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Synthesis of Hetarylquinolines Proceeding from 2-[(2-Methylquinolin-4-yl)sulfanyl]acetohydrazide Substituted in the Benzene Ring

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Abstract—At intramolecular cyclization of phenylhydrazinocarbothioamide in alkaline and acidic media quinolyl-substituted triazoles and thiadiazoles are obtained. Quinolyl-substituted thiazolidines and thiazolidinones were obtained at interaction of phenylhydrazinocarbothioamides with bromoacetophenone and ethyl bromoacetate.

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Quinoline and its derivatives are heteroaromatic compounds which attract much attention due to their biological and pharmacological activity [1–7].

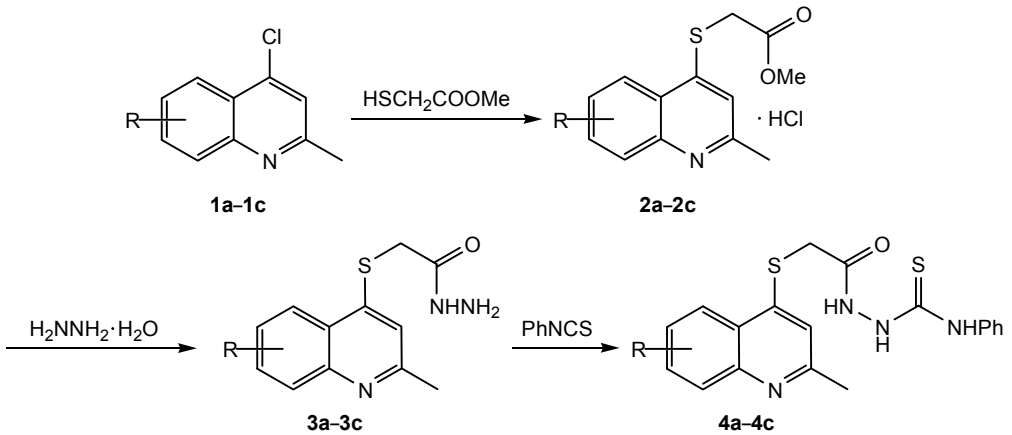
4-Substituted quinoline (triazole, thiadiazole, tiazolidine, thiazolidinone) derivatives consisting of two heterocyclic fragments, one of which is quinoline, are promising antibiotics, antimalarial drugs [8–11], compounds which exhibit anticancer, fungicidal, antiviral, antibacterial, immunomodulatory, and other activities [12–15].

Taking the above in consideration in this work we synthesized new derivatives of triazoles, thiadiazoles, thiazolidines, and thiazolidinons proceeding from 2-{[(2-methylquinolin-4-yl)sulfanyl]acetyl}-*N*-phenylhydrazine-1-carbothioamides substituted in the benzene ring.

In continuation of designing biologically active substances [16] in order to prepare target hetarylquinolines we carried out the reaction of 2-methyl-4-chloroquinolines substituted in the benzene ring **1a–1c** with methyl sulfanylacetate at room temperature in anhydrous acetone under stirring.

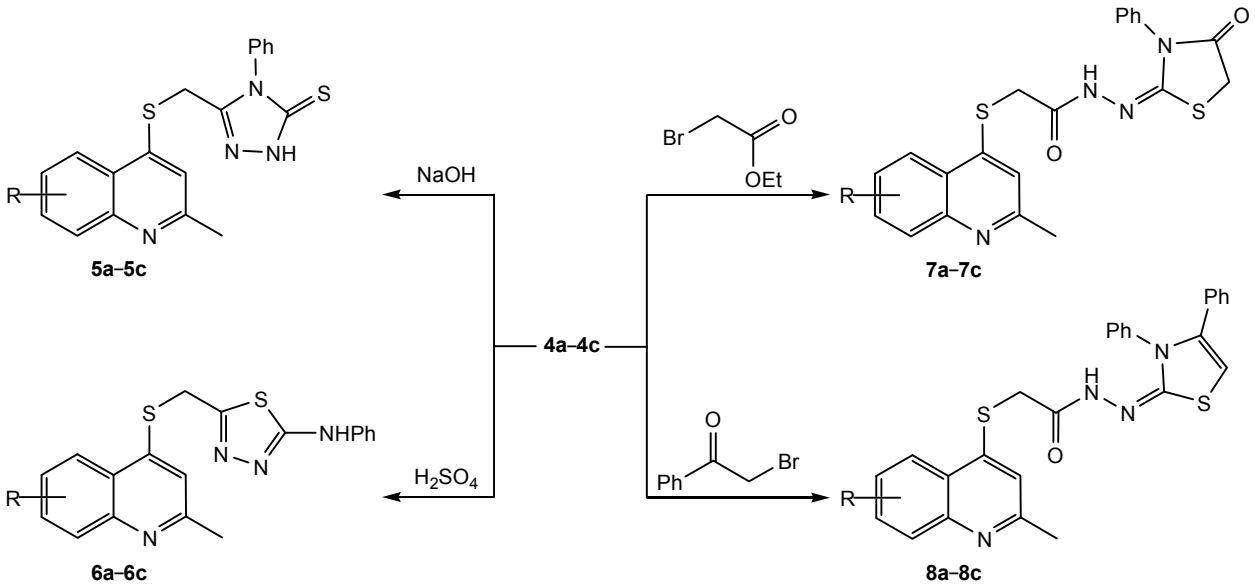
The hydrazinolysis of ethers **2a–2c** by hydrazine hydrate gave the corresponding hydrazides **3a–3c**, whose

