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SYNTHESIS AND EVALUATION OF ANTICONVULSANT ACTIVITY OF *N*-(2,5-DIMETHYLPHENOXY)- AND *N*-[(2,3,5-TRIMETHYLPHENOXY)ALKYL]AMINOALKANOLS

ANNA MARIA WASZKIELEWICZ[1]*, AGNIESZKA GUNIA-KRZYŻAK[1], MAREK CEGŁA[2] and HENRYK MARONA[1]

[1]Department of Bioorganic Chemistry, [2]Chair of Organic Chemistry, Faculty of Pharmacy, Jagiellonian University Medical College, Medyczna 9, 30-688 Kraków, Poland

Abstract: A series of new *N*-(2,5-dimethylphenoxy)- and *N*-(2,3,5-trimethylphenoxy)alkylaminoalkanols [**I–XVII**] was synthesized and evaluated for anticonvulsant activity. Pharmacological tests included maximal electroshock (MES) and subcutaneous pentetrazole seizure threshold (scMet) assays as well as neurotoxicity (TOX) evaluation in mice after intraperitoneal (*i.p.*) administration and/or in rats after oral (*p.o.*) administration. The most active compound was *R*-2*N*-[(2,3,5-trimethylphenoxy)ethyl]aminobutan-1-ol, which exhibited 100% activity in MES at the dose of 30 mg/kg body weight (mice, *i.p.*) and 75% activity in MES at 30 mg/kg b.w. (rats, *p.o.*) without neurotoxicity at the active doses.

Keywords: anticonvulsant, epilepsy, MES, neurotoxicity, aminoalkanols, synthesis

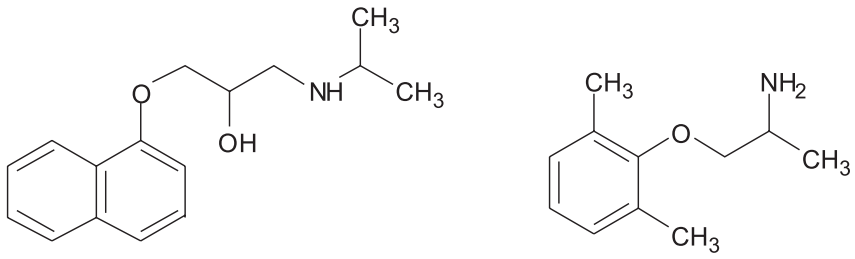
Epilepsy is a set of neurological disorders affecting about 1% of world human population. The disorders have various etiology and progress, resulting in clinically different seizures, which start in the cerebral cortex. Despite great development of pharmacotherapy of epilepsy, about 30% of all seizures are resistant to drugs. Moreover, many patients who manage to control the symptoms using two or three medicines face numerous side effects enlarged by drug interactions. Therefore, there are strong premises for further research in this field (1, 2).

Currently available antiepileptic drugs (AEDs) have been mostly discovered by means of the maximum electroshock (MES), subcutaneous pentetrazole (scMet), and rotarod neutoroxicity (TOX) screens. However, pathophysiology of drug-resistant seizures does not resemble mechanism of the above stimuli, therefore 6 Hz test was introduced. It has been proved that it mimics epileptogenesis – the process where damaged neuronal tissue exhibits pathological processes leading to epilepsy. Examples of drugs active in 6 Hz test and inactive in MES are levetiracetam and its analog – seletracetam (3, 4).

Research concerning anticonvulsant activity of well-known antiarrhythmic drugs, such as propranolol and mexiletine (Fig. 1), has revealed that both these medicines prevent seizures in the maximum electroshock seizure test (MES, mice, *i.p.*). Among the likely mechanisms in both cases there is inhibition of sodium channels, apart from their main molecular mechanisms (blocking β-adrenergic receptors and opening potassium channels, respectively) (5, 6). The effect of potential stabilization within neurons by those two drugs was a starting point for searching new anticonvulsant compounds among aroxyalkylaminoalkanols (7).

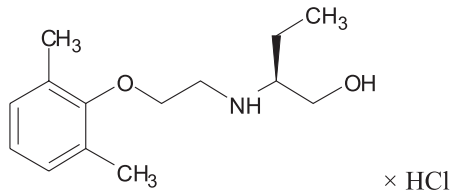
In our previous studies (8–14), we reported anticonvulsant activity of some amido- and aminoalkanols which were examined within the Anticonvulsant Screening Program (ASP) carried out at National Institute of Neurological Disorders and Stroke, National Institutes of Health, Rockville, USA (15). One of them, (*S*)-(+)-2-*N*-[(2,6-dimethylphenoxy)ethyl]aminobutan-1-ol hydrochloride displayed sufficient protection against MES-induced seizures and low toxicity (mice, *i.p.*) with ED_{50} = 7.57 mg/kg and PI = 4.55 (8). Another compound, (*R,S*)-*trans*-2*N*-[(2,6-dimethylphenoxy)ethyl] aminocyclohexan-1-ol exhibited ED_{50} = 7.73 mg/kg and PI = 3.90 (MES, mice, *i.p.*) (Fig. 2) (9). We consistently report lipophilicity parameters as important

* Corresponding author: e-mail: awaszkie@cm-uj.krakow.pl; phone: +48126205576, fax: +48126205405

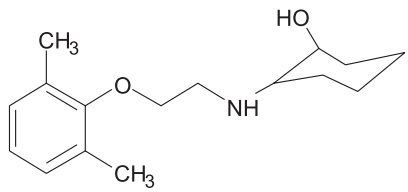


Propranolol Mexiletine

Figure 1. Structures of cardiovascular drugs with anticonvulsant activity



(*S*)-(+)-2-*N*-[(2,6-dimethylphenoxy)ethyl]amino butan-1-ol hydrochloride (8).



(*R,S*)-*trans*-2*N*-[(2,6-dimethylphenoxy)ethyl]aminocyclohexan-1-ol (9).

Figure 2. Structures of (2,6-dimethylphenoxy)ethyl aminoalkanol derivatives with anticonvulsant activity

physicochemical feature in CNS drug discovery (10). From the preliminary assay data, it was proposed that anticonvulsant activity was associated mainly with aminoalkanol type and configuration. Such anticonvulsant activity of the appropriate aminoalkanols drew our attention onto influence of position and type of substituents in the phenyl ring. So far, appropriate derivatives of 4-methylphenol, 2,6-dimethylphenol (8, 9), 4-chlor-3-methylphenol and 2-chlor-5-methylphenol (10), as well as 4-chlor-2-methylphenol (11) have been evaluated. Herein we report results of synthesis and anticonvulsant screening of novel *N*-(2,3-dimethylphenoxy) and *N*-(2,3,5-trimethylphenoxy)alkyl]aminoalkanols [**I–XVII**].

