., 1987, vol. 165, no. 2, p. 299.
3. Volonté, C. and Greene, L.A., *J. Neurochem.*, 1992, vol. 58, no. 2, p. 700.
4. Kochergin, P.M., Aleksandrova, E.V., and Tolvinskaya, L.S., *Pharm. Chem. J*., 2000, vol. 34, no. 11, p. 579.
5. Yadav, V., Chu, C.K., and Rais, R.H., *J. Med. Chem*., 2004, vol. 47, no. 8, p. 1987.
6. Kim, D.G. and Galina, Yu.R., *Chem. Heterocycl. Compd*., 2004, vol. 40, no. 10, p. 1339.
7. Vas'kevich, R.I., Vas'kevich, A.I., Rusanov, E.B., Staninets, V.I., and Vovk, M.V., *Russ. J. Org. Chem*., 2013, vol. 49, no. 1, p. 123.
8. Montgomery, J.A., Balsiger, R.W., Fikes, A.L, and Johnston, T.P., *J. Org. Chem*., 1962, vol. 27, no. 1, p. 195.
9. Press, J.B., Hajos, Z.G., and Sawyers, R.A., *Tetrahedron Lett*., 1990, vol. 31, no. 10, p. 1373.
10. Kochergin, P.M., Gromov, P.Yu., Skachilova, S.Yu.. and Aleksandrova, E.V., *Chem. Heterocycl. Compd*., 1997, vol. 33, no. 7, p. 881.
11. Ratsino, E.V., Radchenko, S.I., Shtil'bans, E.B., Rachkovskaya, L.A., Sokolov, L.B., Alekseeva, G.E., and Shneider, M.A., *Pharm. Chem. J*., 1981, vol. 15, no. 8, p. 581.