DOI 10.1007/s11094-019-1911-0
Pharmaceutical Chemistry Journal, Vol. 52, No. 10, January, 2019 (Russian Original Vol. 52, No. 10, October, 2018)

SYNTHESIS AND NEUROTROPIC ACTIVITY OF 4-PHENYLPYRIDINE-3-CARBOXYLIC ACID AND 3-HYDROXY-4-PHENYLTHIENO[2,3-*b*]-PYRIDINE DERIVATIVES

E. G. Paronikyan,[1] A. V. Ogannisyan,[1,*] R. G. Paronikyan,[1] I. A. Dzhagatspanyan,[1] I. M. Nazaryan,[1] A. G. Akopyan,[1] and N. S. Minasyan[2]

Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 52, No. 10, pp. 22 – 27, October, 2018.

Original article submitted April 4, 2017.

A series of pyridine-3-carboxylic acid derivatives were synthesized via recyclization of a thiopyran ring using cyclic secondary amines and then converted into substituted thieno[2,3-*b*]pyridines. Studies of the neurotropic properties identified several synthesized compounds with anticonvulsant activity against corazole-induced seizures. The compounds were active as psychological sedatives and, in contrast with the tranquilizer diazepam, were inactive as central myorelaxants at anticonvulsant doses.

Keywords: pyridine-3-carboxylic acid derivatives, thieno[2,3-*b*]pyridines, neurotropic activity.

Modeling of a pathology itself in animals and of its separate manifestations is an important and critical factor in the search for new neurotropic compounds for experimental psychopharmacology. Such an approach of differentiated (use of interoceptive irritants, e.g., corazole) and integrated (e.g., open field test) modeling, a biostatistical evaluation of the spectra of pharmacological activity of the compounds, and a comparison of main and side effects allow a more refined selection from newly synthesized compounds.

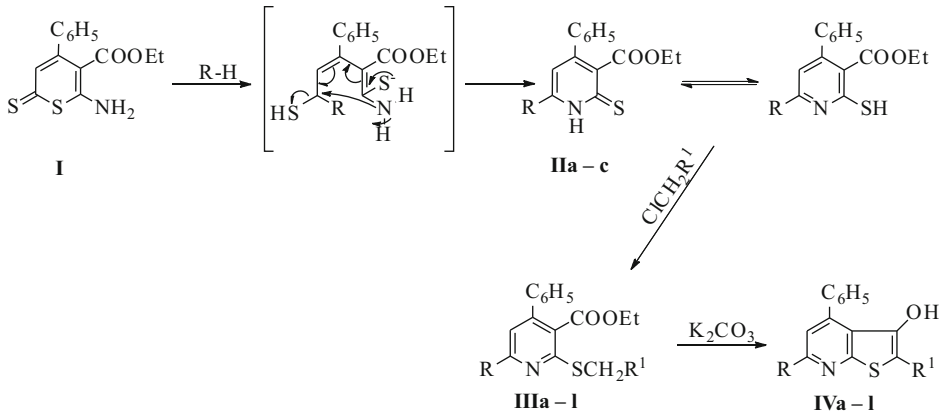
Pyridine and its condensed analogs appear in the structures of many drugs [1]. Thieno[2,3-*b*]pyridines also include compounds with high biological activity [2 – 5].

Condensed thieno[2,3-*b*]pyridines with neurotropic activity were previously prepared by us [6 – 8]. In continuation of this research, ethyl esters of 4-phenyl-2-thioxo-1,2-dihydropyridine-3-carboxylic acid were synthesized and cyclized into thieno[2,3-*b*]pyridines that were studied for neurotropic activity in the present work.

[1] A. L. Mnjoyan Institute of Fine Organic Chemistry, Scientific and Technological Center of Organic and Pharmaceutical Chemistry, National Academy of Sciences of Armenia, 0014 Yerevan, 375014 Armenia.
[2] Molecular Structure Research Center, Scientific and Technological Center of Organic and Pharmaceutical Chemistry, National Academy of Sciences of Armenia, 0014 Yerevan, 375014 Armenia.
[*] e-mail: Haykuhihovhannisyan011@gmail.com

Thieno[2,3-*b*]pyridines (**IVa-l**) were synthesized from ethyl 6-amino-4-phenyl-2-thioxo-2*H*-thiopyran-5-carboxylate [9], reaction of which with morpholine, piperidine, and pyrrolidine occurred with recyclization of the thiopyran ring and rearrangement to produce ethyl 4-phenyl-2-thioxo-1,2-dihydropyridine-3-carboxylates (**IIa-c**). It was proposed that the reaction with the amines involved nucleophilic attack at thiopyran C-2, cleavage of the C(2)–S bond, and formation of a pyridine ring.

Thione–thiol tautomerism is known to occur in 2-thioxopyridines [10]. IR spectra showed that **IIa-c** in the crystalline form existed as the thione because SH absorption bands were missing in the spectra and absorption bands characteristic of C=S and NH appeared at 1200 – 1200 and 3530 cm^{-1}. However, the equilibrium shifted toward the thiol form upon reaction with alkyl halides in basic solution. Ethyl 4-phenyl-2-thioxo-1,2-dihydropyridine-3-carboxylates **IIa-c** were alkylated by various alkyl halides with electron-accepting groups in the α-position. Next, S-substituted pyridine derivatives **IIIa-l** were cyclized by refluxing for 2 h in EtOH in the presence of K_2CO_3. IR spectra of **IVa-l** contained absorption bands for OH at 3180 – 3230 cm^{-1}. PMR spectra had OH singlets at 10.40 – 14.00 ppm.



