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Synthesis and Neurotropic Activity of 6,8-Diamino Derivatives of Pyrano[3,4-*c*]pyridines

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Abstract—New diamino derivatives of pyrano[3,4-*c*]pyridines were synthesized by the pyridine ring recyclization. The presence of the intramolecular hydrogen bond in 6-[(4-methoxyphenyl)amino]-3,3-dimethyl-8-methylamino-3,4-dihydro-1*H*-pyrano[3,4-*c*]pyridin-5-carbonitrile was identified by X-ray diffraction. A pharmacological study of the synthesized compounds was carried out in known tests, such as assay for antagonism induced by corazole subcutaneous injection and the open field test. The method of rotating rod was used to evaluate neurotoxicity. The diamino derivatives of pyrano[3,4-*c*]pyridines were found to possess neutrotropic properties. The synthesized compounds, as well as diazepam, prevent the occurrence of clonic seizures and clonic corazole-induced convulsions in animals; however, they cause a behavior-depressing sedative effect.

Keywords: pyrano[3,4-c]pyridines, rearrangement, neurotropic activity

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INTRODUCTION

Synthesis of pharmaceuticals for the treatment of neuropsychiatric disorders, in particular epilepsy, is a serious challenge for synthetic organic chemistry. In recent years, the pharmacopoeia of antiepileptic agents has expanded significantly. However, most of them are not active enough, and the most effective agents often cause toxic side responses from different organs and systems, emotional disturbances, impaired memory, etc. In this regard, the search and study of anticonvulsants possessing the combined psychotropic properties is of unquestionable interest. In experimental psychopharmacology, while searching for new neurotrophic compounds, it is important and relevant to model both the pathology itself and its individual manifestations in animals. Such an approach of differentiated (application of interoceptive stimuli, such as corazole) and integrative (for example, "open field") modeling, biostatistical evaluation of the spectrum of pharmacological action of substances, and comparison of the major and side effects make it possible to carry out a more detailed selection of promising pharmaceutical agents among newly synthesized compounds.

The derivatives of condensed pyridines are of interest as biologically active substances and widely used in medicine. Thus, alkaloids of the pyrano[3,4-*c*]pyridine series extracted from plants, such as gentianine and gentianadine exert a universal effect: hypotensive, anticonvulsant, antipsychotic, anti-inflammatory, and hypothermic [1–4]. Furthermore, derivatives of pyrano[3,4-*c*]pyridines are the starting compounds for the synthesis of indole alkaloids, in particular camptothecin exhibiting antitumor activity [5, 6]. Information about the synthetic methods for preparation of pyrano[3,4-*c*]pyridine derivatives is also available [7–9].

Previously, we synthesized oxo, thio and amino derivatives of pyrano[3,4-*c*]pyridines [10–13]. In the present work, in continuation of these studies we carried out the synthesis of new pyrano[3,4-*c*]pyridine derivatives and studied their neurotropic properties.

RESULTS AND DISCUSSION

6-Aminopyrano[3,4-*c*]pyridines (**IIIa–g**) were used as the starting compounds in the synthesis of diamino derivatives of pyrano[3,4-*c*]pyridines (**Va–o**) (Scheme 1). Compounds (**IIIa–g**) were obtained via the interaction of thiopyrilium salt (**I**) [14] with substituted anilines, which resulted in imino compounds (**IIa–g**) that were further subjected to the Dimroth rearrangement under the action of sodium ethylate to afford 6-aminopyrano[3,4-*c*]pyridines (**IIIa–g**). Then, to increase the electrophilicity of the C8 atom

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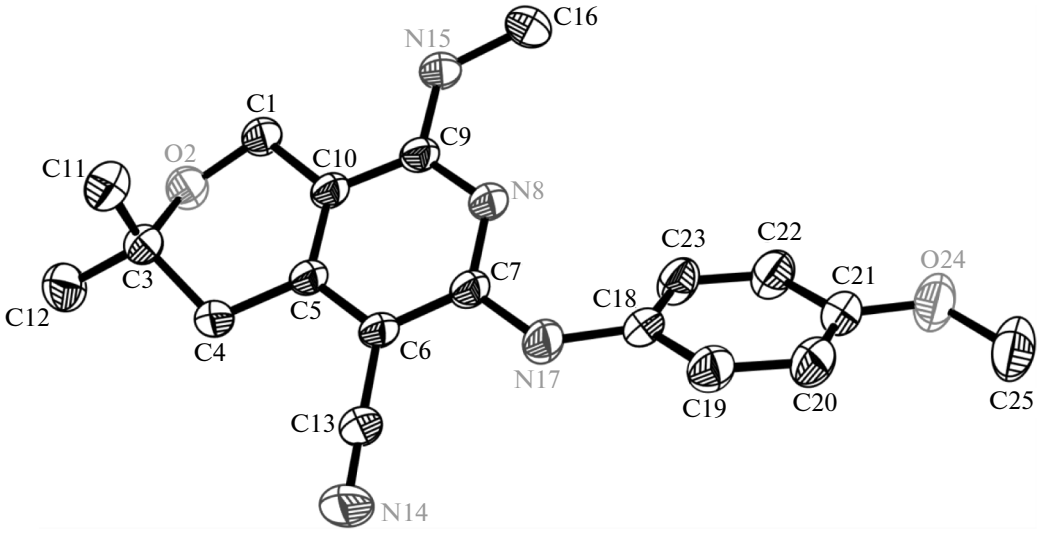

Fig. 1. Crystal structure and the numbering scheme of atoms in compound (**VI**) accepted in structural experiment. Thermal ellipsoids of 50% probability are shown.