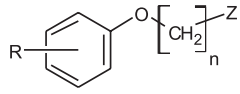
EXPERIMENTAL

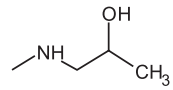
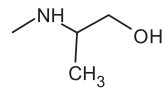
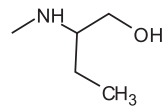
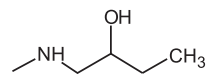
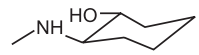
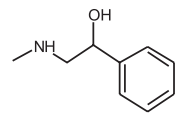
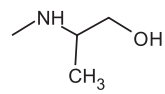
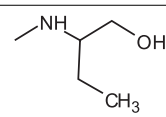
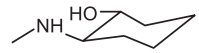
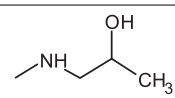
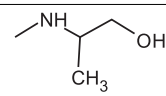
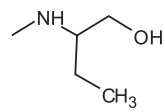
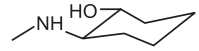
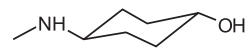
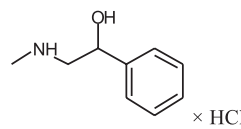
Chemistry

Apparatus and reagents

Melting points (m.p.) were determined by means of a Büchi SMP-20 apparatus (Büchi Labortechnik, Switzerland) and are uncorrected. Elemental analyses were performed on Vario El III (Elementar Analyzensysteme GmbH, Germany). Thin-layer chromatography was performed on precoated aluminum sheets (silica gel 60 F_{254}, Merck) using mobile phase indicated below. The theoretical values of the partition coefficient (LogP) of the tested compounds were calculated by means of ACD-

Table 1. Chemical structures of the tested compounds [**I–XVII**].



R	n	Compound	Z	Configuration
2,5-$(CH_3)_2$	**2**	**I**		*R,S*
		II		*R,S*
		III		*R,S*
		IV		*R,S*
		V		*trans, R,S*
		VI		*R,S*
	3	**VII**		*R,S*
		VIII		*R,S*
		IX		*trans, R,S*
2,3,5-$(CH_3)_3$	**2**	**X**		*R,S*
		XI		*R,S*
		XII		*R,S*
		XIII		*R*
		XIV		*S*
		XV		*trans, R,S*
		XVI		*trans*
		XVII		*R,S*

LABS 12.0 program. Specific rotation (for compounds **XIII** and **XIV**) was measured on Jasco P-2000 polarimeter (1% w/v solutions in CH_3OH, sodium light 589 nm). The proton magnetic resonance spectra were recorded by means of Varian VX 300 spectrometer (USA) or Bruker 500 spectrometer (Germany) using DMSO-d_6 or $CDCl_3$ as solvents and DMSO or TMS as internal standards, respectively. The results are presented in the following format: chemical shift δ (ppm), multiplicity, coupling constants (*J*) values in Hertz (Hz), number of protons, proton's position. Multiplicities are shown as the abbreviations: s (singlet), bs (broad singlet), d (doublet), dd (doublet of doublets), t (triplet), quin (quintet), m (multiplet). *D,L-trans*-2-aminocyclohexan-1-ol for synthesis of compounds **V**, **IX** and **XV** was synthesized according to published procedures (9). Other reagents were purchased from Alfa Aesar (Germany) or Merck (Germany). Solvents were commercially available materials of reagent grade.

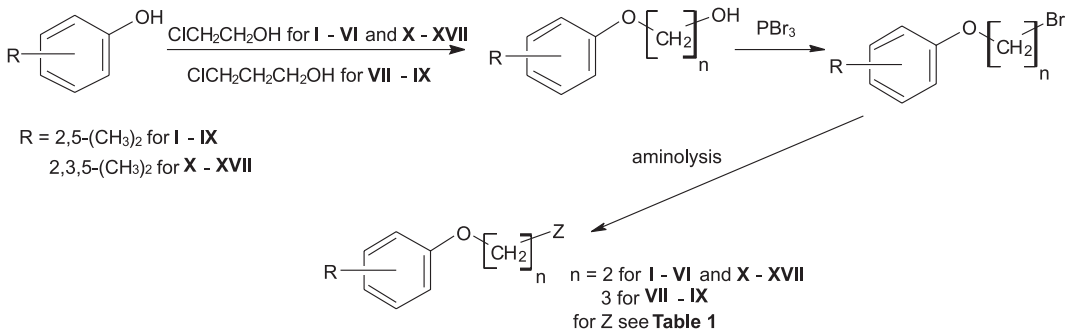
General procedure of synthesis of tested compounds

The tested compounds were synthesized according to formerly published procedures (7–10, 16). The general route of synthesis is shown in Scheme 1 and the chemical structures of the tested compounds in Table 1.

First step of the synthesis included *O*-alkylation of 0.1 mole of appropriate substituted phenol: 2,5-dimethyl for compounds **I**–**IX** or 2,3,5-trimethyl for compounds **X**–**XVII** with use of 10% excess of 2-chloroethanol (for **I**–**VI** and **X**–**XVII**) or 3-chloropropan-1-ol (for **VII**–**IX**). The reaction was carried out in 50% mixture of acetone with sodium ethanolate or sodium propanolate, respectively, at the presence of anhydrous K_2CO_3. The reaction mixture was refluxed for 48 h. Then, it was filtered and 50 mL of 2% aqueous solution of NaOH was added to the filtrate. The mixture was extracted with toluene (2 × 50 mL). Then, organic solvent was separated, dried over Na_2SO_4, and evaporated under reduced pressure. Raw residue was used for bromination reaction by means of 10% excess of PBr_3. The reaction mixture was refluxed for 2 h in water bath, then it was poured on ice. Raw product was extracted by toluene, and the extract was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure yielding bromide derivative. In the final step, a mixture of 0.01 mole of an appropriate aminoalkanol or amine and 0.01 mole of appropriate bromide was refluxed for 6 h in 30 mL of toluene at the presence of 0.015 mole of anhydrous K_2CO_3 as a proton acceptor. Then, inorganic salts were filtered off and organic solvent was evaporated under reduced pressure. Oily residues were recrystallized from toluene/*n*-heptane 1 : 5 v/v mixture. In order to obtain compound **XVII,** the base was converted into hydrochloride salt upon treatment with excess of ethanolic solution of gaseous HCl. The hydrochloride was recrystallized from acetone.