II) **a**: R = morpholin-4-yl; **b**: R = piperidin-1-yl; **c**: R = pyrrolidin-1-yl. **III**, **IV**) **a**-**g**: R = morpholin-4-yl; **III**, **IV**) **h**, **i**: R = piperidin-1-yl; **III**, **IV**) **j**-**l**: R = pyrrolidin-1-yl; **III**, **IV**) **a**, **k**: R^1 = COOMe; **b**, **h**, **j**: R^1 = COOEt; **c**, **l**: R^1 = $CONH_2$; **d**: R^1 = morpholin-4-ylcarbonyl; **e**: R^1 = pyrrolidin-1-ylcarbonyl; **f**: R^1 = *N*-1,3-thiazol-2-ylcarboxamide; **g**: R^1 = (2-methoxyphenyl)aminocarbonyl; **i**: R^1 = COC_6H_5.

EXPERIMENTAL CHEMICAL PART

IR spectra were recorded in mineral oil on a Nicolet Avatar 330 FT-IR spectrometer (USA). PMR and ^{13}C NMR spectra (δ, ppm, SSCC *J*, Hz) were recorded in DMSO-d_6 on a Mercury 300 Vx instrument (USA) at 300 and 75.462 MHz, respectively. The purity of compounds was monitored by TLC on Silufol UV-254 plates using Me_2CO–Et_2O (1:2, **IIa-c**); Et_2O–hexane (3:1, **IIIa-l**); and $CHCl_3$–hexane (3:1, **IVa-l**) and detection by I_2 vapor. Elemental analyses agreed with the empirical formulas.

General method for preparing IIa-c. A mixture of **I** (2.9 g, 10 mmol), the appropriate amine (5 mL), and anhydrous EtOH (15 mL) was refluxed for 4 h, cooled, treated with H_2O (50 mL), and neutralized with HCl (10%). The resulting crystals were filtered off, rinsed with H_2O, and recrystallized from EtOH. IR spectra, ν_{max}, cm^{-1}: 1200 – 1220 (C=S), 1680 – 1695 (CO), 3530 (NH).

Ethyl 6-morpholin-4-yl-4-phenyl-2-thioxo-1,2-dihydropyridine-3-carboxylate (IIa). Yield 2.5 g (73%), mp 109 – 110°C. R_f 0.59. $C_{18}H_{20}N_2O_3S$. PMR spectrum (DMSO-d_6), δ, ppm: 1.02 (t, 3H, J 7.1 Hz, $CH_2\underline{CH_3}$); 3.41 – 3.57 (m, 4H, $N(CH_2)_2$); 3.62 – 3.79 (m, 4H, $O(CH_2)_2$); 3.97 (q, 2H, J 7.1 Hz, $\underline{CH_2}CH_3$); 6.03 (s, 1H, 5-CH); 7.24 – 7.41 (m, 5H, C_6H_5); 12.31 (br.s, 1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 13.1, 46.3, 59.6, 65.5, 98.2, 103.6, 127.0, 127.6, 127.8, 140.2, 151.8, 153.1, 158.2, 166.5.

Ethyl 4-phenyl-6-piperidin-1-yl-2-thioxo-1,2-dihydropyridine-3-carboxylate (IIb). Yield 23.5 g (69%), mp 141 – 142°C. R_f 0.58. $C_{19}H_{22}N_2O_2S$. PMR spectrum (DMSO-d_6), δ, ppm: 0.96 (t, 3H, J 7.1 Hz, $CH_2\underline{CH_3}$), 1.63 – 1.71 (m, 6H, 6-$(CH_2)_3$), 3.46 – 3.55 (m, 4H, $N(CH_2)_2$), 3.79 (q, 2H, J 7.1 Hz, $\underline{CH_2}CH_3$), 5.97 (s, 1H, 5-CH), 7.30 – 7.39 (m, 5H, C_6H_5), 12.19 (br.s, 1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 13.1, 23.5, 24.7, 45.2, 59.5, 103.1, 111.5, 127.0, 127.2, 127.4, 140.6, 152.0, 156.3, 157.1, 166.0.

Ethyl 4-phenyl-6-pyrrolidin-1-yl-2-thioxo-1,2-dihydropyridine-3-carboxylate (IIc). Yield 2.20 g (67%), mp 134 – 135°C. R_f 0.59. $C_{18}H_{20}N_2O_2S$. PMR spectrum (DMSO-d_6), δ, ppm: 1.00 (t, 3 H, J 7.1 Hz, $CH_2\underline{CH_3}$), 2.01 – 2.07 (m, 4H, 6-$(CH_2)_2$), 3.50 – 3.56 (m, 4H, $N(CH_2)_2$), 3.95 (q, 2H, J 7.1 Hz, $\underline{CH_2}CH_3$), 5.71 (s, 1H, 5-CH), 7.29 – 7.42 (m, 5H, C_6H_5), 11.29 (br.s, 1H, NH).