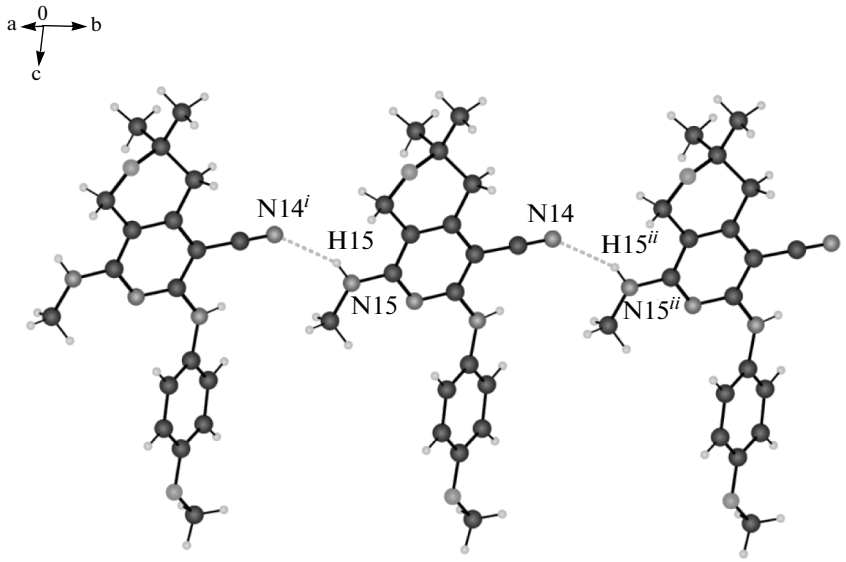

Fig. 2. The chain along [0 1 0] formed by intermolecular hydrogen bonds; symmetry code ($i = x; y - 1; z$, $ii = x; y + 1; z$). Hydrogen bonds are depicted by dashed lines.

of the pyridine ring, we obtained pyridinium salts (**IVa–g**) in the reaction of thiones (**III–g**) with dimethyl sulfate. The interaction of compounds (**IVa–g**) with primary amines is accompanied by rearrangement [15] that affords diamino derivatives (**Va–o**).

Structures of compounds (**Va–o**) were confirmed by the data of ^{1}H and ^{13}C NMR spectroscopy and X-ray diffraction (Fig. 1). While studying the structure of compound (**VI**) it was shown that the dihydropyran ring has a half-chair conformation; the atoms C1, C4, C5, and C10 are located in the plane (maximum deflection 0.0028(3) Å), and the atoms O2 and C3 are deflected from the plane by 0.2736(3) and 0.4652(3) Å, respectively. Analysis of the molecule packing in the crystal lattice showed that the molecules bind via intermolecular hydrogen bonding N15–H15···N14^{i} (length of the donor-acceptor bond 2.924(19) Å) to form infinite chains along the [0 1 0] (Fig. 2).

Neurotropic Activity

We studied the neurotropic activity of 15 newly synthesized 6,8-diamino derivatives of pyrano[3,4-*c*]pyridines (**Va–o**) and the reference drug diazepam by indicators characterizing the anticonvulsant, sedative, and antianxiety activity, as well as the central muscle relaxant effect. The study was carried out in

Table 1. Comparative anticorazole activity of compounds (**Ve**, **g**, **i**, **l–o**) and diazepam

Compound	Antagonism to corazole* (ED_{50} mg/kg)
(Ve)	30.0(17.1–45.6)
(Vg)	32.0(20.0–51.2)
(Vi)	56.0(36.0–80.3)
(Vl)	33.0(24.8–43.8)
(Vm)	50.5(30.0–72.5)
(Vn)	43.0(25.2–73.9)
(Vo)	41.0(23.5–68.0)
Diazepam	0.5(0.4–0.7)

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

200 white mice weighing 18–24 g and 64 male Wistar rats weighing 120–140 g.

In the study of anticonvulsant action, it was found that not all synthesized derivatives have the same pronounced anticorazole activity. Thus, the compound **(Vj)** at a dose of 50 mg/kg, **(Va–d, f, h, k)** at a dose of 100 mg/kg warned convulsions in 20-40% of animals. In the study of anticonvulsant action, it was found that not all of the synthesized derivatives have the same pronounced anticorazole activity. Thus, compounds **(Vj)** at a dose of 50 mg/g and **(Va–d, f, h, k)** at a dose of 100 mg/kg prevented convulsions in 20–40% of animals. At the above mentioned doses, the adverse side effects were observed in animals: coordination of movements was violated and muscle relaxation appeared. Other regularities were observed for compounds **(Ve, g, i, l–o)**. All of them have a pronounced anticonvulsant effect. Administration of the compounds to mice starting from a dose of 25 mg/kg was accompanied by prevention of corazole seizures, and ED_{50} in these animals varied from 30 to 60 mg/kg (Table 1). At these doses, coordination of movements in mice was not substantially violated, the muscle relaxation phenomena were not observed. The exception was compounds **(Vi, m, n)** that possess a pronounced anticonvulsive activity and induce muscle relaxation in animals at therapeutic doses. Therefore, these compounds were not used in the open field model. The diazepam effective dose (ED_{50}) by anticorazole action in mice was 0.5 mg/kg (Table 1).

In the open-field behavioral model, the number of horizontal movements was 18.6 and 22.5; vertical movements, 1.1 and 6.5; and the number of examined chambers, 2.1 and 4.8 in rats of the control group to diazepam and the control group to compounds **(Ve, g, l, o)**, respectively (Table 2). Compounds under investigation caused some changes of the behavior indicators compared to the control: a slight tendency to inhibition of horizontal movements of animals was observed when compounds **(Ve)** and **(Vg)** were injected; and compounds **(Vl)** and **(Vo)** reduced the ability of animals to rise on the hind legs and to examine the chambers, which may be associated with the manifestations of mild sedation induced by these compounds (Table 2). Diazepam (2 mg/kg) caused a significant increase in these parameters, i.e., there was its antianxiety and activating effect.

Study of the relationship between structure of the investigated compounds and their biological activity showed that compounds **(Ve, g, i, l–o)** with the methoxy group in positions 2, 3, and 4 of the aniline residue exhibit anticonvulsant activity. Compounds **(Ve, g, l)**

Table 2. The effect of compounds (**Ve**, **g**, **l**, **o**) and diazepam in the open-field test

Compound	Number of (in absolute values for 5 min)*		
	horizontal movements	vertical movements	examined chambers
Control to compounds	22.5(19.3–25.7)	6.5(4.8–8.2)	4.8(4.0–5.6)
(Ve)	14.0(10.2–17.8)	7.8(5.8–9.9)	3.6(2.3–4.9)
(Vg)	15.2(10.4–18.3)	3.2(2.8–3.6)	2.6(1.0–4.1)
(Vl)	18.3(12.0–24.6)	7.6(5.7–9.5)	3.5(2.4–4.6)
(Vo)	24.3(18.2–39.9)	4.3(2.9–5.7)	2.8(1.1–5.4)
Control to diazepam	18.6(13.7–23.5)	1.1(0.7–1.5)	2.1(1.0–3.2)
Diazepam	33.6(29.4–37.8)	6.4(5.4–7.4)	5.0(3.7–6.3)