Scheme 1.



R = H (**a**), 6-Me (**b**), 8-Me (**c**).

Scheme 2.



R = H (**a**), 6-Me (**b**), 8-Me (**c**).

reaction with thiosemicarbazide in boiling ethanol in the ratio 1 : 1 led to 2-{[(2-methylquinolin-4-yl)sulfanyl]acetyl}-*N*-phenylhydrazine-1-carbothioamides substituted in the benzene ring **4a–4c** (Scheme 1).

In order to obtain new substituted triazoles and thiadiazolines we studied the intramolecular cyclization of hydrazides **4a–4c** under the action of 5% NaOH and conc. H_2SO_4.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Varian Mercury-300 in DMSO-d_6. The homogeneity of the compounds was checked by TLC on Silufol UV-254 plates (development in iodine vapor).

Compounds 2a–2c. A mixture of 0.01 mol of compound **1a–1c** [17], 10 mL of anhydrous acetone, and 0.9 mL (0.01 mol) of methyl sulfanylacetate was stirred for 3 days at room temperature. The obtained precipitate was filtered off and washed with anhydrous acetone.

Methyl [(2-methylquinolin-4-yl)sulfanyl]acetate hydrochloride (2a). Yield 2.58 g (91%), mp 202–204°C, R_f 0.63 (ethanol–toluene 1 : 10). ^{1}H NMR spectrum, δ, ppm: 3.01 s (3H, CH_3), 3.79 s (3H, OCH_3), 4.39 s (2H, SCH_2), 7.74 s (1H$_{arom}$), 7.75–7.82 m (1H$_{arom}$), 7.98–8.04 m (1H$_{arom}$), 8.20–8.24 m (1H$_{arom}$), 8.64–8.70 m (1H$_{arom}$), 9.95 br.s (1H, HCl). Found, %: C 55.38; H 4.68; N 5.21; S 11.68. $C_{13}H_{13}NO_2S$·HCl. Calculated, %: C 55.03; H 4.94; N 4.94; S 11.29.

Methyl [(2,6-dimethylquinolin-4-yl)sulfanyl]acetate hydrochloride (2b). Yield 2.53 g (85%), mp 217–218°C, R_f 0.52 (ethanol–toluene, 1 : 8). Found, %: C 56.16; H 5.98; N 5.92; S 10.42. $C_{14}H_{15}NO_2S$·HCl. Calculated, %: C 56.47; H 5.39; N 4.71; S 10.76.

Methyl [(2,8-dimethylquinolin-4-yl)sulfanyl]acetate hydrochloride (2c). Yield 2.47 g (83%), mp 210–211°C, R_f 0.61 (toluene–ethanol, 1 : 8). ^{1}H NMR spectrum, δ, ppm: 2.55 s (3H, CH_3), 2.69 s (3H, CH_3), 3.69 s (3H, OCH_3), 4.02 s (2H, SCH_2), 7.16 s (1H$_{arom}$), 7.31–7.43 m (1H$_{arom}$), 7.51 d (1H$_{arom}$, *J* 7.1 Hz), 7.82 d (1H$_{arom}$, *J* 7.9 Hz), 9.98 br.s (1H, HCl). Found, %: C 56.89; H 5.07; N 4.37; S 10.35. $C_{14}H_{15}NO_2S$·HCl. Calculated, %: C 56.47; H 5.39; N 4.71; S 10.76.