General method for preparing IIIa-l. A solution of Na_2CO_3 prepared from Na_2CO_3 (0.25 g, 2.3 mmol) and H_2O (8 mL) was treated with **IIa-c** (2.3 mmol). The mixture was stirred until transparent, treated with the appropriate alkyl halide (2.3 mmol) in EtOH (8 mL), and stirred at 20 – 22°C for 6 h. The resulting crystals were filtered off, rinsed with H_2O, and recrystallized from EtOH. IR spectra, ν_{max}, cm^{-1}: 1650 – 1680 and 1690 – 1725 (C=O), 3350 and 3410 (NH) (**IIIf**, **g**), 3144 – 3150 and 3425 – 3430 (NH_2) (**IIIc**, **l**).

Ethyl 2-[(2-methoxy-2-oxoethyl)thio]-6-morpholin-4-yl-4-phenylnicotinate (IIIa). Yield 0.93 g (97%), mp 163 – 164°C. R_f 0.66. $C_{21}H_{24}N_2O_5S$. PMR spectrum (DMSO-d_6), δ, ppm: 0.85 (t, 3 H, J 7.6 Hz, $CH_2\underline{CH_3}$), 3.58 – 3.69 (m, 11H, $N(CH_2)_4O$, OCH_3), 3.79 (s, 2H, SCH_2), 3.89 (q, 2H, J 7.6, $\underline{CH_2}CH_3$), 6.31 (s, 1H, 5-CH), 7.20 – 7.27 (m, 2H, C_6H_5), 7.29 – 7.36 (m, 3H, C_6H_5). ^{13}C NMR spectrum, δ_C, ppm: 12.9, 32.1, 44.4, 51.4, 59.5, 65.7, 102.6, 113.2, 127.1, 127.2, 127.5, 140.2, 151.7, 156.8, 157.1, 165.7, 169.0.

Ethyl 2-[(2-ethoxy-2-oxoethyl)thio]-6-morpholin-4-yl-4-phenylnicotinate (IIIb). Yield 0.95 g (96%), mp 133 – 134°C. R_f 0.67. $C_{22}H_{26}N_2O_5S$. PMR spectrum (DMSO-d_6), δ, ppm: 0.83 (t, 3H, J 7.1 Hz, $CH_2\underline{CH_3}$), 1.26 (t, 3H, J 7.1 Hz, $CH_2\underline{CH_3}$), 3.54 – 3.62 (m, 4H, $N(CH_2)_2$), 3.67 – 3.73 (m, 4H, $O(CH_2)_2$), 3.78 (s, 2H, SCH_2), 3.90 (q, 2H, J 7.1 Hz, $\underline{CH_2}CH_3$), 4.11 (q, 2 H, J 7.1 Hz, $\underline{CH_2}CH_3$), 6.32 (s, 1H, 5-CH), 7.22 – 7.28 (m, 2H, C_6H_5), 7.31 – 7.40 (m, 3H, C_6H_5).

Ethyl 2-[(2-amino-2-oxoethyl)thio]-6-morpholin-4-yl-4-phenylnicotinate (IIIc). Yield 0.80 g (87%), mp 172 – 173°C. R_f 0.62. $C_{20}H_{23}N_3O_4S$. PMR spectrum (DMSO-d_6), δ, ppm: 0.84 (t, 3 H, J 7.1 Hz, $CH_2\underline{CH_3}$),

3.59 – 3.65 (m, 6H, $N(CH_2)_2$, SCH_2), 3.69 – 3.78 (m, 4H, $O(CH_2)_2$), 3.91 (q, 2H, J 7.1 Hz, $\underline{CH_2}CH_3$), 6.31 (s, 1H, 5-CH), 6.85 and 6.94 (br.s, 1H and 1H, NH_2), 7.21 – 7.26 (m, 2H, C_6H_5), 7.28 – 7.38 (m, 3H, C_6H_5).

Ethyl 6-morpholin-4-yl-2-[(2-morpholin-4-yl-2-oxoethyl)thio]-4-phenylnicotinate (IIId). Yield 1.05 g (95%), mp 158 – 160°C. R_f 0.67. $C_{24}H_{29}N_3O_5S$. PMR spectrum (DMSO-d_6), δ, ppm: 0.84 (t, 3H, J 7.2 Hz, $CH_2\underline{CH_3}$), 3.49 – 3.73 (m, 16H, 2[$N(CH_2)_4O$]), 3.86 (q, 2H, J 7.2 Hz, $\underline{CH_2}CH_3$), 3.99 (c, 2H, SCH_2), 6.33 (s, 1H, 5-CH), 7.23 – 7.28 (m, 2H, C_6H_5), 7.30 – 7.39 (m, 3H, C_6H_5).

Ethyl 6-morpholin-4-yl-2-[(2-oxo-2-pyrrolidin-1-ylethyl)thio]-4-phenylnicotinate (IIIe). Yield 0.87 g (79%), mp 177 – 180°C. R_f 0.63. $C_{24}H_{29}N_3O_4S$. PMR spectrum (DMSO-d_6), δ, ppm: 0.85 (t, 3H, J 7.1 Hz, $CH_2\underline{CH_3}$), 1.82 – 1.92 (m, 2H, $NCH_2\underline{CH_2}$), 1.95 – 2.04 (m, 2H, $NCH_2\underline{CH_2}$), 3.37 (t, 2H, J 6.8 Hz, $NCH_2\underline{CH_2}$), 3.36 (t, 2H, J 6.8 Hz, $N\underline{CH_2}CH_2$), 3.58 – 3.63 (m, 4H, 6-$N(CH_2)_2$), 3.68 – 3.73 (m, 4H, 6-$O(CH_2)_2$), 3.89 (c, 2H, SCH_2), 3.91 (q, 2 H, J 7.1 Hz, $\underline{CH_2}CH_3$), 6.32 (c, 1H, 5-CH), 7.24 – 7.29 (m, 2H, C_6H_5), 7.33 – 7.40 (m, 3H, C_6H_5).