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

Table 3. Basic crystallographic characteristics and experimental data for the crystal structure of compound (**VI**)

Crystallographic characteristics	
Chemical formula sum	$C_{19}H_{22}N_4O_2$
Chemical formula weight	338.40
Crystal system	Triclinic
Space group	P-1
a, *b*, *c*, Å	8.4531(17), 9.0608(18), 12.057(2)
a, b, g, deg	99.97(3), 103.72(3), 90.92(3)
V, Å^3	882.0(3)
Z	2
Density (calc.), g/cm^3	1.274
μ(MoK_α), mm^{-1}	0.085
F(000)	360
Crystal size, mm	0.25 × 0.30 × 0.36
Experimental data	
Temperature, K	293
Radiation, Å	0.71073
θ_{min}; θ_{max}, deg	1.8; 30.0
Scanning area	$0 \le h \le 11$, $-12 \le k \le 12$, $-16 \le l \le 16$
Number of collected reflections	5443
Number of observed reflections with [$I > 2.0\ \sigma(I)$]	3703
Calculated data	
Nref, Npar	5120, 314
R, *wR*2, *S*	0.0476, 0.1399, 1.02
Weighing scheme	$W = 1/[\sigma^2(Fo^2) + (0.0696P)^2 + 0.1397P]$, where $P = (Fo^2 + 2Fc^2)/3$

containing both the methylamine fragment in position 8 of pyrano[3,4-*c*]pyridine and methoxy group were the most active.

Thus, while studying neurotropic properties of 6,8-diamino derivatives of pyrano[3,4-*c*]pyridines it was found that some of them possess anticorazole and central myorelaxant effects that were not previously described. However, in contrast to the tranquilizer diazepam that possesses anxiolytic and behavior-activating effects in the open-field test, the sedative effect was observed in some compounds studied.

EXPERIMENTAL

In this work we used commercially available reagents purchased from Fluka (Germany) and Sigma-Aldrich (United States). The solvents were purified according to standard protocols. The melting points were determined on a Boetius microtable. 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. Basic crystallographic characteristics and experimental data for compound (**VI**) are reported in Table 3.

The X-ray diffraction study of compound (**VI**) single crystal was performed in a Enraf-Nonius CAD-4 automatic diffractometer (graphite monochromator, MoK_α radiation, θ/2θ scanning) at ambient temperature. Monoclinic unit cell parameters were determined and refined by 24 reflexes with $10.09° < \theta < 16.67°$. The structure was decoded by the direct method, the coordinates of the hydrogen atoms were determined from the difference Fourier syntheses. The structure was refined using the full-matrix method of least squares in the anisotropic approximation for nonhydrogen atoms; and isotropic approximation for the hydrogen atoms. All structural calculations were performed using SHELXTL software [21].

Crystallographic data for compound (**VI**) were deposited with the Cambridge Crystallographic Data Center (CCDC no. 1411701).

Compounds (**IIa–e**)–(**IVa–e**) were obtained as described in [15, 22].

Compounds (IIf, g). General procedure. Substituted aniline (10 mmol) was added to a suspension of compound (**I**) [14] (1.9 g, 5 mmol) in absolute ethanol (10 mL) with stirring. The reaction mixture was kept at 75°C for 1.5 h, then cooled to room temperature, and poured into cold water. The precipitate was filtered off, washed with water, dried, and recrystallized from ethanol.

6-Amino-3,3-dimethyl-8-[(2-methylphenyl)imino]-4,8-dihydro-1*H*,3*H*-thiopyrano[3,4-*c*]pyran-5-carbonitrile (IIf). Yield 70%, mp 129–130°C. Found, %: C 66.48, H 5.81, N 12.87, S 9.79. $C_{18}H_{19}N_3OS$. Calculated, %: C 66.43, H 5.88, N 12.91, S 9.85. IR (ν, cm^{-1}: 1660 (C=N), 2192 (CN), 3198, 3305 (NH_2). ^{1}H NMR: 1.30 (s, 6 H, C(C***H*$_3$**)$_2$), 2.08 (s, 3 H, C***H*$_3$**), 2.41 (t, 2 H, *J* 1.8, 4-C***H*$_2$**), 4.45 (t, 2 H, *J* 1.8, 1-C***H*$_2$**), 6.66 (dd, 1 H, J^1 7.8, J^2 1.2, ***CH***), 6.95 (td, 1 H, J^1 7.5, J^2 1.2, ***CH***), 7.11–7.21 (m, 2 H, 2C***H***), 7.50 (br. s, 2 H, N***H*$_2$**).

6-Amino-8-[(3-methoxyphenyl)imino]-3,3-dimethyl-4,8-dihydro-1*H*,3*H*-thiopyrano[3,4-*c*]pyran-5-carbonitrile (IIg). Yield 94%, mp 207–209°C. Found, %: C 63.38, H 5.66, N 12.27, S 9.34. $C_{18}H_{19}N_3O_2S$.

Calculated, %: C 63.32, H 5.61, N 12.31, S 9.39. IR (ν, cm^{-1}): 1660 (C=N), 2190 (CN), 3195, 3308 (NH_2). ^1H NMR: 1.29 (s, 6 H, C(C***H***$_3$)$_2$), 2.39 (t, 2 H, *J* 1.7, 4-C***H***$_2$), 3.77 (s, 3 H, OC***H***$_3$), 4.39 (t, 2 H, *J* 1.7, 1-C***H***$_2$), 6.29–6.37 (m, 2 H, 2C***H***), 6.58 (ddd, 1 H, J^1 8.3, J^2 2.5, J^3 0.8, C***H***), 7.22 (t, 1 H, *J* 8.0, C***H***), 7.52 (br. s, 2 H, N***H***$_2$).

Compounds (IIIf, g). General procedure. Corresponding compound (**IIf, g**) (10 mmol) was added to a solution of sodium ethylate obtained from sodium (253 mg, 11 mmol) and absolute ethanol (25 mL). The reaction mixture was kept at 50°C for 30 min, then cooled to room temperature, and poured into cold water. The precipitate was filtered off, washed with water, dried, and recrystallized from nitromethane.