***R,S*-1*N*-[(2,5-dimethylphenoxy)ethyl]aminopropan-2-ol [I]**

Yield 60%; $C_{13}H_{21}NO_2$, M.w. = 223.31, m.p.: 64–66°C. R_f = 0.39 (CH_3OH : ethyl acetate 1 : 1, v/v). Log P = 2.22 ± 0.28. ^{1}H-NMR (500 MHz, DMSO, δ, ppm: 6.98 (d, *J* = 7.4, 1H, Ar-H3); 6.73 (s, 1H, Ar-H6); 6.63 (d, *J* = 7.4 Hz, 1H, Ar-H4); 4.44 (d, *J* = 4.3 Hz, 1H, OH); 4.03–3.94 (m, 2H, CH_2-O); 3.71–3.64 (m, 1H, HO-C<u>H</u>); 2.88 (t, *J* = 5.5 Hz, 2H, O-CH_2-C<u>H</u>$_2$-N); 2.54–2.45 (m, 2H, N-CH_2); 2.25 (s, 3H, Ar-CH_3); 2.09 (s, 3H, Ar-CH_3); 1.85 (bs, 1H, NH); 1.04 (d, *J* = 6.3 Hz, 2H, CH_3-R). Analysis: calcd.: C, 69.92; H, 9.48; N, 6.27%; found: C, 69.90; H, 9.38; N, 6.21%.



Scheme 1. Synthesis of the tested compounds [**I**–**XVII**]

***R,S*-2*N*-[(2,5-dimethylphenoxy)ethyl]aminopropan-1-ol [II]**

Yield 72%; $C_{13}H_{21}NO_2$, M. w. = 223.31, m.p.: 74–76°C. R_f = 0.36 (CH_3OH : ethyl acetate 1 : 1, v/v). Log P = 2.22 ± 0.28. ^{1}H-NMR (500 MHz, DMSO, δ, ppm): 6.98 (d, *J* = 7.4 Hz, 1H, Ar-H3); 6.73 (s, 1H, Ar-H6); 6.63 (d, *J* = 7.4 Hz, 1H, Ar-H4); 4.53 (t, *J* = 5.0 Hz, 1H, OH); 4.04–3.98 (m, 1H, O-C<u>H</u>H); 3.98–3.93 (m, 1H, O-CH<u>H</u>); 3.33–3.28 (m, 1H, N-C<u>H</u>H); 3.24–3.18 (m, 1H, N-CH<u>H</u>); 2.96–2.90 (m, 1H, C<u>H</u>HOH); 2.89–2.84 (m, 1H, CH<u>H</u>OH); 2.71–2.64 (m, 1H, CH); 2.25 (s, 3H, Ar-CH_3); 2.10 (s, 3H, Ar-CH_3); 1.88 (bs, 1H, NH); 0.92 (d, *J* = 6.3 Hz, 3H, CH_3-R). Analysis: calcd.: C, 69.92; H, 9.48; N, 6.27%; found: C, 69.90; H, 9.32; N, 6.19%.

***R,S*-2N-[(2,5-dimethylphenoxy)ethyl]aminobutan-1-ol [III]**

Yield 59%; $C_{14}H_{23}NO_2$, M.w. = 237.34, m.p.: 66–68°C. R_f = 0.44 (CH_3OH : ethyl acetate 1 : 1, v/v). Log P = 2.75 ± 0.28. ^{1}H-NMR (500 MHz, DMSO, δ, ppm): 6.98 (d, *J* = 7.4 Hz, 1H, Ar-H3); 6.73 (s, 1H, Ar-H6); 6.63 (d, *J* = 7.4 Hz, 1H, Ar-H4); 4.40 (t, *J* = 5.4 Hz, 1H, OH); 4.03–3.93 (m, 2H, C<u>H$_2$</u>-O); 3.42–3.22 (m, 2H, C<u>H$_2$</u>-O); 2.90 (t, *J* = 5.5 Hz, 2H, N-C<u>H$_2$</u>); 2.49–2.42 (m, 1H, CH); 2.25 (s, 3H, Ar-CH_3); 2.09 (s, 3H, Ar-CH_3); 1.76 (bs, 1H, NH); 1.41–1.30 (m, 2H, R-CH_2-R); 0.85 (t, *J* = 7.5 Hz, 3H, CH_3-R). Analysis: calcd.: C, 70.85; H, 9.77; N, 5.90%; found: C, 70.76; H, 9.69; N, 5.74%.

***R,S*-1*N*-[(2,5-dimethylphenoxy)ethyl]aminobutan-2-ol [IV]**

Yield 65%; $C_{14}H_{23}NO_2$, M.w. = 237.34, m.p.: 63–65°C. R_f = 0.39 (CH_3OH : ethyl acetate 1 : 1, v/v). Log P = 2.75 ± 0.28. ^{1}H-NMR (500 MHz, DMSO, δ, ppm): 6.97 (d, *J* = 7.4 Hz, 1H, Ar-H3); 6.73 (s, 1H, Ar-H6); 6.63 (d, *J* = 7.4 Hz, 1H, Ar-H4); 4.41 (bs, 1H, OH); 4.03–3.95 (m, 2H, O-C<u>H$_2$</u>); 3.42 (bs, 1H, CH); 2.88 (t, *J* = 5.5 Hz, 2H, O-CH_2-C<u>H$_2$</u>-N); 2.57 (dd, *J* = 11.6, *J* = 4.0 Hz, 1H, N-C<u>H</u>H); 2.48 (dd, *J* = 11.6 Hz, *J* = 4.0 Hz, 1H, N-CH<u>H</u>); 2.26 (s, 3H, Ar-CH_3); 2.10 (s, 3H, Ar-CH_3); 1.84 (bs, 1H, NH); 1.45–1.26 (m, 2H, CH_2); 0.86 (t, *J* = 7.5 Hz, 3H, CH_3-R). Analysis: calcd.: C, 70.85; H, 9.77; N, 5.90%; found: C, 70.80; H, 9.77; N, 5.78%.