Ethyl 6-morpholin-4-yl-2-{[2-oxo-2-(1,3-thiazol-2-yl)-ethyl]thio}-4-phenylnicotinate (IIIf). Yield 0.85 g (77%), mp 159 – 160°C. R_f 0.68. $C_{23}H_{24}N_4O_4S_2$. PMR spectrum (DMSO-d_6), δ, ppm: 0.84 (t, 3 H, J 7.1 Hz, $CH_2\underline{CH_3}$), 3.51 – 3.58 (m, 8H, $N(CH_2)_4O$), 3.91 (q, 2H, J 7.1 Hz, $\underline{CH_2}CH_3$), 3.98 (s, 2H, SCH_2), 6.29 (s, 1H, 5-CH), 6.97 (d, 1H, J 3.6 Hz, S$\underline{CH}$CHN), 7.22 – 7.28 (m, 2H, C_6H_5), 7.32 – 7.37 (m, 3H, C_6H_5), 7.39 (d, 1H, J 3.6 Hz, SCH$\underline{CH}$N), 12.08 (s, 1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 13.0, 33.8, 44.4, 59.5, 65.6, 102.6, 112.3, 113.4, 127.1, 127.2, 127.5, 136.9, 140.2, 151.4, 156.8, 157.2, 157.9, 165.9, 166.3.

Ethyl 2-({2-[(2-methoxyphenyl)amino]-2-oxoethyl}-thio)-6-morpholin-4-yl-4-phenylnicotinate (IIIg). Yield 0.94 g (78%), mp 187 – 189°C. R_f 0.65. $C_{27}H_{29}N_3O_5S$. PMR spectrum (DMSO-d_6), δ, ppm: 0.87 (t, 3 H, J 7.1 Hz, $CH_2\underline{CH_3}$), 3.56 – 3.64 (m, 8H, $N(CH_2)_4O$), 3.77 (s, 3H, OCH_3), 3.86 (s, 2H, SCH_2), 3.94 (q, 2H, J 7.1, $CH_2\underline{CH_3}$), 6.37 (s, 1H, 5-CH), 6.83 – 6.90 (m, 2H, C_6H_4), 6.93 – 6.98 (m, 1H, C_6H_4), 7.24 – 7.30 (m, 2H, C_6H_5), 7.34 – 7.40 (m, 3H, C_6H_5), 8.20 (dd, 1H, J 8.6 Hz, 2.0 C_6H_4), 9.08 (s, 1H, NH).

Ethyl 2-[(2-ethoxy-2-oxoethyl)thio]-6-piperidin-1-yl-4-phenylnicotinate (IIIh). Yield 0.77 g (78%), mp 129 – 130°C. R_f 0.63. $C_{23}H_{28}N_2O_4S$. PMR spectrum (DMSO-d_6), δ, ppm: 0.82 (t, 3H, J 7.1 Hz, $\underline{CH_2}CH_3$), 1.27 (t, 3H, J 7.1 Hz, $\underline{CH_2}CH_3$), 1.58 – 1.74 (m, 6H, 6-$(CH_2)_3$), 3.60 – 3.66 (m, 4H, $N(CH_2)_2$), 3.79 (s, 2H, SCH_2), 3.89 (q, 2H, J 7.1 Hz, $O\underline{CH_2}CH_3$), 4.13 (q, 2H, J 7.1 Hz, $O\underline{CH_2}CH_3$), 6.25 (s, 1H, 5-CH), 7.21 – 7.26 (m, 2H, C_6H_5), 7.31 – 7.38 (m, 3H, C_6H_5).

Ethyl 2-[(2-oxo-2-phenylethyl)thio]-6-piperidin-1-yl-4-phenylnicotinate (IIIi). Yield 0.87 g (79%), mp 169 – 170°C. R_f 0.68. $C_{27}H_{28}N_2O_3S$. PMR spectrum (DMSO-d_6), δ, ppm: 0.82 (t, 3H, J 7.1 Hz, $CH_2\underline{CH_3}$), 1.33 – 1.59 (m, 6H, 6-$(CH_2)_3$), 3.39 – 3.45 (m, 4 H, $N(CH_2)_2$), 3.89 (q, 2H, J 7.1 Hz, $\underline{CH_2}CH_3$), 4.58 (s, 2H, SCH_2), 6.22 (s, 1H, 5-CH), 7.22 – 7.26 (m, 2H, C_6H_5), 7.31 – 7.37 (m, 3H, C_6H_5), 7.46 – 7.62 (m, 3H, C_6H_5), 8.03 – 8.07 (m, 2H, C_6H_5).

