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SHORT COMMUNICATIONS

Synthesis of Hetarylquinolines from 4-(4-Hydroxy-2-methylquinolin-3-yl)butan-2-one Thiosemicarbazones

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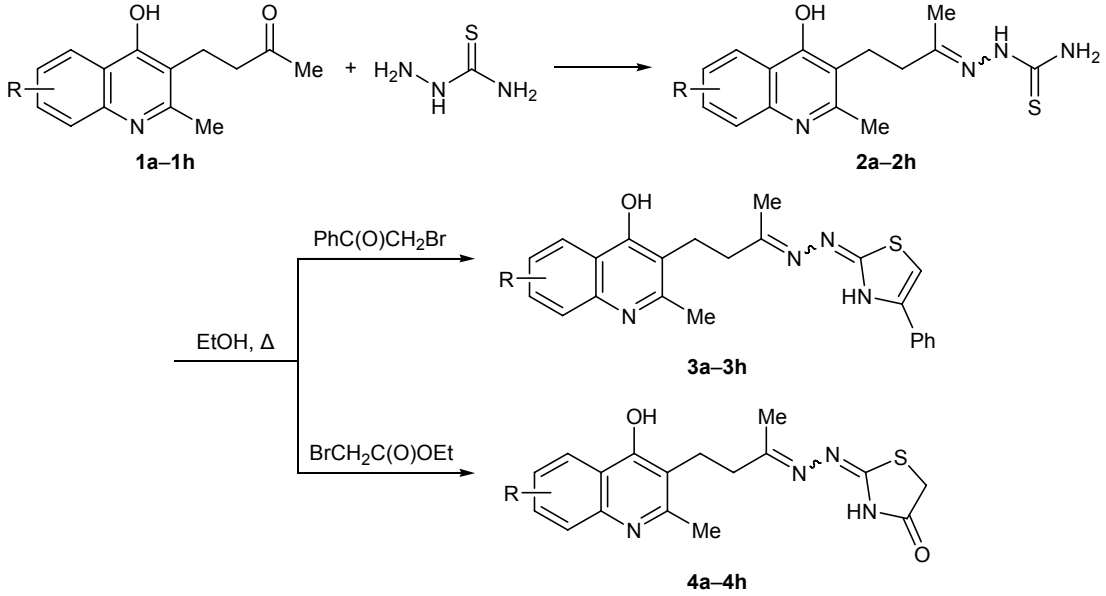
Heterocyclic thiosemicarbazones and thiosemicarbazides, including quinoline derivatives, are polyfunctional substrates that are widely used in the development of methods for the synthesis of biologically active compounds which may be promising as medicinal agents [1–3]. Increased attention is now given to the chemistry of quinoline derivatives, in particular hetarylquinolines, i.e., compounds whose molecules consist of two heterocyclic fragments, one of which is quinoline. Compounds exhibiting anticancer, antifungal, antiviral, antibacterial, and immunomodulatory activity have been found in the series of hetarylquinolines [4–11].

Taking into account the above stated, we made an attempt to synthesize new thiazolidines and thiazolidinones from 6(8)-substituted 4-hydroxy-2-methyl-3-(3-oxobutyl)quinolines **1a**–**1h**. Compounds **1a**, **1b**, **1g**, and **1h** were synthesized by us previously [12, 13], while quinolines **1c**–**1f** were not described. Compounds **1a**–**1h** were prepared by hydrolysis of the corresponding 3-(3-chlorobut-2-en-1-yl)-4-hydroxy-2-methylquinolines in sulfuric acid.

Ketones **1a**–**1h** were treated with 1.1 equiv of thiosemicarbazide in boiling anhydrous ethanol, and thiosemicarbazones **2a**–**2h** thus obtained were subjected to heterocyclization by the action of bromoacetophenone and ethyl bromoacetate. As a result, we isolated thiazolidine and thiazolidinone derivatives **3a**–**3h** and **4a**–**4h**, respectively.

6(8)-Substituted 4-hydroxy-2-methyl-3-(3-oxobutyl)quinolines 1c–1f were synthesized according to the procedure described in [12, 13] by hydrolysis of



R = H (**a**), 6-Me (**b**), 8-Me (**c**), 6-OMe (**d**), 8-OMe (**e**), 6-OEt (**f**), 6-Br (**g**), 6-COOH (**h**).