6-Amino-3,3-dimethyl-7-(2-methylphenyl)-8-thioxo-3,4,7,8-tetrahydro-1*H*-pyrano[3,4-*c*]pyridine-5-carbonitrile (IIIf). Yield 68%, mp 296–297°C. Found, %: C 66.50, H 5.83, N 12.96, S 9.77. $C_{18}H_{19}N_3OS$. Calculated, %: C 66.43, H 5.88, N 12.91, S 9.85. IR (ν, cm^{-1}): 1245 (C=S), 2204 (CN), 3205, 3308 (NH_2). ^1H NMR: 1.31 (s, 6 H, C(C***H***$_3$)$_2$), 2.07 (s, 3 H, C***H***$_3$), 2.55 (br. s, 2 H, 4-C***H***$_2$), 4.35 (d, 1 H, *J* 16.5, 1-C***H***H), 4.41 (d, 1 H, *J* 16.5, 1-CH***H***), 6.48 (br. s, 2 H, N***H***$_2$), 7.03–7.08 (m, 1 H, C***H***$_{Ar}$), 7.38–7.43 (m, 3 H,3C***H***$_{Ar}$).

6-Amino-3,3-dimethyl-7-(3-methoxyphenyl)-8-thioxo-3,4,7,8-tetrahydro-1*H*-pyrano[3,4-*c*]pyridine-5-carbonitrile (IIIg). Yield 97%, mp 298–300°C. Found, %: C 63.37, H 5.68, N 12.25, S 9.33. $C_{18}H_{19}N_3O_2S$. Calculated, %: C 63.32, H 5.61, N 12.31, S 9.39. IR (ν, cm^{-1}): 1250 (C=S), 2220 (CN), 3200, 3290 (NH_2). ^1H NMR: 1.31 (s, 6 H, C(C***H***$_3$)$_2$), 2.54 (br. s, 2 H, C***H***$_2$), 3.84 (s, 3 H, OC***H***$_3$), 4.36 (br. s, 2 H, 1-C***H***$_2$), 6.54 (br. s, 2 H, N***H***$_2$), 6.70–6.75 (m, 2 H, 2C***H***$_{Ar}$), 7.01–7.05 (m, 1 H, C***H***$_{Ar}$), 7.45–7.52 (m, 1 H, C***H***). ^{13}C NMR: 25.8, 25.9, 37.4, 54.8, 61.6, 68.7, 78.5, 113.4, 115.1, 115.2, 119.7, 122.7, 130.6, 138.5, 141.5, 153.9, 160.7, 177.9.

Compounds (IVf, g). General procedure. A mixture of corresponding thione (**IIIf, g**) (10 mmol), dimethylsulfate (1.9 g, 15 mmol), and toluene (20 mL) was refluxed for 10–15 min. After cooling, the precipitate was filtered off, washed with cold MeOH, dried, and recrystallized from 1,4-dioxane.

6-Amino-3,3-dimethyl-7-(2-methylphenyl)-8-methylthio-5-cyano-3,4-dihydro-1*H*-pyrano[3,4-*c*]pyridinium-7-methanesulfonate (IVf). Yield 78%, mp 198–200°C. Found, %: C 53.26, H 5.63, N 9.27, S 14.14. $C_{20}H_{25}N_3O_5S_2$. Calculated, %: C 53.20, H 5.58, N 9.31, S 14.20. IR (ν, cm^{-1}): 2220 (CN), 3220, 3318 (NH_2). ^1H NMR: 1.38 (s, 3 H, C(C***H***$_3$)$_2$), 1.39 (s, 3 H, C(C***H***$_3$)$_2$), 2.10 (s, 3 H, C***H***$_3$), 2.25 (s, 3 H, SC***H***$_3$), 2.94 (d, 1 H, *J* 18.1, 4-C***H***H), 3.01 (d, 1 H, *J* 18.1, 4-CH***H***), 3.58 (s, 3 H, OC***H***$_3$), 4.71 (d, 1 H, *J* 15.9, 1-C***H***H), 4.79 (d, 1 H, *J* 15.9, 1-CH***H***), 7.47–7.66 (m, 4 H, 4CH), 8.38 (br. s, 2 H, N***H***$_2$).

6-Amino-5-cyano-3,3-dimethyl-8-methylthio-7-(3-methoxyphenyl)-3,4-dihydro-1*H*-pyrano[3,4-*c*]pyridinium-7-methanesulfonate (IVg). Yield 74%, mp 186–187°C. Found, %: C 51.45, H 5.47, N 8.92, S 13.67. $C_{20}H_{25}N_3O_6S_2$. Calculated, %: C 51.38, H 5.39, N 8.99, S 13.72. IR (ν, cm^{-1}): 2230 (CN), 3217, 3315 (NH_2). ^1H NMR: 1.37 (s, 6 H, C(C***H***$_3$)$_2$), 2.23 (s, 3 H, SC***H***$_3$), 2.94 (d, 1 H, *J* 18.2, 4-CH***H***), 3.01 (d, 1 H, *J* 18.2, 4-CH***H***), 3.58 (s, 3 H, SOC***H***$_3$), 3.89 (s, 3 H, COC***H***$_3$), 4.71 (d, 1 H, *J* 15.9, 1-CH***H***), 4.79 (d, 1 H, *J* 15.9, 1-CH***H***), 7.15–7.20 (m, 2 H, 2C***H***), 7.56–7.67 (m, 2 H, 2C***H***), 8.45 (br. s, 2 H, N***H***$_2$).

Compounds (Va–c, f, h–k, m–o). General procedure. A mixture of pyridinium salt (**IVa, b, d, e, g**) (5 mmol) and corresponding amine (50 mmol) in MeOH (20 mL) was refluxed for 2 h, then cooled to room temperature. The precipitate formed was filtered off, washed with water, dried, and recrystallized from ethanol.