Ethyl 2-[(2-ethoxy-2-oxoethyl)thio]-6-pyrrolidin-1-yl-4-phenylnicotinate (IIIj). Yield 0.75 g (78%), mp 159 – 160°C. R_f 0.67. $C_{22}H_{26}N_2O_4S$. PMR spectrum (DMSO-d_6), δ, ppm: 0.82 (t, 3H, J 7.1 Hz, $CH_2\underline{CH_3}$), 1.27 (t, 3H, J 7.1 Hz, $CH_2\underline{CH_3}$), 2.00 – 2.06 (m, 4H, 6-$(CH_2)_2$), 3.47 – 3.54 (m, 4H, $N(CH_2)_2$), 3.82 (s, 2H, SCH_2), 3.87 (q, 2H, J 7.1 Hz, $O\underline{CH_2}CH_3$), 4.15 (q, 2H J 7.1 Hz, $OCH_2\underline{CH_3}$), 5.97 (s, 1H, 5-CH), 7.21 – 7.26 (m, 2H, C_6H_5), 7.31 – 7.38 (m, 3H, C_6H_5). ^{13}C NMR spectrum, δ_C, ppm: 12.9, 13.7, 24.8, 32.3, 46.1, 59.2, 60.0, 102.5, 111.3, 126.9, 127.0, 127.4, 140.6, 151.3, 155.1, 157.3, 166.0, 168.6.

Ethyl 2-[(2-methoxy-2-oxoethyl)thio]-6-pyrrolidin-1-yl-4-phenylnicotinate (IIIk). Yield 0.67 g (72%), mp 176 – 177°C. R_f 0.65. $C_{21}H_{24}N_2O_4S$. PMR spectrum (DMSO-d_6), δ, ppm: 0.81 (t, 3H, J 7.1 Hz, $CH_2\underline{CH_3}$), 1.97 – 2.09 (m, 4H, 6-$(CH_2)_2$), 3.44 – 3.55 (m, 4H, $N(CH_2)_2$), 3.68 (s, 3H, OCH_3), 3.83 (s, 2H, SCH_2), 3.87 (q, 2H, J 7.1 Hz, $\underline{CH_2}CH_3$), 5.96 (s, 1H, 5-CH), 7.20 – 7.26 (m, 2H, C_6H_5), 7.29 – 7.38 (m, 3H, C_6H_5).

Ethyl 2-[(2-amino-2-oxoethyl)thio]-6-pyrrolidin-1-yl-4-phenylnicotinate (IIIl). Yield 0.66 g (73%), mp 181 – 182°C. R_f 0.69. $C_{20}H_{23}N_3O_3S$. PMR spectrum (DMSO-d_6), δ, ppm: 0.82 (t, 3H, J 7.1 Hz, $CH_2\underline{CH_3}$), 2.01 – 2.06 (m, 4H, 6-$(CH_2)_2$), 3.51 – 3.57 (m, 4H, $N(CH_2)_2$), 3.66 (s, 2H, SCH_2), 3.87 (q, 2H, J 7.1 Hz, $\underline{CH_2}CH_3$), 5.98 (s, 1H, 5-CH), 6.80 and 6.90 (br.s, 1H and 1H, NH_2), 7.22 – 7.26 (m, 2H, C_6H_5), 7.31 – 7.39 (m, 3H, C_6H_5). ^{13}C NMR spectrum, δ_C, ppm: 13.0, 24.8, 33.5, 46.2, 59.3, 102.5, 111.8, 127.0, 127.1, 127.4, 140.5, 151.1, 155.2, 157.0, 166.1, 170.0.

General method for preparing IVa-l. A mixture of **IIIa-l** (2 mmol), K_2CO_3 (0.28 g, 2 mmol), and anhydrous EtOH (5 mL) was refluxed for 2 h. The resulting crystals were filtered off, placed into a beaker, and treated with conc. HCl (2 mL) until white crystals formed. These crystals were filtered off, rinsed with H_2O until neutral, and recrystallized from $CHCl_3$–EtOH (1:1). IR spectra, ν_{max}, cm^{-1}: 1655 – 1716 (CO), 3180 – 3230 (OH), 3320 and 3380 (NH) (**IVf**, **g**), 3330 and 3380 (NH_2) (**IVc**, **l**).

Methyl 3-hydroxy-6-morpholin-4-yl-4-phenylthieno-[2,3-*b*]pyridine-2-carboxylate (IVa). Yield 0.7 g (92%), mp 214 – 215°C. R_f 0.67. $C_{19}H_{18}N_2O_4S$. PMR spectrum (DMSO-d_6), δ, ppm: 3.68 – 3.80 (m, 8H, $N(CH_2)_4O$), 3.88 (s, 3H, OCH_3), 6.63 (s, 1H, 5-CH), 7.38 – 7.46 (m, 5H, C_6H_5), 10.40 (s, 1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 44.7, 51.1, 65.8, 104.4, 106.1, 112.2, 127.0, 127.6, 128.7, 137.2, 148.2, 158.2, 158.7, 161.1, 166.7.

Ethyl 3-hydroxy-6-morpholin-4-yl-4-phenylthieno-[2,3-*b*]pyridine-2-carboxylate (IVb). Yield 0.74 g (99%), mp 160 – 161°C. R_f 0.62. $C_{20}H_{20}N_2O_4S$. PMR spectrum

(DMSO-d_6), δ, ppm: 1.39 (t, 3H, J 7.1 Hz, $CH_2\underline{CH_3}$), 3.65 – 3.76 (m, 8H, $N(CH_2)_4O$), 4.34 (q, 2H, J 7.1 Hz, $\underline{CH_2}CH_3$), 6.55 (s, 1H, 5-CH), 7.33 – 7.45 (m, 5H, C_6H_5), 10.48 (s, 1H, OH).