0.01 mol of the corresponding 3-(3-chlorobut-2-en-1-yl)-4-hydroxy-2-methylquinolines in 85% H_2SO_4.

4-(4-Hydroxy-2,8-dimethylquinolin-3-yl)butan-2-one (1c). Yield 2.13 g (93%), mp 203–204°C, R_f 0.58 (ethanol–toluene, 1:3). Found, %: C 73.86; H 6.82; N 5.55. $C_{15}H_{17}NO_2$. Calculated, %: C 74.07; H 7.00; N 5.76.

4-(4-Hydroxy-6-methoxy-2-methylquinolin-3-yl)butan-2-one (1d). Yield 2.35 g (96%), mp 255–256°C, R_f 0.52 (ethanol–toluene, 1:2). Found, %: C 69.75; H 6.36; N 5.58. $C_{15}H_{17}NO_3$. Calculated, %: C 69.50; H 6.56; N 5.41.

4-(4-Hydroxy-8-methoxy-2-methylquinolin-3-yl)butane-2-one (1e). Yield 2.35 g (96%), mp 185–186°C, R_f 0.56 (ethanol–toluene, 1:2). Found, %: C 69.32; H 6.68; N 5.29. $C_{15}H_{17}NO_3$. Calculated, %: C 69.50; H 6.56; N 5.41.

4-(6-Ethoxy-4-hydroxy-2-methylquinolin-3-yl)-butan-2-one (1f). Yield 2.43 g (94%), mp 240–241°C, R_f 0.52 (ethanol–toluene, 1:2). Found, %: C 71.62; H 6.85; N 5.27. $C_{16}H_{19}NO_3$. Calculated, %: C 71.80; H 6.96; N 5.13.

Thiosemicarbazones 2f–2h were synthesized according to the procedure described in [14] from 1.00 g (0.011 mol) of thiosemicarbazide and 0.01 mol of ketone **1a**–**1h**.

4-(6-Ethoxy-4-hydroxy-2-methylquinolin-3-yl)-butan-2-one thiosemicarbazone (2f). Yield 3.25 g (98%), mp 256–257°C, R_f0.53 (ethanol–toluene, 1:3). Found, %: C 56.56; H 6.21; N 15.61; S 8.61. $C_{17}H_{22}N_4O_3S$. Calculated, %: C 56.35; H 6.08; N 15.46; S 8.83.

4-(6-Bromo-4-hydroxy-2-methylquinolin-3-yl)-butan-2-one thiosemicarbazone (2g). Yield 3.41 g (93%), mp 262–263°C (decomp.), R_f 0.51 (ethanol–toluene, 1:2). Found, %: C 47.31; H 4.29; N 14.52; S 8.54. $C_{15}H_{17}BrN_4OS$. Calculated, %: C 47.24; H 4.46; N 14.70; S 8.40.

3-[3-(Carbamothioylhydrazinylidene)butyl]-4-hydroxy-2-methylquinoine-6-carboxylic acid (2h). Yield 3.29 g (99%), mp 350°C (decomp.), R_f 0.63 (ethanol). Found, %: C 55.37; H 5.29; N 16.01; S 9.42. $C_{16}H_{18}N_4O_3S$. Calculated, %: C 55.49; H 5.10; N 16.18; S 9.25.

6(8)-Substituted 2-methyl-3-{3-[4-phenyl-1,3-thiazol-2(3*H*)-ylidenehydrazinylidene]butyl}quinolin-4-ols 3a–3h (*general procedure*). A mixture of 1 mmol of compound **2a**–**2h**, 4–5 mL of anhydrous ethanol, 0.082 g (0.001 mol) of anhydrous sodium acetate, and 0.199 g (1 mmol) of bromoacetophenone was heated for 4–5 h under reflux with stirring. The mixture was cooled, and the precipitate was filtered off, washed with ethanol, and recrystallized from ethanol.