6-Anilino-3,3-dimethyl-8-[(3-methoxypropyl)amino]-3,4-dihydro-1*H*-pyrano[3,4-*c*]-pyridine-5-carbonitrile (Va). Yield 69%, mp 116–117°C. Found, %: C 68.77, H 7.08, N 15.34. $C_{21}H_{26}N_4O_2$. Calculated, %: C 68.83, H 7.15, N 15.29. IR (ν, cm^{-1}): 2200 (CN), 3370 (NH), 3395 (NH). ^1H NMR: 1.27 (s, 6 H, C(C***H***$_3$)$_2$), 1.76–1.85 (m, 2 H, NHCH$_2$C***H***$_2$), 2.57 (br. s, 2 H, 4-C***H***$_2$), 3.27 (s, 3 H, OC***H***$_3$), 3.36–3.41 (m, 4 H, NHC***H***$_2$ and C***H***$_2$OCH$_3$), 4.31 (br. s, 2 H, 1-C***H***$_2$), 6.31 (br. t, 1 H, *J* 5.4, N***H***CH$_2$), 6.86–6.93 (m, 1 H, C***H***), 7.15–7.21 (m, 2 H, 2C***H***), 7.58–7.63 (m, 2 H, 2C***H***), 7.83 (br. s, 1 H, N***H***).

6-Anilino-8-{[3-(dimethylamino)propyl]amino}-3,3-dimethyl-3,4-dihydro-1*H*-pyrano[3,4-*c*]-pyridine-5-carbonitrile (Vb). Yield 61%, mp 150–151°C. Found, %: C 69.68, H 7.75, N 18.37. $C_{22}H_{29}N_5O$. Calculated, %: C 69.63, H 7.70, N 18.45. IR (ν, cm^{-1}): 2206 (CN), 3365 (NH), 3405 (NH). ^1H NMR: 1.27 (s, 6 H, C(C***H***$_3$)$_2$), 1.67–1.76 (m, 2 H, NHCH$_2$C***H***$_2$), 2.18 (s, 6 H, N(C***H***$_3$)$_2$), 2.38 (t, 2 H, *J* 6.8, NC***H***$_2$), 2.56 (br. s, 2 H, 4-C***H***$_2$), 3.41 (td, 2 H, J^1 6.9, J^2 5.2, NHC***H***$_2$), 4.26 (br. s, 2 H, 1-C***H***$_2$), 6.75 (br. t, 1 H, *J* 5.2, N***H***CH$_2$), 6.85–6.92 (m, 1 H, C***H***), 7.18–7.24 (m, 2 H, 2C***H***), 7.58–7.65 (m, 2 H, 2C***H***), 7.79 (br. s, 1 H, N***H***).

6-Anilino-3,3-dimethyl-8-[(tetrahydrofuran-2-ylmethyl)amino]amino-3,4-dihydro-1*H*-pyrano[3,4-*c*]-pyridine-5-carbonitrile (Vc). Yield 62%, mp 166–168°C. Found, %: C 69.88, H 6.87, N 14.73. $C_{22}H_{26}N_4O_2$. Calculated, %: C 69.82, H 6.92, N 14.80. IR (ν, cm^{-1}): 2210 (CN), 3330 (NH), 3405 (NH). ^1H NMR: 1.27 (s, 6 H, C(C***H***$_3$)$_2$), 1.58–1.83 (m, 4 H, 2C***H***$_2$), 2.55 (br. s, 2 H, 4-C***H***$_2$), 3.24–4.03 (m, 5 H, C***H***$_2$, C***H***, NHC***H***$_2$), 4.35 (br. s, 2 H, 1-C***H***$_2$), 6.33 (br. t, 1 H, *J* 5.4, N***H***CH$_2$), 6.85–6.94 (m, 1 H,

C***H***), 7.18–7.23 (m, 2 H, 2C***H***), 7.56–7.61 (m, 2 H, 2C***H***), 7.84 (br. s, 1 H, N***H***).

8-[(2-Furanylmethyl)amino]-3,3-dimethyl-6-[(3-methylphenyl)amino]-3,4-dihydro-1*H*-pyrano[3,4-*c*]-pyridine-5-carbonitrile (Vf). Yield 71%, mp 193–194°C. Found, %: C 71.18, H 6.27, N 14.50. $C_{23}H_{24}N_4O_2$. Calculated, %: C 71.11, H 6.23, N 14.42. IR (ν, cm^{-1}): 2200 (CN), 3365 (NH), 3387 (NH). ^{1}H NMR: 1.28 (s, 6 H, C(C***H*****$_3$**$)_2$), 2.24 (s, 3 H, C***H*****$_3$**), 2.55 (s, 2 H, 4-C***H*****$_2$**), 4.37 (s, 2 H, 1-C***H*****$_2$**), 4.54 (d, 2 H, *J* 5.6, NHC***H*****$_2$**), 6.00 (dd, 1 H, J^1 3.2, J^2 0.8, C***H***-furyl), 6.24 (dd, 1 H, J^1 3.1, J^2 1.8, C***H***-furyl), 6.70 (br. d, 1 H, *J* 7.3, C***H***), 6.85 (br. t, 1 H, *J* 5.6, N***H***CH_2), 7.04 (dd, 1 H, J^1 8.2, J^2 7.3, C***H***), 7.29 (br. d, 1 H, *J* 8.2, C***H***), 7.36 (dd, 1 H, J^1 1.8, J^2 0.8, CH-furyl), 7.42 (br. s, 1 H, C***H***), 7.85 (br. s, 1 H, N***H***). ^{13}C NMR: 20.9, 25.8, 37.3, 37.5, 58.2, 69.0, 79.1, 104.2, 106.0, 109.8, 116.7, 117.3, 120.8, 122.1, 127.4, 136.6, 139.7, 140.6, 144.5, 152.8, 153.4, 155.0.

6-[(3-Methoxyphenyl)amino]-3,3-dimethyl-8-[(pyridine-3-ylmethyl)amino]-3,4-dihydro-1*H*-pyrano[3,4-*c*]-pyridine-5-carbonitrile (Vh). Yield 63%, mp 200–202°C. Found, %: C 67.49, H 6.62, N 16.50. $C_{24}H_{25}N_5O_2$. Calculated, %: C 69.38, H 6.06, N 16.86. IR (ν, cm^{-1}): 2205 (CN), 3386 (NH), 3401 (NH). ^{1}H NMR: 1.28 (s, 6 H, C(C***H*****$_3$**$)_2$), 2.56 (br. s, 2 H, 4-C***H*****$_2$**), 3.70 (s, 3 H, OC***H*****$_3$**), 4.40 (br. s, 2 H, 1-C***H*****$_2$**), 4.56 (d, 2 H, *J* 5.8, NHC***H*****$_2$**), 6.44 (dt, 1 H, J^1 7.1, J^2 2.1, N***H***CH_2), 6.93–7.05 (m, 3 H, 3C***H***), 7.10–7.16 (m, 2 H, 2C***H***), 7.52 (dt, 1 H, J^1 7.8, J^2 2.0, C***H***), 7.92 (s, 1 H, N***H***), 8.33 (dd, 1 H, J^1 6.2, J^2 1.5, C***H***), 8.41 (d, 1 H, *J* 2.0, C***H***).