3-Hydroxy-6-morpholin-4-yl-4-phenylthieno[2,3-*b*]pyridine-2-carboxamide (IVc). Yield 0.66 g (88%), mp 249 – 250°C. R_f 0.65. $C_{18}H_{17}N_3O_3S$. PMR spectrum (DMSO-d_6), δ, ppm: 3.62 – 3.78 (m, 8H, $N(CH_2)_2O$), 6.61 (s, 1H, 5-CH), 7.32 – 7.49 (m, 7H, C_6H_5, NH_2), 13.08 (s, 1H, OH).

3-Hydroxy-6-morpholin-4-yl-2-(morpholin-4-ylcarbonyl)-4-phenylthieno[2,3-*b*]pyridine (IVd). Yield 0.51 g (60%), mp 196 – 197°C. R_f 0.62. $C_{22}H_{23}N_3O_4S$. PMR spectrum (DMSO-d_6), δ, ppm: 3.66 – 3.81 (m, 16H, $2[N(CH_2)_4O]$), 6.62 (s, 1H, 5-CH), 7.37 – 7.47 (m, 5H, C_6H_5), 13.36 (s, 1H, OH).

3-Hydroxy-6-morpholin-4-yl-4-phenyl-2-(pyrrolidin-1-ylcarbonyl)thieno[2,3-*b*]pyridine (IVe). Yield 0.82 g (99%), mp 162 – 163°C. R_f 0.64. $C_{22}H_{23}N_3O_3S$. PMR spectrum (DMSO-d_6), δ, ppm: 2.01 (s, 4H, $N(CH_2\underline{CH_2})_2$), 3.66 – 3.74 (m, 12H, $N(\underline{CH_2}CH_2)_2$, $N(CH_2)_4O$), 6.62 (s, 1H, 5-CH), 7.37 – 7.48 (m, 5H, C_6H_5), 13.95 (s, 1H, OH).

3-Hydroxy-6-morpholin-4-yl-4-phenyl-*N*-1,3-thiazol-2-ylthieno[2,3-*b*]pyridine-2-carboxamide (IVf). Yield 0.6 g (68%). mp 253 – 254°C. R_f 0.64. $C_{21}H_{18}N_4O_3S_2$. PMR spectrum (DMSO-d_6), δ, ppm: 3.62 – 3.80 (m, 8H, $N(CH_2)_4O$), 6.58 (s, 1H, 5-CH), 6.81 (d, 1H, J 4.6 Hz, S$\underline{CH}$CHN), 7.23 (d, 1H, J 4.6 Hz, SCH$\underline{CH}$N), 7.38 – 7.50 (m, 5H, C_6H_5), 12.78 (br, 2H, NH, OH).

3-Hydroxy-*N*-(2-methoxyphenyl)-6-morpholin-4-yl-4-phenylthieno[2,3-*b*]pyridine-2-carboxamide (IVg). Yield 0.55 g (60%), mp 171 – 172°C. R_f 0.68. $C_{25}H_{23}N_3O_4S$. PMR spectrum (DMSO-d_6), δ, ppm: 3.68 – 3.74 (m, 8H, $N(CH_2)_4O$), 3.93 (s, 3H, OCH_3), 6.64 (s, 1H, 5-CH), 6.89 – 7.08 (m, 3H, C_6H_4), 7.39 – 7.51 (m, 5H, C_6H_5), 8.07 (dd, 1H, J 8.6 Hz, 2.0, C_6H_4), 8.52 (s, 1H, NH), 11.81 (s, 1H, OH).

Ethyl 3-hydroxy-4-phenyl-6-piperidin-1-ylthieno-[2,3-*b*]pyridine-2-carboxylate (IVh). Yield 0.6 g (77%), mp 189 – 190°C. R_f 0.64. $C_{21}H_{22}N_2O_3S$. PMR spectrum (DMSO-d_6), δ, ppm: 1.40 (t, 3H, J 7.1 Hz, CH_2CH_3), 1.61 – 1.76 (m, 6H, 6-$(CH_2)_3$), 3.69 – 3.77 (m, 4H, $N(CH_2)_2$), 4.34 (q, 2H, J 7.1 Hz, $\underline{CH_2}CH_3$), 6.56 (s, 1H, 5-CH), 7.36 – 7.47 (m, 5H, C_6H_5), 10.48 (s, 1H, OH).

(3-Hydroxy-4-phenyl-6-piperidin-1-ylthieno[2,3-*b*]pyridin-2-yl)(phenyl)methanone (IVi). Yield 0.75 g (90%), mp 169 – 170°C. R_f 0.7. $C_{25}H_{22}N_2O_2S$. PMR spectrum (DMSO-d_6), δ, ppm: 1.61 – 1.80 (m, 6H, 6-$(CH_2)_3$), 3.72 – 3.84 (m, 4H, $N(CH_2)_2$), 6.61 (s, 1H, 5-CH), 7.39 – 7.60 (m, 3H, C_6H_5 and 5H, 4-C_6H_5), 7.91 – 7.97 (m, 2H, C_6H_5), 13.98 (br.s, 1H, OH).