Compounds 3a–3c. A mixture of 5 mmol of compound **2a–2c**, 20 mL of ethanol, and 3 mL of 85% sodium hydrazine hydrate was stirred at room temperature and left overnight. The obtained precipitate was filtered off and washed with ethanol.

2-[(2-Methylquinoline-4-yl)sulfanyl]acetohydrazide (3a). Yield 0.99 g (80%), mp 189–190°C, R_f 0.59 (ethanol–toluene, 3 : 1). ^{1}H NMR spectrum, δ, ppm: 2.65 s (3H, CH_3), 3.76 s (2H, SCH_2), 4.11 br.s (2H, NH_2), 7.35 s (1H$_{arom}$), 7.43–7.49 m (1H$_{arom}$), 7.59–7.66 m (1H$_{arom}$), 7.85 br.d (1H$_{arom}$, *J* 8.3 Hz), 8.01 br.d (1H$_{arom}$, *J* 8.4 Hz), 9.40 br.s (1H, NH). Found, %: C

58.54; H 5.18; N 17.11; S 13.15. $C_{12}H_{13}N_3OS$. Calculated, %: C 58.30; H 5.26; N 17.00; S 12.96.

2-[(2,6-Dimethylquinolin-4-yl)sulfanyl]acetohydrazide (3b). Yield 1.12 g (86%), mp 221–222°C, R_f 0.58 (ethanol–toluene, 1 : 2). Found, %: C 59.62; H 5.53; N 16.38; S 12.36. $C_{13}H_{15}N_3OS$. Calculated, %: C 59.77; H 5.75; N 16.09; S 12.26.

2-[(2,8-Dimethylquinolin-4-yl)sulfanyl]acetohydrazide (3c). Yield 1.11 g (85%), mp 206–207°C, R_f 0.62 (ethanol–toluene, 1 : 2). Found, %: C 59.91; H 5.88; N 15.93; S 12.11. $C_{13}H_{15}N_3OS$. Calculated, %: C 59.77; H 5.75; N 16.09; S 12.26.

Compounds 4a–4c. A mixture of 5 mmol of compound **3a–3c**, 30 mL of ethanol, and 0.68 g (0.06 mL, 5 mmol) of phenyl isothiocyanate was stirred for 3–4 h at boiling. After cooling, the resulting precipitate was filtered off and washed with ethanol.

2-{[(2-Methylquinolin-4-yl)sulfanyl]acetyl}-*N*-phenylhydrazine-1-carbothioamide (4a). Yield 1.66 g (87%), mp 196–197°C, R_f 0.59 (ethanol–toluene, 1 : 3). Found, %: C 59.84; H 4.86; N 14.93; S 16.52. $C_{19}H_{18}N_4OS_2$. Calculated, %: C 59.69; H 4.71; N 14.66; S 16.75.

2-{[(2,6-Dimethylquinolin-4-yl)sulfanyl]acetyl}-*N*-phenylhydrazine-1-carbothioamide (4b). Yield 1.76 g (89%), mp 204–206°C, R_f 0.62 (ethanol–toluene, 1 : 3). ^{1}H NMR spectrum, δ, ppm: 2.55 (3H, CH_3), 2.62 s (3H, CH_3), 3.97 s (2H, SCH_2), 7.11 t (1H$_{arom}$, *J* 7.5 Hz), 7.29 t (3H$_{arom}$, *J* 7.9 Hz), 7.46 d.d (1H$_{arom}$, *J* 8.7, 1.5 Hz), 7.53 d (2H$_{arom}$, *J* 7.9 Hz), 7.75 d (1H$_{arom}$, *J* 8.7 Hz), 7.79 br.s (1H$_{arom}$), 9.42–9.77 m (2H, NH), 10.34 br.s (1H, NH). Found, %: C 60.85; H 5.25; N 14.01; S 16.32. $C_{20}H_{20}N_4OS_2$. Calculated, %: C 60.61; H 5.05; N 14.14; S 16.16.

2-{[(2,8-Dimethylquinolin-4-yl)sulfanyl]acetyl}-*N*-phenylhydrazine-1-carbothioamide (4c). Yield 1.43 g (72%), mp 202–203°C, R_f 0.65 (ethanol–toluene, 1 : 3). Found, %: C 60.43; H 4.87; N 14.32; S 15.96. $C_{20}H_{20}N_4OS_2$. Calculated, %: C 60.61; H 5.05; N 14.14; S 16.16.