***R,S-trans*-2*N*-[(2,5-dimethylphenoxy)ethyl]aminocyclohexan-1-ol [V]**

Yield 65%; $C_{16}H_{25}NO_2$, M.w. = 263.38, m.p.: 99–101°C. R_f = 0.57 (CH_3OH : ethyl acetate 1 : 1, v/v). Log P = 2.90 ± 0.27. ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 7.01 (d, *J* = 7.4 Hz, 1H, Ar-H4); 6.67 (d, *J* = 7.4 Hz, 1H, Ar-H3); 6.64 (s, 1H, Ar-H6); 4.05 (t, *J* = 5.4 Hz, 2H, O-CH_2); 3.26–3.14 (m, 2H, -C<u>H</u>H-NH + C<u>H</u>-OH); 2.92–2.85 (m, 1H, CH<u>H</u>-NH); 2.31 (s, 3H, Ar-CH_3), 2.17 (s, 3H, Ar-CH_3); 2.29–0.95 (m, 9H, cyclohexyl). Analysis: calcd.: C, 72.97; H, 9.57; N, 5.32%; found: C, 73.10; H, 9.83; N, 5.49%.

***R,S*-2*N*-[(2,5-dimethylphenoxy)ethyl]amino-1-phenylethan-1-ol [VI]**

Yield 60%; $C_{18}H_{23}NO_2$, M.w. = 285.38, m.p.: 124–126°C. R_f = 0.62 (CH_3OH); Log P = 3.54 ± 0.30. ^{1}H-NMR (500 MHz, DMSO, δ, ppm): 7.39–7.26 (m, 4H, Ar-H); 7.25–7.20 (m, 1H, Ar-H); 6.98 (d, *J* = 7.4 Hz, 1H, Ar-H3); 6.73 (s, 1H, Ar-H6); 6.63 (d, *J* = 7.4 Hz, 1H, Ar-H4); 5.26 (d, *J* = 3.5 Hz, 1H, OH); 4.68–4.61 (m, 1H, CH); 3.98 (t, *J* = 5.5 Hz, 2H, O-CH_2); 2.92 (t, *J* = 5.5 Hz, 2H, O-CH_2-C<u>H$_2$</u>-N); 2.72 (d, *J* = 6.2 Hz, 2H, N-C<u>H$_2$</u>-CH); 2.25 (s, 3H, Ar-CH_3); 2.05 (s, 3H, Ar-CH_3); 1.89 (bs, 1H, NH). Analysis: calcd.: C, 75.76; H, 8.12; N, 4.91%; found: C, 75.49; H, 8.05; N, 4.90%.

***R,S*-2*N*-[(2,5-dimethylphenoxy)propyl]aminopropan-1-ol [VII]**

Yield 76%; $C_{14}H_{23}NO_2$, M. w. = 237.34, m.p.: 80–81°C. R_f = 0.16 (CH_3OH : ethyl acetate 1 : 1, v/v). Log P = 2.47 ± 0.27. ^{1}H NMR (500 MHz, DMSO, δ, ppm): 7.00 (d, *J* = 7.44 Hz, 1 H, Ar-H3), 6.61–6.71 (m, 2 H, Ar-H4,6), 4.04 (t, *J* = 5.96 Hz, 2 H, O-C<u>H$_2$</u>-CH_2-CH_2-N), 3.61 (dd, *J* = 10.64, 3.98 Hz, 1 H, C<u>H$_2$</u>-OH), 3.29 (dd, *J* = 10.77, 7.05 Hz, 1 H, C<u>H$_2$</u>-OH), 2.98 (dt, *J* = 11.70, 6.91 Hz, 1 H, O-CH_2-CH_2-C<u>H$_2$</u>-N), 2.73–2.91 (m, 2 H, O-CH_2-CH_2-C<u>H$_2$</u>-N, C<u>H</u>-NH), 2.34 (bs, 2 H, OH, NH), 2.31 (s, 3 H, Ar-CH_3), 2.17 (s, 3 H, Ar-CH_3), 2.02 (quin, *J* = 6.41 Hz, 2 H, O-CH_2-C<u>H$_2$</u>-CH_2-N), 1.10 (d, *J* = 6.54 Hz, 3 H, C<u>H$_3$</u>-CH). Analysis: calcd.: C, 70,85; H, 9.77; N, 5.90%; found: C, 70.80; H, 9.61; N, 5.91%.

***R,S*-2*N*-[(2,5-dimethylphenoxy)propyl]aminobutan-1-ol [VIII]**

Yield 66%; $C_{15}H_{25}NO_2$, M.w. = 251.36, m.p.: 53–54°C. R_f = 0.22 (CH_3OH : ethyl acetate 1 : 1, v/v). Log P = 3.00 ± 0.27. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 7.00 (d, *J* = 7.4 Hz, 1H, Ar-H3), 6.71–6.61 (m, 2H, Ar-H4,6), 4.04 (t, *J* = 6.0 Hz, 2H, Ar-O-C<u>H$_2$</u>), 3.62 (dd, *J* = 10.5, *J* = 4.1 Hz, 1H, CH-C<u>H$_2$</u>-OH), 3.27 (dd, *J* = 10.6, *J* = 6.6 Hz, 1H, CH-C<u>H$_2$</u>-OH), 2.97–2.86 (m, 1H, C<u>H$_2$</u>-NH), 2.82–2.72 (m, 1H, C<u>H$_2$</u>-NH), 2.61–2.51 (m, 1H, NH-C<u>H</u>-CH_2-OH), 2.31 (s, 3H, Ar-CH_3), 2.17 (s, 3H, Ar-CH_3), 1.97 (quin, *J* = 6.4 Hz, 2 H, CH-C<u>H$_2$</u>-CH_3), 1.62–1.31 (m, 2H, O-CH_2-C<u>H$_2$</u>-CH_2-NH), 0.91 (t, *J*

= 7.5 Hz, 1 H, CH-CH_2-C$\underline{H}_3$). Analysis: calcd.: C, 71.67; H, 10.02; N, 5.57%; found: C, 71.39; H, 9.95; N, 5.51%.