2-Methyl-3-{3-[4-phenyl-1,3-thiazol-2(3*H*)-ylidenehydrazinylidene]butyl}quinolin-4-ol (3a). Yield 0.38 g (95%), mp 262–263°C, R_f 0.65 (ethanol–toluene, 1 :3). ^{1}H NMR spectrum, δ, ppm: 2.17 br.s (3H, CH_3), 2.43–2.58 m (7H, CH_3, CH_2), 7.01 s (1H, =CH), 7.12 d.d (1H, H_{arom}, J = 9.13, 2.78 Hz), 7.26–7.35 m (2H, H_{arom}), 7.45 t (1H, H_{arom}, J = 7.54 Hz), 7.58 br.s (2H, H_{arom}), 7.68–7.95 m (3H, H_{arom}), 10.13–10.76 m (1H, NH), 11.59–12.31 m (1H, OH). Found, %: C 68.48; H 5.26; N 14.06; S 8.13. $C_{23}H_{22}N_4OS$. Calculated, %: C 68.66; H 5.47; N 13.93; S 7.96.

2,6-Dimethyl-3-{3-[4-phenyl-1,3-thiazol-2(3*H*)-ylidenehydrazinylidene]butyl}quinolin-4-ol (3b). Yield 0.39 g (93%), mp 275–276°C, R_f 0.50 (ethanol–toluene, 1:4). ^{1}H NMR spectrum, δ, ppm: 1.95–2.11 m (3H, CH_3), 2.33–2.53 m (8H, CH_3, CH_2), 2.54–2.83 m (2H, CH_2), 6.82–6.93 m (1H, =CH), 7.16–7.27 m (1H, H_{arom}), 7.27–7.41 m (4H, H_{arom}), 7.75–7.91 m (3H, H_{arom}), 10.98 s (1H, NH), 11.30 s (1H, OH). Found, %: C 69.39; H 5.67; N 13.28; S 7.85. $C_{24}H_{24}N_4OS$. Calculated, %: C 69.23; H 5.77; N 13.46; S 7.70.

2,8-Dimethyl-3-{3-[4-phenyl-1,3-thiazol-2(3*H*)-ylidenehydrazinylidene]butyl}quinolin-4-ol (3c). Yield 0.38 g (91%), mp 163–164°C, R_f 0.61 (ethanol–toluene, 1:4). ^{1}H NMR spectrum, δ, ppm: 1.94 m (3H, CH_3), 2.12 br.s (3H, CH_3), 2.54–2.86 m (7H, CH_3, CH_2), 6.97 s (1H, =CH), 7.23 d.d (1H, H_{arom}, J = 9.13, 2.78 Hz), 7.09–7.23 m (1H, H_{arom}), 7.36 t (1H, H_{arom}, J = 7.54 Hz), 7.53 br.s (2H, H_{arom}), 7.68–7.91 m (3H, H_{arom}), 10.08–10.89 m (1H, NH), 11.62–12.25 m (1H, OH). Found, %: C 69.01; H 5.90; 13.52; S 7.58. $C_{24}H_{24}N_4OS$. Calculated, %: C 69.23; H 5.77; N 13.46; S 7.70.

6-Methoxy-2-methyl-3-{3-[4-phenyl-1,3-thiazol-2(3*H*)-ylidenehydrazinylidene]butyl}quinolin-4-ol (3d). Yield 0.37 g (86%), mp 253–254°C, R_f 0.60 (ethanol–toluene, 1:3). Found, %: C 66.81; H 5.46; N 12.78; S 7.63. $C_{24}H_{24}N_4O_2S$. Calculated, %: C 66.67; H 5.56; N 12.96; S 7.41.

8-Methoxy-2-methyl-3-{3-[4-phenyl-1,3-thiazol-2(3*H*)-ylidenehydrazinylidene]butyl}quinolin-4-ol (3e). Yield 0.40 g (93%), mp 143–144°C, R_f 0.6 (ethanol–toluene, 1:3). ^{1}H NMR spectrum, δ, ppm: 1.56–1.98 m (3H, CH_3), 2.08–2.25 m (3H, OCH_3),

2.43–2.64 m (5H, CH_3, CH_2), 2.68–2.91 m (2H, CH_2), 7.02–7.21 m (1H, =CH), 7.45–7.57 m (1H, H_{arom}), 7.63–7.79 m (4H, H_{arom}), 7.86–7.97 m (3H, H_{arom}), 11.02 s (1H, NH), 11.34 s (1H, OH). Found, %: C 66.83; H 5.46; N 12.83; S 7.60. $C_{24}H_{24}N_4O_2S$. Calculated, %: C 66.67; H 5.56; N 12.96; S 7.41.