6-[(3-Methoxyphenyl)amino]-3,3-dimethyl-8-[(2-morpholin-4-ylethyl)amino]-3,4-dihydro-1*H*-pyrano[3,4-*c*]-pyridine-5-carbonitrile (Vi). Yield 67%, mp 165–166°C. Found, %: C 65.82, H 7.20, N 16.15. $C_{24}H_{31}N_5O_3$. Calculated, %: C 65.88, H 7.14, N 16.01. IR (ν, cm^{-1}): 2200 (CN), 3376 (NH), 3394 (NH). ^{1}H NMR: 1.27 (s, 6 H, C(C***H*****$_3$**$)_2$), 2.33–2.37 (m, 4 H, N(C***H*****$_2$**$)_2$), 2.47 (t, 2 H, *J* 6.9, NC***H*****$_2$**), 2.55 (br. s, 2 H, 4-C***H*****$_2$**), 3.44–3.51 (m, 2 H, NHC***H*****$_2$**), 3.52–3.57 (m, 4 H, O(C***H*****$_2$**$)_2$), 3.77 (s, 3 H, OC***H***$_3$), 4.32 (br. s, 2 H, 1-C***H*****$_2$**), 6.15 (br. t, 1 H, *J* 5.2, N***H***CH_2), 6.45 (ddd, 1 H, J^1 8.0, J^2 3.5, J^3 1.0, C***H***), 7.06 (t, 1 H, *J* 8.0, C***H***), 7.15 (ddd, 1 H, J^1 8.0, J^2 2.9, J^3 1.0, C***H***), 7.26 (t, 1 H, *J* 2.2, C***H***), 7.86 (br. s, 1 H, N***H***).

8-[(3-Hydroxypropyl)amino]-3,3-dimethyl-6-[(4-methylphenyl)amino]-3,4-dihydro-1*H*-pyrano[3,4-*c*]-pyridine-5-carbonitrile (Vj). Yield 65%, mp 217–218°C. Found, %: C 68.89, H 7.20, N 15.24. $C_{21}H_{26}N_4O_2$. Calculated, %: C 68.83, H 7.15, N 15.29. IR (ν, cm^{-1}): 2208 (CN), 3280–3350 (NH, OH). ^{1}H NMR: 1.27 (s, 6 H, C(C***H*****$_3$**$)_2$), 1.64–1.77 (m, 2 H, NHCH$_2$C***H*****$_2$**), 2.30 (s, 3 H, C***H*****$_3$**), 2.52 (br. s, 2 H, 4-C***H*****$_2$**), 3.40–3.52 (m, 4 H, NHC***H*****$_2$** and C***H*****$_2$**OH), 4.13 (t, 1 H, *J* 5.1, OH), 4.31 (br. s, 2 H, 1-C***H*****$_2$**), 6.33 (br. t, 1 H, *J* 5.1, N***H***CH_2), 6.79–7.05 (m, 2 H, 2C***H***), 7.46–7.54 (m, 2 H, 2C***H***), 7.70 (br. s, 1 H, N***H***).

8-[(2-Methoxyethyl)amino]-3,3-dimethyl-6-[(4-methylphenyl)amino]-3,4-dihydro-1*H*-pyrano[3,4-*c*]-pyridine-5-carbonitrile (Vk). Yield 68%, mp 195–196°C. Found, %: C 68.87, H 7.22, N 15.23. $C_{21}H_{26}N_4O_2$. Calculated, %: C 68.83, H 7.15, N 15.29. IR (ν, cm^{-1}): 2203 (CN), 3328 (NH), 3356 (NH). ^{1}H NMR: 1.27 (s, 6 H, C(C***H*****$_3$**$)_2$), 2.30 (s, 3 H, C***H*****$_3$**), 2.54 (br. s, 2 H, 4-C***H*****$_2$**), 3.41–3.53 (m, 4 H, NHC***H*****$_2$**C***H*****$_2$**), 4.32 (br. s, 2 H, 1-C***H*****$_2$**), 6.29 (br. t, 1 H, *J* 5.2, N***H***CH_2), 6.96–7.03 (m, 2 H, 2C***H***), 7.42–7.48 (m, 2 H, 2C***H***), 7.75 (br. s, 1 H, N***H***). ^{13}C NMR: 20.2, 25.8, 37.5, 40.3, 57.8, 58.2, 69.0, 70.5, 78.3, 103.9, 116.9, 120.3, 128.0, 130.1, 137.4, 144.2, 153.8, 155.2.

8-[(2-Methoxyethyl)amino]-6-[(4-methoxyphenyl)amino]-3,3-dimethyl-3,4-dihydro-1*H*-pyrano[3,4-*c*]-pyridine-5-carbonitrile (Vm). Yield 70%, mp 225–226°C. Found, %: C 65.89, H 6.91, N 14.70. $C_{21}H_{26}N_4O_3$. Calculated, %: C 65.95, H 6.85, N 14.65. IR (ν, cm^{-1}): 2210 (CN), 3345 (NH), 3380 (NH). ^{1}H NMR: 1.27 (s, 6 H, C(C***H*****$_3$**$)_2$), 2.53 (br. s, 2 H, 4-C***H*****$_2$**), 3.31 (s, 3 H, OC***H*****$_3$**), 3.51–3.62 (m, 4 H, NHC***H*****$_2$**C***H*****$_2$**), 3.76 (s, 3 H, CH$_2$OC***H*****$_3$**), 4.35 (br. s, 2 H, 1-C***H*****$_2$**), 6.22 (t, 1 H, *J* 5.2, N***H***CH_2), 6.85–6.90 (m, 2 H, 2C***H***), 7.53–7.65 (m, 2 H, 2C***H***), 7.83 (br. s, 1 H, NH).