***R,S-trans*-2*N*-[(2,5-dimethylphenoxy)propyl]aminocyclohexan-1-ol [IX]**

Yield 67%; $C_{17}H_{27}NO_2$, M. w. = 277.41, m.p.: 92–93°C. R_f = 0.30 (CH_3OH : ethyl acetate 1 : 1, v/v). Log P = 3.15 ± 0.25. ^{1}H NMR (500 MHz, DMSO, δ, ppm): 7.00 (d, *J* = 7.6 Hz, 1H, Ar-H3), 6.71–6.60 (m, 2H, Ar-H4,6), 4.03 (t, *J* = 6.0 Hz, 2H, Ar-O-C$\underline{H}_2$), 3.20–3.10 (m, 1H, cyclohexyl-H1/C$\underline{H}$-OH), 3.03 (dt, *J* = 11.6, *J* = 6.9 Hz; 1 H, C$\underline{H}_2$-NH), 2.68 (dt, *J* = 11.6, *J* = 6.7 Hz, 1H, C$\underline{H}_2$-NH), 2.31 (s, 3H, Ar-CH_3), 2.26-2.18 (m, 1H, cyclohexyl-H2/C$\underline{H}$-NH), 2.17 (s, 3H, Ar-CH_3), 2.15–2.03 (m, 2H, cyclohexyl-H6), 2.02–1.91 (m, 2H, cyclohexyl-H3), 1.78–1.66 (m, 2H, cyclohexyl-H5), 1.34–1.15 (m, 2H, cyclohexyl-H4). Analysis: calcd.: C, 73.61; H, 9.81; N, 5.05%; found: C, 74.01; H, 9.84; N, 5.03%.

***R,S*-1*N*-[(2,3,5-trimethylphenoxy)ethyl]aminopropan-2-ol [X]**

Yield 69%; $C_{14}H_{23}NO_2$, M.w. = 237.3, m.p.: 74–76°C. R_f = 0.52 (CH_3OH : ethyl acetate 1 : 1, v/v). Log P = 2.68 ± 0.28. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 6.62 (s, 1H, Ar-H4), 6.54 (s, 1H, Ar-H6), 4.05 (t, *J* = 5.1 Hz, 2H, O-C$\underline{H}_2$-CH_2-N), 3.81 (quin, *J* = 9.4, *J* = 6.3, *J* = 3.1 Hz, 1H, CH_2-C$\underline{H}$(OH)-CH_3), 3.16–2.96 (m, 2H, O-CH_2-C$\underline{H}_2$-N), 2.83 (dd, *J* = 12.1, *J* = 3.1 Hz, 1 H, C$\underline{H}_2$-CH(OH)-CH_3), 2.56 (bs., 2H, OH, NH), 2.49 (dd, *J* = 12.1, *J* = 9.5 Hz, 1 H, C$\underline{H}_2$-CH(OH)-CH_3), 2.28 (s, 3H, Ar-CH_3), 2.23 (s, 3H, Ar-CH_3), 2.10 (s, 3H, Ar-CH_3), 1.17 (d, *J* = 6.2 Hz, 3H, CH_2-CH(OH)-C$\underline{H}_3$). Analysis: calcd.: C, 70.79; H, 9.77; N, 5.90%; found: C, 70.85; H, 9.46; N, 5.59%.

***R,S*-2*N*-[(2,3,5-trimethylphenoxy)ethyl]aminopropan-1-ol [XI]**

Yield 62%; $C_{14}H_{23}NO_2$, M.w. = 237.3, m.p.: 73–75°C. R_f = 0.25 (CH_3OH : benzene (1 : 5, v/v). Log P = 2.68 ± 0.28. ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 6.62 (s, 1H, Ar-H4); 6.54 (s, 1H, Ar-H6); 4.05–4.02 (m, 2H, Ar-O-CH_2); 3.61 (dd, *J* = 4.1, *J* = 10.5 Hz, 1H, C$\underline{H}$HOH); 3.27 (dd, *J* = 5.0, *J* = 10.5 Hz, 1H, CH$\underline{H}$OH); 3.15–3.11 (m, 1H, C$\underline{H}$H-N); 2.96–2.91 (m, 1H, CH$\underline{H}$-N); 2.88–2.84 (m, 1H, N-CH); 2.28 (s, 3H, Ar-CH_3); 2.23 (s, 3H, Ar-CH_3); 2.10 (s, 3H, Ar-CH_3); 1.10 (d, *J* = 6.5 Hz 3H, CH-C$\underline{H}_3$); 2.50–1.50 (bs, 2H, NH, OH). Analysis: calcd.: C, 70.79; H, 9.77; N, 5.90%; found: C, 71.13; H, 9.36; N, 5.78%.

***R,S*-2*N*-[(2,3,5-trimethylphenoxy)ethyl]aminobutan-1-ol [XII]**

Yield 60%; $C_{15}H_{25}NO_2$, M.w. = 251.35, m.p.: 61–62°C (toluene : heptane 1 : 1, v/v); R_f = 0.63 (CH_3OH : ethyl acetate 5 : 1, v/v). Log P = 3.21 ± 0.28. ^{1}H-NMR (500 MHz, DMSO, δ, ppm): 6.59 (s, 1H, Ar-H4); 6.56 (s, 1H, Ar-H6); 4.45 (bs, 1H, OH); 3.95 (t, *J* = 5.3 Hz, 2H, Ar-O-CH_2); 3.50–3.20 (m, 2H, C$\underline{H}_2$-OH); 2.90 (t, 2H, C$\underline{H}_2$-N); 2.55–2.40 (m, 1H, CH); 2.21 (s, 3H, Ar-CH_3); 2.16 (s, 3H, Ar-CH_3); 2.02 (s, 3H, Ar-CH_3); 1.45–1.3 (m, C$\underline{H}_2$-CH_3); 0.85 (t, *J* = 7.2 Hz, 3H, CH_2-C$\underline{H}_3$). Analysis: calcd.: C, 71.68; H, 10.03; N, 5.57%; found: C, 71.30; H, 9.90; N, 5.54%.