6-Ethoxy-2-methyl-3-{3-[4-phenyl-1,3-thiazol-2(3*H*)-ylidenehydrazinylidene]butyl}quinolin-4-ol (3f). Yield 0.42 g (94%), mp 256–257°C, R_f 0.68 (ethanol–toluene, 1:3). ^{1}H NMR spectrum, δ, ppm: 1.46 t (3H, C**H**$_3$CH$_2$, J = 6.75 Hz), 2.03 br.s (3H, CH_3), 2.45–2.90 m (7H, CH_3, CH_2), 4.04–4.25 m (2H, OCH_2), 6.90 s (1H, =CH), 7.14 d.d (1H, H_{arom}, J = 9.13, 2.78 Hz), 7.18–7.27 m (1H, H_{arom}), 7.34 t (1H, H_{arom}, J = 7.54 Hz), 7.57 br.s (2H, H_{arom}), 7.71–7.94 m (3H, H_{arom}), 10.08–10.94 m (1H, NH), 11.61–12.33 m (1H, OH). Found, %: C 67.54; H 5.71; N 12.28; S 7.39. $C_{25}H_{26}N_4O_2S$. Calculated, %: C 67.26; H 5.83; N 12.56; S 7.17.

6-Bromo-2-methyl-3-{3-[4-phenyl-1,3-thiazol-2(3*H*)-ylidenehydrazinylidene]butyl}quinolin-4-ol (3g). Yield 0.45 g (94%), mp 287–288°C, R_f 0.61 (ethanol–toluene, 1:4). ^{1}H NMR spectrum, δ, ppm: 1.96–2.13 m (3H, CH_3), 2.32–2.50 m (5H, CH_3, CH_2), 2.62–2.82 m (2H, CH_2), 6.89 s (1H, =CH), 7.16–7.27 m (1H, H_{arom}), 7.27–7.48 m (3H, H_{arom}), 7.50–7.63 m (1H, H_{arom}), 7.72–7.90 m (2H, H_{arom}), 8.24 s (1H, H_{arom}), 10.27–11.17 m (1H, NH), 11.17–11.70 m (1H, OH). Found, %: C 57.21; H 4.23; N 11.86; S 6.52. $C_{23}H_{21}BrN_4OS$. Calculated, %: C 57.38; H 4.37; N 11.64; S 6.65.

4-Hydroxy-2-methyl-3-{3-[4-phenyl-1,3-thiazol-2(3*H*)-ylidenehydrazinylidene]butyl}quinoline-6-carboxylic acid (3h). Yield 0.40 g (90%), mp 273–274°C, R_f 0.60 (ethanol–toluene, 1:3). Found, %: C 64.29; H 4.82; N 12.74; S 7.52. $C_{24}H_{22}N_4O_3S$. Calculated, %: C 64.56; H 4.93; N 12.55; S 7.18.

2-{[4-(4-Hydroxy-2-methylquinolin-3-yl)butan-2-ylidene]hydrazinylidene}-1,3-thiazolidin-4-ones 4a–4h (*general procedure*). A mixture of 1 mmol of compound **2a**–**2h**, 4–5 mL of anhydrous ethanol, 0.082 g (1 mmol) of anhydrous sodium acetate, and 0.22 g (0.15 mL, 1.3 mmol) of ethyl bromoacetate was heated for 4–5 h under reflux with stirring. The mixture was cooled, and the precipitate was filtered off, washed with ethanol, and recrystallized from ethanol.

2-{[4-(4-Hydroxy-2-methylquinolin-3-yl)butan-2-ylidene]hydrazinylidene}-1,3-thiazolidin-4-one (4a). Yield 0.33 g (96%), mp 306–307°C, R_f 0.50 (ethanol–toluene, 1:3). ^{1}H NMR spectrum, δ, ppm: 1.91–2.15 m (3H, CH_3), 2.35–2.48 m (3H, CH_3), 2.52–2.84 m (4H, CH_2), 3.48–3.79 m (2H, CH_2), 7.16 t (1H, H_{arom}, J = 7.14 Hz), 7.34–7.56 m (2H, H_{arom}), 7.96–8.17 m (1H, H_{arom}), 11.13 br.s (2H, NH, OH). Found, %: C 59.78; H 5.52; N 16.12; S 9.58. $C_{17}H_{18}N_4O_2S$. Calculated, %: C 59.65; H 5.26; N 16.36; S 9.36.