Compounds 5a–5c. To 1 mmol of compound **4a–4c** was added 15 mL of 5% NaOH solution and the mixture was boiled for 3 hours with stirring. Then 20 mL of water was added, the product was filtered off, the filtrate was acidified to pH 3.0–3.5. The precipitate was filtered off and recrystallized from 50% ethanol.

5-{[(2-Methylquinolin-4-yl)sulfanyl]methyl}-4-phenyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (5a). Yield 0.34 g (94%), mp 261–262°C, R_f 0.54 (ethanol–toluene, 1 : 3). ^{1}H NMR spectrum, δ, ppm: 2.63 s (3H, CH_3), 4.27 s (2H, SCH_2), 7.32 s (1H$_{arom}$), 7.40–7.54 m (6H$_{arom}$), 7.60–7.67 m (1H$_{arom}$), 7.83–7.88 m (2H$_{arom}$), 13.78 br.s (1H, NH). Found, %: C 62.48; H 4.65; N 15.18; S 17.34. $C_{19}H_{16}N_4S_2$. Calculated, %: C 62.64; H 4.40; N 15.38; S 17.58.

5-{[(2,6-Dimethylquinolin-4-yl)sulfanyl]methyl}-4-phenyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (5b). Yield 0.34 g (90%), mp 253–254°C, R_f 0.52 (ethanol–toluene, 1 : 3). Found, %: C 63.67; H 4.42; N 14.97; S 16.72. $C_{20}H_{18}N_4S_2$. Calculated, %: C 63.49; H 4.76; N 14.81; S 16.93.

5-{[(2,8-Dimethylquinolin-4-yl)sulfanyl]methyl}-4-phenyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (5c). Yield 0.37 g (98%), mp 223–224°C, R_f 0.60 (ethanol–toluene, 1 : 3). Found, %: C 63.61; H 4.97; N 14.93; S 17.04. $C_{20}H_{18}N_4S_2$. Calculated, %: C 63.49; H 4.76; N 14.81; S 16.93.

Compounds 6a–6c. To 1 mmol of compound **4a–4c** was added 2 mL of conc. H_2SO_4 and the solution was stirred for 3 hours at room temperature, then 20 g of crushed ice was added and the formed precipitate was filtered off and recrystallized from ethanol–water 1 : 2 mixture.

5-{[(2-Methylquinolin-4-yl)sulfanyl]methyl}-*N*-phenyl-1,3,4-thiadiazol-2-amine (6a). Yield 0.35 g (95%), mp 151–152°C, R_f 0.53 (ethanol–toluene, 1 : 3). Found, %: C 62.51; H 4.13; N 15.53; S 17.29. $C_{19}H_{16}N_4S_2$. Calculated, %: C 62.64; H 4.40; N 15.38; S 17.58.

5-{[(2,6-Dimethylquinolin-4-yl)sulfanyl]methyl}-*N*-phenyl-1,3,4-thiadiazol-2-amine (6b). Yield 0.36 g (95%), mp 198–199°C, R_f 0.63 (ethanol–toluene, 1 : 2). ^{1}H NMR spectrum, δ, ppm: 2.58 s (3H, CH_3), 2.62 s (3H, CH_3), 5.14 s (2H, SCH_2), 7.02 s (1H$_{arom}$), 7.21–7.42 m (2H$_{arom}$), 7.45–7.61 m (3H$_{arom}$), 7.83–8.01 m (3H$_{arom}$), 10.38 br.s (1H, NH). Found, %: C 63.62; H 4.51; N 14.68; S 17.05. $C_{20}H_{18}N_4S_2$. Calculated, %: C 63.49; H 4.76; N 14.81; S 16.93.

5-{[(2,8-Dimethylquinoline4-yl)sulfanyl]-methyl}-*N*-phenyl-1,3,4-thiadiazol-2-amine (6c). Yield 0.36 g (95%), mp 155–156°C, R_f 0.64 (ethanol–toluene, 1 : 3).

Compounds 7a–7c. A mixture of 1 mmol of substance **4a–4c**, 10 mL of anhydrous ethanol, 0.246 g

(3 mmol) of anhydrous sodium acetate, and 0.22 g (0.15 mL, 1.3 mmol) of ethyl bromoacetate was stirred for 10–12 h at boiling. After cooling some water was added to the mixture, it was filtered, and neutralized. The precipitate was filtered off and recrystallized from ethanol–water mixture, 1 : 2.