***R-(-)*-2*N*-[(2,3,5-trimethylphenoxy)ethyl]aminobutan-1-ol [XIII]**

Yield 58%; $C_{15}H_{25}NO_2$, M.w. = 251.35, m.p.: 47–49°C. R_f = 0.37 (CH_3OH : benzene 1 : 5, v/v). $[\alpha]^{20}_D$ = –19.4. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 6.62 (s, 1H, Ar-H4), 6.53 (s, 1H, Ar-H6), 4.12–3.95 (m, 2 H, Ar-O-C$\underline{H}_2$), 3.64 (dd, *J* = 10.6, *J* = 4.1 Hz, 1H, CH-C$\underline{H}$H-OH), 3.32 (dd, *J* = 10.6, *J* = 6.4 Hz, 1H, CH-CH$\underline{H}$-OH), 3.17–3.04 (m, 1H, C$\underline{H}$H-NH), 3.01–2.89 (m, 1H, CH$\underline{H}$-NH), 2.70–2.58 (m, 1H, NH-C$\underline{H}$-CH_2-OH), 2.28 (s, 3H, Ar-CH_3), 2.23 (s, 3H, Ar-CH_3), 2.10 (s, 3H, Ar-CH_3), 1.61–1.38 (m, 2H, CH-C$\underline{H}_2$-CH_3), 0.95 (t, *J* = 7.4 Hz, 3H, CH-CH_2-C$\underline{H}_3$). Analysis: calcd.: C, 71.66; H, 10.02; N, 5.57%; found: C, 71.01; H, 9.80; N, 5.37%.

***S-(+)*-2*N*-[(2,3,5-trimethylphenoxy)ethyl]aminobutan-1-ol [XIV]**

Yield 56%; $C_{15}H_{25}NO_2$, M.w. = 251.35, m.p.: 47–49°C. R_f = 0.37 (CH_3OH : benzene 1 : 5, v/v). $[\alpha]^{20}_D$ = 22.2. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 6.62 (s, 1H, Ar-H4), 6.53 (s, 1H, Ar-H6), 4.13–3.99 (m, 2H, Ar-O-C$\underline{H}_2$), 3.67 (dd, *J* = 10.8, *J* = 4.0 Hz, 1H, CH-C$\underline{H}_2$-OH), 3.36 (dd, *J* = 10.8, *J* = 6.4 Hz, 1H, CH-C$\underline{H}_2$-OH), 3.20–3.08 (m, 1H, C$\underline{H}_2$-NH), 3.04–2.94 (m, 1H, C$\underline{H}_2$-NH), 2.75–2.64 (m, 1H, NH-C$\underline{H}$-CH_2-OH), 2.27 (s, 3H, Ar-CH_3), 2.23 (s, 3H, Ar-CH_3), 2.10 (s, 3H, Ar-CH_3), 1.67–1.42 (m, 2H, CH-C$\underline{H}_2$-CH_3), 0.96 (t, *J* = 7.4 Hz, 3H, CH-CH_2-C$\underline{H}_3$). Analysis: calcd.: C, 71.66; H, 10.02; N, 5.57%; found: C, 71.31; H, 9.95; N, 5.48%.

***R,S-trans*-2*N*-[(2,3,5-trimethylphenoxy)ethyl]aminocyclohexan-1-ol [XV]**

Yield 70%; $C_{17}H_{27}NO_2$, M.w. = 277.47, m.p.: 117–119°C. R_f = 0.54 (CH_3OH : benzene 1 : 5, v/v). Log P = 3.36 ± 0.27. ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 6.59 (d, *J* = 8.8, 1H, Ar-H4); 6.56 (d, *J* = 3.0,

1H, Ar-H6); 4.62 (d, *J* = 5.1 Hz, 1H, OH); 4.04–3.98 (m, 1H, Ar-O-CHH); 3.94–3.86 (m, 1H, Ar-O-CHH); 3.13–3.04 (m, 1H, HO-CH); 2.97–2.89 (m, 1H, CHH-N); 2.86–2.78 (m, 1H, CHH-N); 2.23–2.15 (m, 1H, NH); 2.21 (s, 3H, Ar-CH_3); 2.15 (s, 3H, Ar-CH_3); 2.02 (s, 3H, Ar-CH_3); 1.96–1.88 (m, 1H, cyclohex.); 1.83–1.75 (m, 1H, cyclohex.); 1.66–1.54 (m, 2H, cyclohex); 1.24–1.09 (m, 3H, cyclohex.); 0.96–0.86 (m, 1H, cyclohex.). Analysis: calcd.: C, 73.58; H, 9.81; N, 5.07%; found: C, 72.83; H, 9.48; N, 5.24%.

***R,S-trans*-4*N*-[(2,3,5-trimethylphenoxy)ethyl] aminocyclohexan-1-ol [XVI]**

Yield 68%; $C_{17}H_{27}NO_2$, M.w. = 277.41 m.p.: 109–111°C. R_f = 0.45 ($CHCl_3$: CH_3OH 1 : 1, v/v). Log P = 3.22 ± 0.26. ^{1}H NMR (500 MHz, DMSO, δ, ppm): 6.62 (s, 1H, Ar-H4), 6.53 (s, 1H, Ar-H6), 4.06 (t, *J* = 5.3 Hz, 2H, O-CH_2-CH_2-N), 3.71–3.56 (m, 1H, CH-OH), 3.06 (t, *J* = 5.2 Hz, 2 H, O-CH_2-CH_2-N), 2.68–2.51 (m, 1H, CH-NH), 2.27 (s, 3H, Ar-CH_3), 2.22 (s, 3H, Ar-CH_3), 2.10 (s, 3H, Ar-CH_3), 2.00 (m, 4H, cyclohex-H2,6), 1.88 (bs, 2H, OH, NH), 1.43–1.12 (m, 4H, cyclohex-H3,5). Analysis: calcd.: C, 73.61; H, 9.81; N, 5.05%; found: C, 73.59; H, 9.89; N, 5.06%.

***R,S*-2*N*-[(2,3,5-trimethylphenoxy)ethyl]amino-1-phenylethan-1-ol hydrochloride [XVII]**

Yield 58%; $C_{19}H_{26}NO_2Cl$, M.w. = 335.86; m.p.: 146–148°C. R_f = 0.36 (CH_3OH : benzene 1 : 5, v/v). Log P = 4.00 ± 0.30. ^{1}H-NMR (300 MHz, DMSO, δ, ppm): 9.37 (bs, 2H, NH_2^+); 7.48–7.23 (m, 5H, Ar-H); 6.62 (d, *J* = 4.7 Hz, 2H, Ar-H); 6.26 (d, *J* = 4.7 Hz, 1H, OH); 5.13–5.00 (m, 1H, CH); 4.34–4.19 (m, 2H, O-CH_2); 3.40–3.03 (m, 4H, CH_2-N); 2.22 (s, 3H, Ar-CH_3); 2.15 (s, 3H, Ar-CH_3); 2.02 (s, 3H, Ar-CH_3). Analysis: calcd.: C, 67.94; H, 7.80; N, 4.17%; found: C, 67.91; H, 7.8042; N, 4.02%.