2-{[4-(4-Hydroxy-2,6-dimethylquinolin-3-yl)-butan-2-ylidene]hydrazinylidene}-1,3-thiazolidin-4-one (4b). Yield 0.32 g (91%), mp 275–276°C, R_f 0.58 (ethanol–toluene, 1:2.5). ^{1}H NMR spectrum, δ, ppm: 1.91–2.04 m (3H, CH_3), 2.31–2.45 m (8H, CH_3, CH_2), 2.53–2.81 m (2H, CH_2), 3.63–3.82 m (2H, CH_2), 7.31–7.47 m (2H, H_{arom}), 7.84 s (1H, H_{arom}), 11.29 br.s (1H, OH), 11.64 br.s (1H, NH). Found, %: C 60.46; H 5.48; N 15.89; S 8.75. $C_{18}H_{20}N_4O_2S$. Calculated, %: C 60.67; H 5.62; N 15.73; S 8.99.

2-{[4-(4-Hydroxy-2,8-dimethylquinolin-3-yl)-butan-2-ylidene]hydrazinylidene}-1,3-thiazolidin-4-one (4c). Yield 0.33 g (92%), mp 321–322°C, R_f 0.65 (ethanol–toluene, 1:3). Found, %: C 60.55; H 5.82; N 15.56; S 9.14. $C_{18}H_{20}N_4O_2S$. Calculated, %: C 60.67; H 5.62; N 15.73; S 8.99.

2-{[4-(4-Hydroxy-6-methoxy-2-methylquinolin-3-yl)butan-2-ylidene]hydrazinylidene}-1,3-thiazolidin-4-one (4d). Yield 0.35 g (93%), mp 308–309°C, R_f 0.58 (ethanol–toluene, 1:2). ^{1}H NMR spectrum, δ, ppm: 1.86–1.99 m (3H, CH_3), 2.06–2.14 br.s (3H, OCH_3), 2.27–2.34 m (5H, CH_3, CH_2), 2.61–2.87 m (2H, CH_2), 3.58–3.78 m (2H, CH_2), 7.41–7.53 m (2H_{arom}), 7.85 s (1H_{arom}), 11.18 br.s (1H, OH), 11.59 br.s (1H, NH). Found, %: C 58.23; H 5.21; N 15.26; S 8.46. $C_{18}H_{20}N_4O_3S$. Calculated, %: C 58.06; H 5.38; N 15.05; S 8.60.

2-{[4-(4-Hydroxy-8-methoxy-2-methylquinolin-3-yl)butan-2-ylidene]hydrazinylidene}-1,3-thiazolidin-4-one (4e). Yield 0.36 g (96%), mp 248–249°C, R_f 0.55 (ethanol–toluene, 1:3). ^{1}H NMR spectrum, δ, ppm: 2.04–2.16 m (3H, CH_3), 2.19–2.21 br.s (3H, OCH_3), 2.27–2.30 m (5H, CH_3, CH_2), 2.67–2.87 m (2H, CH_2), 3.45–3.69 m (2H, CH_2), 7.49–7.55 m (2H, H_{arom}), 7.79 s (1H, H_{arom}), 11.09 br.s (1H, OH), 11.53 br.s (1H, NH). Found, %: C 58.26; H 5.62; N 14.86; S 8.79. $C_{18}H_{20}N_4O_3S$. Calculated, %: C 58.06; H 5.38; N 15.05; S 8.60.

2-{[4-(6-Ethoxy-4-hydroxy-2-methylquinolin-3-yl)butan-2-ylidene]hydrazinylidene}-1,3-thiazolidin-4-one (4f). Yield 0.38 g (96%), mp 309–311°C, R_f 0.56 (ethanol–toluene, 1:3). ^{1}H NMR spectrum, δ, ppm: 1.56 t (3H, C**H**$_3$CH$_2$, J = 6.72 Hz), 2.10 br.s (3H, CH_3), 2.46–2.89 m (5H, CH_3, CH_2), 4.11–4.26 m (2H,

OCH_2), 2.65–2.88 m (2H, CH_2), 3.61–3.75 m (2H, CH_2), 7.46–7.60 m (2H, H_{arom}), 7.84 s ($1H_{arom}$), 11.22 br.s (1H, OH), 11.57 br.s (1H, NH). Found, %: C 59.28; H 5.61; N 14.65; S 8.19. $C_{19}H_{22}N_4O_3S$. Calculated, %: C 59.08; H 5.70; N 14.51; S 8.29.