2-[(2-Methylquinolin-4-yl)sulfanyl]-*N*'-(4-oxo-3-phenyl-1,3-thiazolidin-2-ylidene)acetohydrazide (7a). Yield 0.32 g (75%), mp 251–252°C, R_f 0.47 (ethanol–toluene, 1 : 3). Found, %: C 59.87; H 4.42; N 13.11; S 15.31. $C_{21}H_{18}N_4O_2S_2$. Calculated, %: C 59.72; H 4.27; N 13.27; S 15.17.

2-[(2,6-Dimethylquinolin-4-yl)sulfanyl]-*N*'-(4-oxo-3-phenyl-1,3-thiazolidin-2-ylidene)acetohydrazide (7b). Yield 0.34 g (77%), mp 272–273°C, R_f 0.57 (ethanol–toluene, 1 : 3). ^{1}H NMR spectrum, δ, ppm: 2.53 s (3H, CH_3), 2.56 s (3H, CH_3), 4.02 d (1H, SCH_2, *J* 16.3 Hz), 4.06 d (1H, SCH_2, *J* 16.3 Hz), 4.06 s (2H, SCH_2), 6.86–6.91 m (2H$_{arom}$), 7.10 br.s (1H$_{arom}$, *J* 7.3 Hz), 7.27–7.34 m (3H$_{arom}$), 7.47 d.d (1H$_{arom}$, J_1 8.6, J_2 1.5 Hz), 7.75 d (1H$_{arom}$, *J* 8.6 Hz), 7.81 d (1H$_{arom}$, *J* 1.5 Hz), 11.08 s (1H, NH). Found, %: C 60.36; H 4.38; N 12.97. $C_{22}H_{20}N_4O_2S_2$. Calculated, %: C 60.55; H 4.59; N 12.84; S 14.68.

2-[(2,8-Dimethylquinolin-4-yl)sulfanyl]-*N*'-(4-oxo-3-phenyl-1,3-thiazolidin-2-ylidene)acetohydrazide (7c). Yield 0.32 g (72%), mp 225–226°C, R_f 0.57 (ethanol–toluene, 1 : 3). Found, %: C 60.41; H 4.61; N 12.99; S 14.72. $C_{22}H_{20}N_4O_2S_2$. Calculated, %: C 60.55; H 4.59; N 12.84; S 14.68.

Compounds 8a–8c. A mixture of 1 mmol of compound **4a–4c**, 10 mL of anhydrous ethanol, 0.246 g (3 mmol) of anhydrous sodium acetate, and 0.199 g (1 mmol) of bromoacetophenone was stirred for 20–25 h at boiling. After cooling and neutralization the formed precipitate was filtered off and recrystallized from 50% ethanol.

***N*'-[3,4-Diphenyl-1,3-thiazol-2(3*H*)-ylidene]-2-[(2-methylquinoline-4-yl)sulfanyl]acetohydrazide (8a).** Yield 0.4 g (83%), mp 201–202 °C, R_f 0.56 (ethanol–toluene, 1 : 3). ^{1}H NMR spectrum, δ, ppm: 2.61 s (3H, CH_3), 3.82 s (2H, SCH_2), 6.94 s (1H, =CH), 7.14 s (1H$_{arom}$), 7.28–7.51 m (7H$_{arom}$), 7.58–7.69 m (2H$_{arom}$), 7.73–7.89 m (3H$_{arom}$), 7.91–8.05 m (2H$_{arom}$) 10.26 br.s (1H, NH). Found, %: C 67.35; H 4.61; N 11.48; S 13.52. $C_{27}H_{22}N_4OS_2$. Calculated, %: C 67.22; H 4.56; N 11.62; S 13.28.

***N*'-[3,4-Diphenyl-1,3-thiazol-2(3*H*)-ylidene]-2-[(2,6-dimethylquinolin-4-yl)sulfanyl]acetohydrazide (8b).** Yield 0.39 g (79%), mp 231–232°C, R_f 0.55 (ethanol–toluene, 1 : 3). Found, %: C 67.53; H 4.68; N 11.09; S 12.73. $C_{28}H_{24}N_4OS_2$. Calculated, %: C 67.74; H 4.84; N 11.29; S 12.90.