Pharmacology

Evaluation of anticonvulsant activity and neurotoxicity was carried out according to the Anticonvulsant Screening Program (ASP) at National Institute of Neurological Disorders and Stroke (NINDS), National Institutes of Health (NIH), Rockville, USA. Tests were performed in mice (adult male Carworth Farms No. 1) after intraperitoneal (*i.p.*) administration and/or in rats (Sprague-Dawley) after oral (*p.o.*) administration. The tested compounds were administered as solutions or suspensions in 0.5% methylcellulose. The total volume of used suspension was 0.01 mL/1 g b.w. for mice and 0.04 mL/10 g b.w. for rats. Initial dosage for evaluation in mice was 30, 100, and 300 mg/kg, and in rats 30 mg/kg. Tests were performed at certain time points after administration of the compound i.e., at 0.5 and 4.0 h after *i.p.* administration or at 0.25, 0.5, 1.0, 2.0 and 4.0 h after *p.o.* administration. All procedures were published elsewhere (15, 17), below we provide short description of the experiments.

Maximal electroshock (MES)

At certain time after administration of the tested compound, 60 Hz alternating current at 50 mA for mice or 150 mA for rats was delivered for 0.2 s *via* corneal electrodes. Protection in MES test was defined as the abolition of the hindlimb tonic extension component of the seizure (15, 17).

Subcutaneous pentetrazole induced seizures (scMet)

The scMet was conducted in mice at certain time after administration of the tested compound by subcutaneous administration of pentetrazole dissolved in 0.9% NaCl solution at the dose of 85 mg/kg. The animal was placed in isolation cage and observed for next 30 min. Failure of observing even a threshold seizure (a single episode of clonic spasm which remains at least 5 s) was classified as protection (15, 17).

Neurotoxicity assays (TOX)

Neurotoxicity in mice was measured by the rotarod test. A mouse was placed on a 1 inch diameter knurled plastic rod rotating at 6 rpm. Neurotoxicity was indicated by the inability of the animal to maintain equilibrium on the rod for at least 1 min in each of the three trials. In rats, neurological deficit was indicated by ataxia, loss of placing response and muscle tone (15, 17).

6 Hz psychomotor seizure test

The 6 Hz model test was carried out according to the protocol originally described by Brown et al. (18) and more recently by Barton et al. (19) and Kaminski et al. (20). 6 Hz test was performed in mice. Seizures were induced by delivering 0.2 ms pulses of electric current at 6 Hz and 32 mA for 3 s *via* corneal electrodes. Untreated animals display seizures after such stimulation described as minimal clonic phase, whereas mice not displaying this behavioral are considered protected.

RESULTS

The synthesis of the tested compounds consisted of *O*-alkylation of the appropriate substituted

Table 2. Anticonvulsant activity of the tested compounds (**I–XVII**) (mice, *i.p.*).

Compound	Dose [mg/kg b.w.]	MES [a]		scMet [a]		TOX [b]		ASP class [c]
		0.5 h	4.0 h	0.5 h	4.0 h	0.5 h	4.0 h	
I	30 100 300	0/1 **3/3** I	0/1 0/3 I	0/1 0/1 I	0/1 0/1 I	0/4 **8/8** **4/4**	0/2 **1/4** I	1
II	30 100 300	0/1 **3/3** **1/1**	0/1 **3/3** I	0/1 0/1 0/1	0/1 0/1 I	2/4 **8/8** **4/4**	**1/2** **1/4** I	4
III	30 100 300	0/1 **3/3** I	0/1 0/3 I	0/1 0/1 I	0/1 0/1 I	0/4 **8/8** **4/4**	0/4 0/4 I	1
IV	30 100 100	0/1 **3/3** **1/1**	0/1 0/3 I	0/1 0/1 I	0/1 0/1 I	0/4 **8/8** **4/4**	0/2 0/4 I	1
VI	30 100 300	0/1 0/3 0/1	0/1 0/3 0/1	0/1 0/1 0/1	0/1 0/1 0/1	0/4 **7/8** **3/4**	0/2 0/4 1/2	3
VII	30 100 300	0/1 **2/2** I	0/1 0/3 I	0/1 0/1 I	0/1 0/1 I	0/4 **8/8** **4/4**	0/2 0/4 I	1
VIII	30 100 300	0/1 **2/2** I	0/1 0/3 I	0/1 0/1 I	0/1 0/1 I	0/4 **8/8** **4/4**	0/2 0/4 I	1
IX	30 100 300	0/1 **1/3** I	0/1 0/3 0/1	0/1 I I	0/1 0/1 I	0/4 **4/8** **4/4**	0/2 0/4 0/2	1
X	30 100 300	0/1 **3/3** I	0/1 0/3 I	0/1 0/1 I	0/1 0/1 I	**3/4** **8/8** **4/4**	**1/2** **1/4** I	4
XI	3 10 30 100 300	0/4 0/4 **1/1** **3/3** I	I I I	I I 0/1 **2/2** I	I I 0/1 0/1 I	0/4 0/4 **1/4** **8/8** **4/4**	I I **1/2** **1/3** I	4
XII	3 10 30 100 300	0/4 0/4 **1/1** **3/3** I	I I 0/1 **1/3** 0/1	I I 0/1 0/1 I	I I 0/1 0/1 I	0/4 0/4 0/4 **7/8** **4/4**	I I 0/2 0/4 0/2	1
XIII	3 10 30 100 300	I 0/4 **1/1** **2/3** I	I I 0/1 **1/3** I	I I 0/1 0/1 I	I I 0/1 0/1 I	I 0/4 0/4 **4/8** **4/4**	I I 0/2 0/4 I	1
XIV	3 10 30 100 300	0/4 0/4 **1/1** **3/3** I	I I 0/1 0/3 I	I I 0/1 I I	I I 0/1 0/1 I	0/4 0/4 **3/4** **7/8** **4/4**	I I 0/2 0/4 I	4
I **XV**	3 10 30 100 300	0/4 0/4 **1/1** **3/3** I	I I 0/1 0/3 I	I I 0/1 0/1 I	I I 0/1 0/1 I	0/4 0/4 1/**4** **7/8** **4/4**	I I 0/2 **1/4** I	4
XVI	30 100 300	0/1 **3/3** I	0/1 0/3 I	0/1 0/1 I	0/1 0/1 I	0/4 **8/8** **4/4**	0/2 0/4 I	1
XVII	30 100 300	0/1 **3/3** **1/1**	0/1 **1/3** I	0/1 0/1 I	0/1 0/1 0/1	**3/4** **8/8** **4/4**	1/2 **4/4** **1/1**	4

[a] Number of animals protected / number of animals tested; [b] number of animals exhibiting toxicity / number of animals tested in the rotorod test; [c] ASP classification: 1 – anticonvulsant activity at dose 100 mg/kg or less; 2 – anticonvulsant activity at doses greater than 100 mg/kg; 3 – compound inactive at 300 mg/kg; 4 – compound either active or inactive but toxic at dose of 30 mg/kg; I – the compound was not tested in the particular conditions.