2-{[4-(6-Bromo-4-hydroxy-2-methylquinolin-3-yl)butan-2-ylidene]hydrazinylidene}-1,3-thiazolidin-4-one (4g). Yield 0.41 g (97%), mp 329–331°C, R_f 0.67 (ethanol–toluene, 1:4). ^{1}H NMR spectrum, δ, ppm: 2.10–2.16 m (3H, CH_3), 2.29–2.32 m (5H, CH_3, CH_2), 2.65–2.85 m (2H, CH_2), 3.63–3.81 m (2H, CH_2), 7.39–7.51 m (2H, H_{arom}), 7.68 s (1H, H_{arom}), 11.34 br.s (1H, OH), 11.62 br.s (1H, NH). Found, %: C 48.65; H 4.21; N 13.19; S 7.43. $C_{17}H_{17}BrN_4O_2S$. Calculated, %: C 48.46; H 4.04; N 13.30; S 7.60.

4-Hydroxy-2-methyl-3-{3-[(4-oxo-1,3-thiazolidin-2-ylidene)hydrazinylidene]butyl}quinoline-6-carboxylic acid (4h). Yield 0.37 g (96%), mp 361–362°C, R_f 0.44 (ethanol–toluene, 3:1). Found, %: C 55.81; H 4.41; N 14.72; S 8.42. $C_{18}H_{18}N_4O_4S$. Calculated, %: C 55.96; H 4.66; N 14.51; S 8.29.

The ^{1}H NMR spectra were recorded from solutions in DMSO-d_6 on a Varian Mercury-300 spectrometer (300 MHz). The purity of the isolated compounds was checked by TLC on Silufol UV-254 plates; spots were visualized by treatment with iodine vapor.

REFERENCES

1. Waghamale, S. and Piste, P., *Int. J. Biol. Sci*., 2013, vol. 4, p. 310.
2. Saad, H.A., Osman, N.A., and Moustafa, A.H., *Molecules*, 2011, vol. 16, p. 10187.
3. Shaker, R.M., *Arkivoc*, 2006, part (ix), p. 59.
4. Abhinit, M., Ghodke, M., and Pratima, N.A., *Int. J. Pharm. Pharm. Sci*., 2009, vol. 1, no. 1, p. 47.
5. Archana, Srivastav, V.K., and Kumar, A., *Eur. J. Med. Chem*., 2002, vol. 37, p. 873.
6. Neuenfeldt, P.D., Duval, A.R., Drawanz, B.B., Rosales, P.F., Gomes, C.R., Pereira, C.M.P., and Cunico, W., *Ultrason. Sonochem*., 2011, vol. 18, p. 65.
7. Rawal, R.K., Tripathi, R., Katti, S.B., Pannecoupe, C., and De Clercq, E., *Bioorg. Med. Chem*., 2007, vol. 15, p. 3134.
8. Abdel-Moty, S.G., Abdel-Rahman, M.H., Elsherief, H.A., and Kafafy, A.H.N., *Bull. Pharm. Sci*., 2005, vol. 28, p. 79.
9. Normad-Bayel, M., Benard, C., Zouhiri, V., Mouscadet, J., Leh, H., Thomas, C., Mbemba, G., Desmaele, D., and d'Angelo, J., *Bioorg. Med. Chem. Lett*., 2005, vol. 15, p. 4019.
10. Hazeldine, S.T., Polin, L., Kushner, J., White, K., Corbett, T.H., Biehl, J., and Horwitz, J.P., *Bioorg. Med. Chem*., 2005, vol. 13, p. 1069.
11. He, J., Yun, L., Yang, R., Xiao, Z., Cheng, J., Zhou, W., and Zhang, Y., *Bioorg. Med. Chem. Lett*., 2005, vol. 15, p. 2980.
12. Gyul'budagyan, L.V., Margaryan, I.L., and Durgaryan, V.G., *Chem. Heterocycl. Compd*., 1971, vol. 7, p. 1562.
13. Gyul'budagyan, L.V. and Durgaryan, V.G., *Chem. Heterocycl. Compd*., 1972, vol. 8, p. 487.
14. Avetisyan, A.A., Aleksanyan, I.L., and Pivazyan, A.A., *Chem. Heterocycl. Compd*., 2005, vol. 41, p. 471.