Ethyl 3-hydroxy-4-phenyl-6-pyrrolidin-1-ylthieno-[2,3-*b*]pyridine-2-carboxylate (IVj). Yield 0.73 g (84%), mp 173 – 174°C. R_f 0.62. $C_{20}H_{20}N_2O_3S$. PMR spectrum (DMSO-d_6), δ, ppm: 1.39 (t, 3H, J 7.1 Hz, $CH_2\underline{CH_3}$), 2.03 – 2.09 (m, 4H, 6-$(CH_2)_2$), 3.55 – 3.62 (m, 4H, $N(CH_2)_2$), 4.34 (q, 2 H, J 7.1 Hz, $\underline{CH_2}CH_3$), 6.29 (s, 1H, 5-CH), 7.36 – 7.48 (m, 5H, C_6H_5), 10.50 (s, 1H, OH).

Methyl 3-hydroxy-4-phenyl-6-pyrrolidin-1-ylthieno-[2,3-*b*]pyridine-2-carboxylate (IVk). Yield 0.73 g (91%), mp 220 – 221°C. R_f 0.63. $C_{19}H_{18}N_2O_3S$. PMR spectrum (DMSO-d_6), δ, ppm: 2.01 – 2.11 (m, 4H, 6-$(CH_2)_2$), 3.54 – 3.63 (m, 4H, $N(CH_2)_2$), 3.87 (s, 3H, OCH_3), 6.29 (s, 1H, 5-CH), 7.35 – 7.47 (m, 5H, C_6H_5), 10.43 (s, 1H, OH).

3-Hydroxy-4-phenyl-6-pyrrolidin-1-ylthieno[2,3-*b*]pyridine-2-carboxamide (IVl). Yield 0.36 g (79%), mp 251 – 252°C. R_f 0.65. $C_{18}H_{17}N_3O_2S$. PMR spectrum (DMSO-d_6), δ, ppm: 2.01 – 2.11 (m, 4H, 6-$(CH_2)_2$), 3.54 – 3.61 (m, 4H, $N(CH_2)_2$), 6.26 (s, 1H, CH), 7.20 (br.s, 2H, $N\mathbf{H}_2$), 7.35 – 7.49 (m, 5H, C_6H_5), 13.08 (br.s, 1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 24.8, 46.4, 94.6, 106.1, 111.6, 126.8, 127.3, 128.7, 147.3, 156.0, 158.3, 159.3, 160.2, 169.1.

EXPERIMENTAL BIOLOGICAL PART

Biological experiments were conducted in full compliance with the *European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes* (European Treaty Series No. 123, Strasbourg, Mar. 18, 1986).

Neurotropic activity of the synthesized compounds was studied with respect to anticonvulsant activity with corazole antagonism, exploratory activity in the open field test, and central myorelaxant activity. The synthesized compounds and reference drug diazepam were studied in 300 laboratory white mice of both sexes (18 – 24 g) and 48 male Wistar rats (120 – 140 g).

Anticonvulsant activity was assessed from the prevention of the clonic seizure component induced in mice by s.c. injection of corazole (90 mg/kg) [11, 12]. Corazole antagonism was also a predictive test for tranquilizing activity of the compounds. Adverse side effects in these same animals, i.e., a central myorelaxant effect and uncoordinated movements, were studied using the rotating rod method [13]. The

TABLE 1. Comparative Anti-Corazole Activity of **IIIa**, **d-f**, and Diazepam*

Compound $n = 8$	Corazole antagonism, ** (ED_{50}, mg/kg)
IIIa	36.0 (30.0 ÷ 43.2)
IIId	41.0 (31.5 ÷ 53.3)
IIIc	30.0 (24.0 ÷ 37.5)
IIIf	42.0 (22.5 ÷ 74.6)
Diazepam	0.51(0.39 ÷ 0.69)

* Diazepam (Polfa, Poland) was used as a solution for injection (1 mL = 5 mg);
** Confidence intervals at probability level $p = 0.05$.

TABLE 2. Exploratory Activity of **IIIa**, **d-f**, and Diazepam in the Open Field Model

Compound (n = 8)	Number of, absolute values for 5 min*		
	Horizontal movements	Vertical movements	Explored cells
Control, emulsifier	23.8 ± 3.2	5.6 ± 1.2	1.8 ± 0.6
IIIa	14.4 ± 3.5**	3.2 ± 1.0**	1.4 ± 0.6
IIId	12.8 ± 2.1**	2.6 ± 1.1**	3.2 ± 0.8**
IIIe	13.6 ± 3.4**	2.6 ± 1.1**	1.0 ± 0.4**
IIIf	16.2 ± 2.9**	2.7 ± 1.5**	3.8 ± 1.2**
Diazepam	33.6 ± 4.2**	8.3 ± 1.1**	5.0 ± 1.3**

* $p \le 0.05$.
** Differences statistically significant vs. the control and diazepam.

compounds were administered at doses of 25 – 100 mg/kg; reference drug diazepam, 0.1 – 2 mg/kg i.p. 45 min before injection of corazole as a suspension with carboxymethylcellulose and Tween-80. Control animals received emulsifier. Each dose of the compounds was studied in eight animals. Anticonvulsant activity was used to determine ED_{50} of the tested drugs by the Litchfield and Wilcoxon method [14].