***N*'-[3,4-Diphenyl-1,3-thiazol-2(3*H*)-ylidene]-2-[(2,8-dimethylquinolin-4-yl)sulfanyl]acetohydrazide (8c).** Yield 0.39 g (79%), mp 225–226°C, R_f 0.58 (ethanol–toluene, 1 : 3). Found, %: C 67.91; H 4.63; N 11.41; S 13.06. $C_{28}H_{24}N_4OS_2$. Calculated, %: C 67.74; H 4.84; N 11.29; S 12.90.

REFERENCES

1. Abdel-Moty, S.G., Abdel-Rahman, M.H., Elsherief, H.A., and Kafafy, A.H.N., *Bull. Pharm. Sci*., 2005, vol. 28, p. 79.
2. Normand-Bayle, M., Bénard, C., Zouhiri, V., Mouscadet, J., Leh, H., Thomas, C., Mbemba, G., Desmaële, D., and d'Angelo, J., *Bioorg. Med. Chem. Lett*., 2005, vol. 15, p. 4019. doi 10.1016/j.bmcl.2005.06.036
3. Hazeldine, T., Polin, L., Kushner, J., White, K., Corbett, T.H., Biehl, J., and Horwitz, J.P., *Bioorg. Med. Chem*., 2005, vol. 13, p. 1069. doi 10.1016/j.bmc.2004.11.034
4. He, J., Yun, L., Yang, R., Xiao, Z., Cheng, J., Zhou, W., and Zhang, Y., *Bioorg. Med. Chem. Lett*., 2005, vol. 15, p. 2980. doi 10.1016/j.bmcl.2005.04.040
5. Kravchenko, D.V., Kysil, V.V., Ilyn, A.P., Tkachenko, S.E., Maliarchouk, S., Okun, I.M., and Ivachtchenko, A.V., *Bioorg. Med. Chem. Lett*., 2005, vol. 15, p. 1841. doi 10.1016/j.bmcl.2005.02.027
6. Dardari, Z., Lemrani, M., Bahloul, A., Sebban, A., Hassar, M., Kitane, S., Berrada, M., and Boudoum, M., *Farmaco*, 2004, vol. 59, p. 195.
7. Goda, F.E., Abdel-Aziz, A.A., and Ghoneim, H.A., *Bioorg. Med. Chem*., 2005, vol. 13, p. 3175. doi 10.1016/j.bmc.2005.02.050
8. Mashkovskii, M.D., *Lekarstvennye sredstva* (Drugs), Moscow: Novaya Volna, 2010.
9. Waghamale, S. and Piste, P., *Int. J. Pharm. Bio. Sci*., 2013, vol. 4, p. 310.
10. Saad, H.A., Osman, N.A., and Moustafa, A.H., *Molecules*, 2011, vol. 16, p. 10187. doi 10.3390/molecules161210187

11. Shaker, R.M., *Arkivoc*, 2006, part (ix), p. 59.
12. Neuenfeldt, P.D., Duval, A.R., Drawanz, B.B., Rosales, P.F., Gomes, C.R.B., Pereira, C.M.P., and Cunico, W., *Ultrason. Sonochem*., 2011, vol. 18, p. 65. doi 10.1016/j.ultsonch.2010.07.008
13. Hussein, M., Kafafy, A.H., Abdel-Moty, S., and Abou-Ghadir, O., *Acta Pharm*., 2009, vol. 59, p. 365. doi 10.2478/v10007-009-0033-8
14. Abhinit, M., Ghodke, M., and Pratima, N.A., *Int. J. Pharm. Pharm. Sci*., 2009, vol. 1, p. 47.
15. Rawal, R.K., Tripathi, R., Katti, S.B., Pannecouque, C., and De Clercq, E., *Bioorg. Med. Chem*., 2007, vol. 15, p. 3134. doi 10.1016/j.bmc.2007.02.044
16. Malakyan, M.G., Badzhinyan, S.A., Vardevanyan, L.A., Grigoryan, D.S., Egiazaryan, D.E., Avetisyan, A.A., Aleksanyan, I.L., Ambartsumyan, L.P., and Sargsyan, K.S., *Pharm. Chem. J*., 2009, vol. 43, p. 7. doi 10.1007/s11094-009-0220-4
17. Avetisyan, A.A., Aleksanyan, I.L., and Ambartsumyan, L.P., *Russ. J. Org. Chem*., 2007, vol. 43, p. 1048. doi 10.1134/S1070428007070184