Table 3. Anticonvulsant activity of compounds **XIII** and **XV** tested in rats, *p.o.*

Compound	Test	Dose	Time [h]				
		[mg/kg b.w.]	0.25	0.5	1.0	2.0	4.0
XIII ED_{50} **(1 h) > 120**	MES[a)]	30	**1/4**	**3/4**	**2/4**	0/4	0/4
	TOX[a)]	30	0/4	0/4	0/4	0/4	0/4
XV	MES[a)]	30	0/4	0/4	0/4	**1/4**	**2/4**
	TOX[a)]	30	0/4	0/4	0/4	0/4	0/4

[a)] Number of animals protected / number of animals tested in anticonvulsant or neurotoxicity assays.

Table 4. Anticonvulsant activity in 6-Hz test of compounds **I** and **V** (mice, *i.p.*).

Compound	Test	Dose	Time [h]				
		[mg/kg b.w.]	0.25	0.5	1.0	2.0	4.0
I	6-Hz [a)]	30	**1/4**	**3/4**	**2/4**	0/4	0/4
	TOX [b)]	30	0/4	0/4	0/4	0/4	0/4
V	6-Hz [a)]	30	0/4	0/4	0/4	**1/4**	**2/4**
	TOX [b)]	30	0/4	0/4	0/4	0/4	0/4

[a)] Number of animals protected / number of animals tested; [b)] number of animals exhibiting toxicity / number of animals tested in the rotorod test.

phenol by means of 2-chloroethanol or 3-chloropropan-1-ol in the first step. Then, the obtained 2-phenoxyalkanols were converted to bromides by means of phosphorus tribromide. Finally, the obtained bromide derivatives were used in *N*-alkylation of chosen aminoalkanols.

After confirmation of structure and chemical purity, the synthesized compounds were subjected to anticonvulsant and neurotoxicity evaluation according to the protocols within Anticonvulsant Screening Program (ASP). Pharmacological tests were performed at National Institute of Neurological Disorders and Stroke, National Institutes of Health, Rockville, USA. Most of the compounds were qualified to standard procedures and tested in mice after *i.p.* administration. The results are shown in Table 2. The protective activity in MES was found for majority of the compounds. Most of substances showed full protection at the dose 100 mg/kg. Compounds **XI**–**XV** were also active at 30 mg/kg. Considering scMet evaluation, compound **XI** was the only one in the series which showed protection. Anticonvulsant properties of the tested substances were in all cases accompanied by neurotoxicity, especially at the doses of 100 and 300 mg/kg. Most promising compounds, **XII**, **XIII**, and **XIV** proved anticonvulsant activity at 30 mg/kg and no neurotoxicity at the same dose. They are derivatives of 2-aminobutan-1-ol – the racemate and the two enantiomers.

Additional tests in rats after oral administration (*p.o.*) were performed for compounds **XIII** and **XV**, results are presented in Table 3. Both substances caused no neurological impairment at all tested time points. Interestingly, compound **XIII** showed protection until 1.0 h after administration while **XV** only at 2.0 and 4.0 h, whereas in mice *i.p.* evaluation both compounds were active at 0.5 h. Compound **XIII** was also used in a more advanced test in order to find ED_{50} value. ED_{50} indicates dose in which the compound is effective in 50% of tested animals (17). The dose was found to be more than 120 mg/kg b. w. (rats, *p.o.*) while tested after 1 h of administration of the compound.

Compound **V** was qualified to modified protocols and was tested initially in 6 Hz model. The obtained results were not good enough to have the

compound tested in MES. On the other hand, compound **I** was qualified for 6 Hz evaluation after successful MES screen. Results of 6 Hz model are shown in Table 4. Both compounds showed some protection.

DISCUSSION AND CONCLUSION

The anticonvulsant activity and neurotoxicity of all synthesized compounds **I–XVII** were evaluated according to the protocols of ASP, NIH, USA (15, 17). The reported series of compounds was characterized by good anticonvulsant activity in MES (mice, *i.p.*). It is visible that among aminoalkanols used as moieties – aminopropanol and aminobutanol with various configuration are more promising compared to more bulky moieties such as 2-amino-1-phenylethanol – compounds **I–IV** and **X–XIV** are the most active. Within this group, the use of ethyl or propyl linker does not make any significant difference in terms of activity – comparing compounds **II** and **VII** as well as **III** and **VIII** in pairs in Table 2.

In terms of substitution of the phenyl ring it is clearly visible that 2,3,5-trimethyl derivatives are more active than 2,5-dimethyl ones – the most active compound is **XIII** – *R*-2*N*-(2,3,5-trimethylphenoxy)ethyl]aminobutan-1-ol which was advanced to testing in rats, *p.o.*

The activity of **I–XVII** was mostly accompanied by neurotoxicity which excluded the compounds from further testing. The important factors in the group are the values of calculated partition coefficient (log P) ranging from 2.22 ± 0.28 to 4.00 ± 0.30. Literature references indicate that in order to reach optimum activity within the central nervous system log P as a measure of lipophilicity should be around 2 (21, 22). In case of some more lipophilic compounds one of the reason of neurotoxicity might be high values of log P.

In terms of structure-anticonvulsant activity relationship, the obtained results in the reported series of compounds combined together with former results indicated that parameters such as type of substituents and their location in the phenyl ring, the aminoalkanol moiety, configuration may have impact on anticonvulsant activity. In conclusion, in the light of formerly published results, the conducted research confirmed that aroxyalkyl derivatives of aminoalkanols are an interesting group in terms of anticonvulsant activity, although 2,5-dimethyl and 2,3,5-trimethyl derivatives exhibit concomitant neurotoxicity.

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