8-{[(2-Dimethylamino)ethyl]amino}-6-[(4-methoxyphenyl)amino]-3,3-dimethyl-3,4-dihydro-1*H*-pyrano[3,4-*c*]-pyridine-5-carbonitrile (Vn). Yield 72%, mp 163–165°C. Found, %: C 66.87, H 7.32, N 17.65. $C_{22}H_{29}N_5O_2$. Calculated, %: C 66.81, H 7.39, N 17.71. IR (ν, cm^{-1}): 2207 (CN), 3370 (NH), 3400 (NH). ^{1}H NMR: 1.27 (s, 6 H, C(C***H*****$_3$**$)_2$), 2.16 (s, 6 H, N(C***H*****$_3$**$)_2$), 2.39 (t, 2 H, *J* 6.8, NC***H*****$_2$**), 2.53 (br. s, 2 H, 4-C***H*****$_2$**), 3.35–3.43 (m, 2 H, NHC***H*****$_2$**), 3.77 (s, 3 H, OC***H***$_3$), 4.31 (br. s, 2 H, 1-C***H*****$_2$**), 5.97 (br. t, 1 H, *J* 5.4, N***H***CH_3), 6.71–6.78 (m, 2 H, 2C***H***), 7.43–7.50 (m, 2 H, 2C***H***), 7.70 (br. s, 1 H, N***H***).

6-[(4-Methoxyphenyl)amino]-3,3-dimethyl-8-[(tetrahydrofuran-4-ylmethyl)amino]-3,4-dihydro-1*H*-pyrano[3,4-*c*]-pyridine-5-carbonitrile (Vo). Yield 67%, mp 158–159°C. Found, %: C 66.87, H 7.32, N 17.65. $C_{23}H_{28}N_4O_3$. Calculated, %: C 67.63, H 6.91, N 13.72. IR (ν, cm^{-1}): 2205 (CN), 3378 (NH), 3395 (NH). ^{1}H NMR: 1.26 (s, 6 H, C(C***H*****$_3$**$)_2$), 1.56–1.81 (m, 4 H, 2C***H*****$_2$**), 2.54 (br. s, 2 H, 4-C***H*****$_2$**), 3.38–3.64 (m, 5 H, NHC***H*****$_2$**, C***H*****$_2$**, C***H***), 3.78 (s, 3 H, OC***H***$_3$), 4.36 (br. s, 2 H, 1-C***H*****$_2$**), 6.12 (br. t, 1 H, *J* 5.1, N***H***CH_2), 6.73–6.78 (m, 2 H, 2C***H***), 7.43–7.51 (m, 2 H, 2C***H***), 7.76 (br. s, 1 H, N***H***).

Compounds (Vd, e, g, l). General procedure. A mixture of pyridinium salt (**IVc, e, f, g**) (5 mmol) and 7 M methanolic solution of methylamine (30 mL) was kept

at 40–50°C for 1 h and then cooled to room temperature. The resulting precipitate was filtered off, washed with water, dried, and recrystallized from a $CHCl_3$–EtOH mixture (1 : 2).

3,3-Dimethyl-8-methylamino-6-[(2-methylphenyl)amino]-3,4-dihydro-1*H*-pyrano[3,4-*c*]pyridine-5-carbonitrile (Vd). Yield 65%, mp 134–135°C. Found, %: C 70.85, H 6.83, N 17.34. $C_{19}H_{22}N_4O$. Calculated, %: C 70.78, H 6.88, N 17.38. IR (ν, cm^{-1}): 2205 (CN), 3372 (NH), 3395 (NH). ^{1}H NMR: 1.27 (s, 6 H, C(C***H***$_3$)$_2$), 2.31 (s, 3 H, C***H***$_3$), 2.54 (br. s, 2 H, 4-C***H***$_2$), 2.92 (d, 3 H, *J* 4.5, NHC***H***$_3$), 4.32 (br. s, 2 H, 1-C***H***$_2$), 6.38 (q, 1 H, *J* 4.5, N***H***CH$_2$), 6.87–6.93 (m, 1 H, C***H***), 7.05–7.17 (m, 3 H, 3C***H***), 7.86 (br. s, 1 H, N***H***).

6-[(2-Methoxyphenyl)amino]-3,3-dimethyl-8-methylamino-3,4-dihydro-1*H*-pyrano[3,4-*c*]pyridine-5-carbonitrile (Ve). Yield 61%, mp 173–174°C. Found, %: C 67.51, H 6.49, N 16.62. $C_{19}H_{22}N_4O_2$. Calculated, %: C 67.44, H 6.55, N 16.56. IR (ν, cm^{-1}): 2200 (CN), 3365 (NH), 3387 (NH). ^{1}H NMR: 1.27 (s, 6 H, C(C***H***$_3$)$_2$), 2.53 (br. s, 2 H, 4-C***H***$_2$), 2.95 (d, 3 H, *J* 4.4, NHC***H***$_3$), 3.96 (s, 3 H, OC***H***$_3$), 4.35 (br. s, 2 H, 1-C***H***$_2$), 6.39 (q, 1 H, *J* 4.4, N***H***CH$_2$), 6.82–6.91 (m, 3 H, 3C***H***), 7.57 (br. s, 1 H, N***H***), 8.51–8.57 (m, 1 H, C***H***).

6-[(3-Methoxyphenyl)amino]-3,3-dimethyl-8-methylamino-3,4-dihydro-1*H*-pyrano[3,4-*c*]pyridine-5-carbonitrile (Vg). Yield 69%, mp 188–189°C. Found, %: C 67.49, H 6.62, N 16.50. $C_{19}H_{22}N_4O_2$. Calculated, %: C 67.44, H 6.55, N 16.56. IR (ν, cm^{-1}): 2204 (CN), 3372 (NH), 3395 (NH). ^{1}H NMR: 1.27 (s, 6 H, C(C***H***$_3$)$_2$), 2.54 (br. s, 2 H, 4-C***H***$_2$), 2.93 (d, 3 H, *J* 4.4, NHC***H***$_3$), 3.76 (s, 3 H, OC***H***$_3$), 4.32 (br. s, 2 H, 1-C***H***$_2$), 6.39 (q, 1 H, *J* 4.4, N***H***CH$_3$), 6.43 (dd, 1 H, J^1 8.4, J^2 2.1, C***H***), 7.01–7.11 (m, 1 H, C***H***), 7.17 (br. d, 1 H, *J* 8.4, C***H***), 7.41–7.47 (m, 1 H, C***H***), 7.84 (br. s, 1 H, N***H***).