Sedative, activating, and anxiolytic activities of the selected most active compounds were studied using rats in the open field test and their locomotor and orienting-exploratory activity [15]. Tests were conducted during the day with natural lighting. Spontaneous behavior of each separate animal was recorded for 5 min. Sedative and activating activity were evaluated from the number of horizontal (squares crossed) and vertical movements (rearings on hind paws). Anxiolytic effects were assessed from the number of cells explored by test and control animals. The compounds, the control, and diazepam were tested using eight animals each. Tested compounds were injected i.p. to rats at the most effective dose of 50 mg/kg; the reference drug, at a dose of 2 mg/kg. Control animals were injected with emulsifier. Results were processed statistically at probability level $p \le 0.05$ [14].

Studies of anticonvulsant activity found that all synthesized pyridine derivatives possessed anti-corazole activity. Thus, **IIa-c**, **IIIb**, **c**, **g-l**, and **IVa-l** at a dose of 50 mg/kg prevented seizures in 20 – 40% of the animals. Compounds **IIIa**, **d-f** possessed pronounced anticonvulsant activity. Corazole seizures were prevented by these compounds starting at a dose of 12.5 mg/kg injected into mice. The ED_{50} values were 30 – 42 mg/kg (Table 1). Locomotor coordination was not disrupted and myorelaxation was not observed at doses of 50 – 75 mg/kg in mice. The anticonvulsant activities of the compounds were inferior to that of diazepam.

The ED_{50} (mg/kg) of diazepam for anti-corazole activity in mice was 0.5 mg/kg (Table 1). However, diazepam already at a dose of 2 mg/kg in mice caused central myorelaxation. Differences from the control and diazepam were statistically significant because P.R. > fP.R. [14].

The most effective compounds (**IIIa**, **d-f**) were studied in the open field tests. The number of horizontal movements was 23.8; vertical, 5.6; explored cells, 1.8 in the open field test for rats in the control group for diazepam and **IIIa**, **d-f** (Table 2).

The tested compounds caused statistically significant behavioral changes as compared to the control and diazepam. Injection of all compounds inhibited horizontal and vertical movements of the animals, i.e., a psychosedative effect was observed. Two of the selected compounds (**IIIe**, **f**) increased the number of explored cells, which could be related to slight anxiolytic activity for them (Table 2). Diazepam (2 mg/kg) caused a significant increase of all these parameters as compared to the control, i.e., activating and anxiolytic activities were present.

Structure–activity relationship studies showed that compounds with a pyridine ring (**IIIa**, **d-f**) had the strongest anticonvulsant activity. Formation of a thiophene ring weakened the activity. However, the most active compounds contained a 6-morpholine moiety on the pyridine ring.

REFERENCES

1. E. Lukevits, *Chem. Heterocycl. Compd.*, **31**(6), 723 – 734 (1995).
2. L. J. Gao, S. Kovackova, and M. Sala, *J. Med. Chem.*, **57**, 7624 – 7643 (2014).
3. N. Wang, W. Zoo, Y. Xu, and C. Gao, *Bioorg. Med. Chem. Lett.*, **24**, 5860 – 5870(2014).
4. J. M. Hung., H. J. Arabsham, E. Leung, et al., *Eur. J. Med. Chem.*, **86**, 420 – 437 (2014).
5. B. H. Naguib and H. B. El-Nassan, *J. Enzyme Inhib. Med. Chem.*, **31**, 1718 – 1725 (2016).
6. E. G. Paronikyan, G. V. Mirzoyan, A. S. Noravyan, et al., *Khim.-farm. Zh.*, **31**(10), 34 – 36 (1997); *Pharm. Chem. J.*, **31**(10), 540 – 542 (1997).
7. E. G. Paronikyan, Sh. F. Akopyan, A. S. Noravyan, et al., *Khim.-farm. Zh.*, **44**(4), 19 – 21 (2010); *Pharm. Chem. J.*, **44**(4), 183 – 185 (2010).
8. E. G. Paronikyan, Sh. F. Akopyan, A. S. Noravyan, et al., *Khim.-farm. Zh.*, **46**(3), 25 – 27 (2012); *Pharm. Chem. J.*, **46**(3), 154 – 156 (2012).
9. K. J. Gewald, *J. Prakt. Chem.*, **31**(4), 205 – 213 (1966).
10. Yu. A. Sheiker, *Izv. Akad. Nauk SSSR, Ser. Khim.*, No. 1, 37 – 46 (1980).
11. H. G. Vogel and W. H. Vogel, *Psychotropic and Neurotropic Activity*, in: *Drug Discovery and Evaluation: Pharmacological Assays*, H. G. Vogel (ed.), Springer-Verlag, Berlin, Heidelberg (2008), pp. 569 – 874.
12. E. A. Swinyard, in: *Experimental Models of Epilepsy*, Raven Press, New York (1992), pp. 433 – 458.
13. N. W. Dunham and T. S. Miya, *J. Am. Pharm. Assoc. Sci. Ed.*, **46**(3), 208 – 209 (1957).
14. M. L. Belen'kii, *Elements of Quantitative Assessment of Pharmacological Effects* [in Russian], Meditsina, Leningrad (1961).
15. S. E. File, *Behav. Brain Res.*, **125**, 151 – 157 (2001).