6-[(4-Methoxyphenyl)amino]-3,3-dimethyl-8-methylamino-3,4-dihydro-1*H*-pyrano[3,4-*c*]pyridine-5-carbonitrile (Vl). Yield 68%, mp 218–219°C. Found, %: C 67.49, H 6.50, N 16.62. $C_{19}H_{22}N_4O_2$. Calculated, %: C 67.44, H 6.55, N 16.56. IR (ν, cm^{-1}): 2208 (CN), 3337 (NH), 3360 (NH). ^{1}H NMR: 1.26 (s, 6 H, C(C***H***$_3$)$_2$), 2.53 (br. s, 2 H, 4-C***H***$_2$), 2.85 (d, 3 H, *J* 4.5, NHC***H***$_3$), 3.76 (s, 3 H, OC***H***$_3$), 4.30 (br. s, 2 H, 1-C***H***$_2$), 6.27 (q, 1 H, *J* 4.5, N***H***CH$_3$), 6.72–6.78 (m, 2 H, 2C***H***), 7.51–7.56 (m, 2 H, 2C***H***), 7.69 (br. s, 1 H, N***H***). ^{13}C NMR: 25.8, 27.7, 37.4, 54.6, 58.3, 69.0, 77.2, 103.6, 112.8, 117.1, 121.8, 133.1, 143.6, 154.2, 154.5, 155.5.

Biologic 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, i.e., by antagonism to corazole. Unwanted side effects in these animals, namely the central myorelaxant effect and impaired motor coordination were examined by the rotating rod method [16]. The compounds under investigation were injected in a dose range of 25, 50, and 100 mg/kg; reference drug diazepam (Polfa, Poland), at doses of 0.1–0.3 and 1.0 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). Control animals were administered an emulsifier before corazole injection. A 50% effective dose (ED_{50}) of the tested compounds, i.e., dose causing anticonvulsant effect in 50% of animals, was determined by anticonvulsant effect according the Litchfield and Wilcoxon method [17].

Sedative, activating, and anxiolytic effects of the selected most active compounds were studied in rats in the open field test [18–20]. Experiments were carried out during the daytime at natural lighting. Registration 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; anxiolytic effect was evaluated by the number of examined chambers in 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 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. Only an emulsifier was injected to control animals. Because the experiments were carried out on different days, the corresponding control data were obtained for the tested compounds and diazepam. The results were statistically processed at a probability level of $P = 0.05$ [17].

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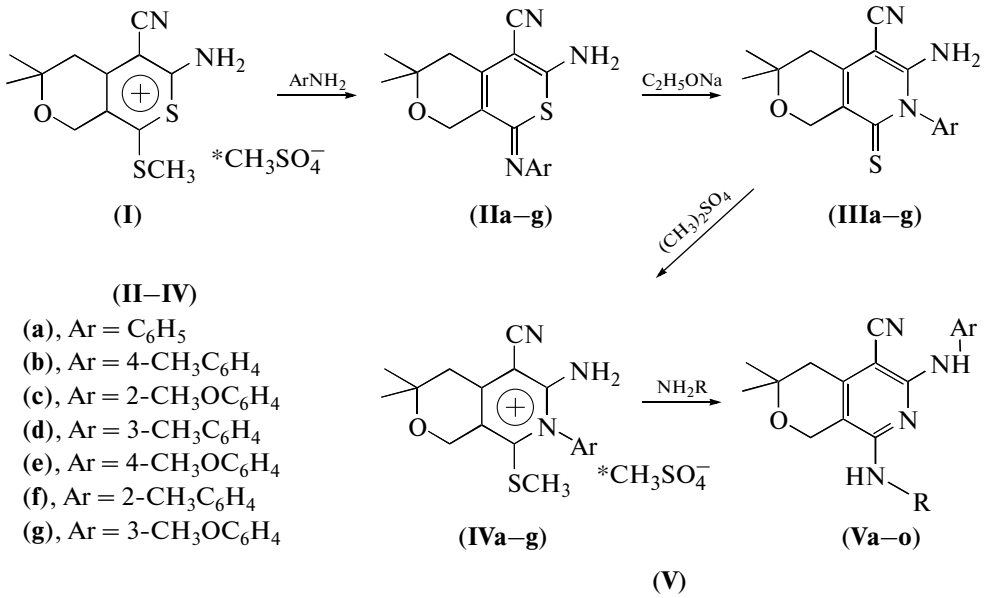

(I) (IIa–g) (IIIa–g)

(II–IV)

(**a**), Ar = C_6H_5
(**b**), Ar = 4-$CH_3C_6H_4$
(**c**), Ar = 2-$CH_3OC_6H_4$
(**d**), Ar = 3-$CH_3C_6H_4$
(**e**), Ar = 4-$CH_3OC_6H_4$
(**f**), Ar = 2-$CH_3C_6H_4$
(**g**), Ar = 3-$CH_3OC_6H_4$

(IVa–g) (Va–o)

(V)

(**a**), Ar = C_6H_5, R = $(CH_2)_3OCH_3$
(**b**), Ar = C_6H_5, R = $(CH_2)_3N(CH_3)_2$
(**c**), Ar = C_6H_5, R = CH_2-2-tetrahydrofuranyl
(**d**), Ar = 2-$CH_3C_6H_4$, R = CH_3
(**e**), Ar = 2-$CH_3OC_6H_4$, R = CH_3
(**f**), Ar = 3-$CH_3C_6H_4$, R = CH_2-2-furanyl
(**g**), Ar = 3-$CH_3OC_6H_4$, R = CH_3
(**h**), Ar = 3-$CH_3OC_6H_4$, R = CH_2-3-pyridinyl
(**i**), Ar = 3-$CH_3OC_6H_4$, R = $(CH_2)_2$-4-morpholinyl
(**j**), Ar = 4-$CH_3C_6H_4$, R = $(CH_2)_3OH$
(**k**), Ar = 4-$CH_3C_6H_4$, R = $(CH_2)_2OCH_3$
(**l**), Ar = 4-$CH_3OC_6H_4$, R = CH_3
(**m**), Ar = 4-$CH_3OC_6H_4$, R = $(CH_2)_2OCH_3$
(**n**), Ar = 4-$CH_3OC_6H_4$, R = $(CH_2)_2N(CH_3)_2$
(**o**), Ar = 4-$CH_3OC_6H_4$, R =CH_2-2-tetrahydrofuranyl

Scheme 1.

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