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SYNTHESIS AND PRELIMINARY EVALUATION OF ANTICONVULSANT ACTIVITY OF SOME [4-(BENZYLOXY)BENZOYL]- AND [4-(BENZYLOXY)BENZYL]AMINOALKANOL DERIVATIVES

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Abstract: A variety of appropriate [4-(benzyloxy)benzoyl]- and [4-(benzyloxy)benzyl]aminoalkanol derivatives [**I-XVII**] was synthesized and evaluated for anticonvulsant activity using the maximal electroshock (MES) and subcutaneous pentylenetetrazole (ScMet) tests in mice and rats. Neurotoxicity (TOX) was determined by the rotorod test. The most active compounds in the MES test in mice were the appropriate 4-(benzyloxy)benzyl derivatives of (*R,S*)- and *S*-(+)-2-amino-1-butanol [**XI, XIII**], 3-[4-(benzyloxy)benzyl]amino-3-methyl-1-butanol [**XV**], and *S*-(+)-2-[4-(benzyloxy)benzyl]amino-3-methyl-1-butanol [**XVI**] – all exhibiting 100% anti-MES protection (at 30 mg/kg, mice, *i.p.*) and non-toxic in the active doses. 4-[4-(Benzyloxy)benzyl]amino-1-butanol [**X**] exhibited activity in both MES and ScMet (100 mg/kg, mice, *i.p.*, 100% anticonvulsant protection, 0.5 h and 4 h after administration, respectively).

Keywords: synthesis, aminoalkanols, anticonvulsant activity

Epilepsy is one of the major neurological disorders. In fact, it is a syndrome of different cerebral disorders. This syndrome is characterized by paroxysmal, excessive and hypersynchronous discharges of large number of neurons, causing fluctuations in brain electrochemical balance. About 1% of the entire world population is suffering from seizures being the effect of the disorders. There are many antiepileptic drugs (AEDs), such as gabapentin, lamotrigine, levetiracetam, and zonisamide, however, they cause adverse effects, among which there are headache, dizziness, sleepiness, ataxia, double vision, and cerebellum atrophy, nausea, vomiting, etc. (1). Some drugs cause specific adverse effects such as aplastic anemia (felbamate) (2) or cystic ovaries or hirsutism (valproic acid) (3). Moreover, many patients exhibit seizures resistant to pharmacological treatment, which constitutes about 25% of all cases. Such conditions have large influence on psycho-social, intellectual, behavioral as well as financial aspects of life.

Antiepileptic drugs belong to many chemical groups and therefore they have different mechanisms of action. It is a serious aspect of epilepsy that epileptic attacks are often managed by two AEDs, and once they are no more effective, a third one may be introduced. It is not surprising, if it is for interactions that are due to influence on liver microsomal enzymes. For instance, valproic acid inhibits lamotrigine glucuronidation, which may result in delirium (4). A separate problem is epilepsy in patients like women of child-bearing age (5), children (6), and generally patients suffering from accompanying diseases, such as depression or migraine (7, 8).

Although several new antiepileptic drugs have been approved in the recent years or are in the process of being approved, e.g. lamotrigine, felbamate, zonisamide, levetiracetam, rufinamide, serotolide, etc. (9), there is no AED that would act specifically on each kind of seizures and would be completely safe. Different chemical groups of AEDs are specific for certain kinds of seizures. A well chosen drug should completely eliminate seizure events, have a large protection index (PI), low toxicity, and it ought to be well tolerated, absorbed easily from the digestive tract and it should be easy to

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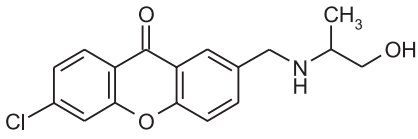
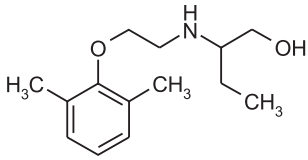
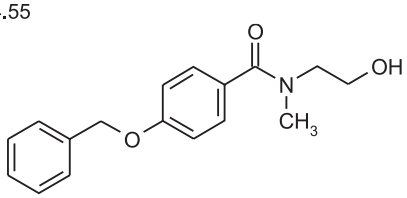


R,S-2-(6-chloro-2-xanthonemethyl)amino-1-propanol (10)
ED_{50} (MES, mice, *i.p.*) = 56.2 mg/kg b.w.
PI = 5.84



S-(+)-2-[(2,6-dimethyl)phenoxyethyl]amino-1-butanol (11)
ED_{50} (MES, mice, *i.p.*) = 7.57 mg/kg b.w.
PI = 4.55



2-[4-(benzyloxy)benzoyl]-2*N*-methylamino-1-ethanol (12)
ED_{50} (MES, mice, *i.p.*) = 51.8 mg/kg b.w.
PI = 2.54

Figure 1. Chemical structures, ED_{50} and protective indices of the most promising compounds from the previous studies (10-12).

monitor its concentration. Since there is no drug that would fulfill all these criteria, there are strong premises for further research in this field.

In previous studies (10-12) we reported anticonvulsant activity of some appropriate amido- and aminoalkanols which were examined according to the Anticonvulsant Screening Project (ASP, National Institute of Neurological and Communicative Disorders and Stroke NINCDS, Bethesda, USA). Some of them displayed protection against MES-induced seizures and low neurotoxicity. From the preliminary assay data, it was ascertained that anticonvulsant activity was associated mainly with one of the aminoalkanol types. The most promising compounds were: (*R,S*)-2-(6-chloro-2-xanthonemethyl)amino-1-propanol (10), (*S*)-(+)-2-[(2,6-dimethyl)phenoxyethyl]amino-1-butanol (11) and 2-[4-(benzyloxy)benzoyl]-2*N*-methylamino-1-ethanol (12). Their anti-MES ED_{50} (mg/kg, mice, *i.p.*) values and protective indices (PI) are presented in Figure 1. Moreover, 2-(4-benzyloxy)benzoyl-2*N*-methylaminoethanol was demonstrated to be effective against the subcutaneous pentylenetetrazole induced seizures (ScMet) with ED_{50} = 142.98 mg/kg, and PI (ScMet) = 0.919 (mice, *i.p.*). Such anticonvulsant activity of the appropriate amino- or amidoalkanols drew our attention onto other related derivatives, including different aminoalkanols also with a chiral center. In designing new aminoalkanol derivatives, a general pattern derived from the reference literature has been adopted.

This report describes synthesis and preliminary evaluation of anticonvulsant activity of a series of [4-(benzyloxy)benzoyl]-aminoalkanols [**I-V**] and their alkanolamine analogues [**VI-XVII**] (Table 1); some of the latter [**VI**, **XI**, **XVII**] are amine analogues of formerly examined amides (12).

RESULTS AND DISCUSSION

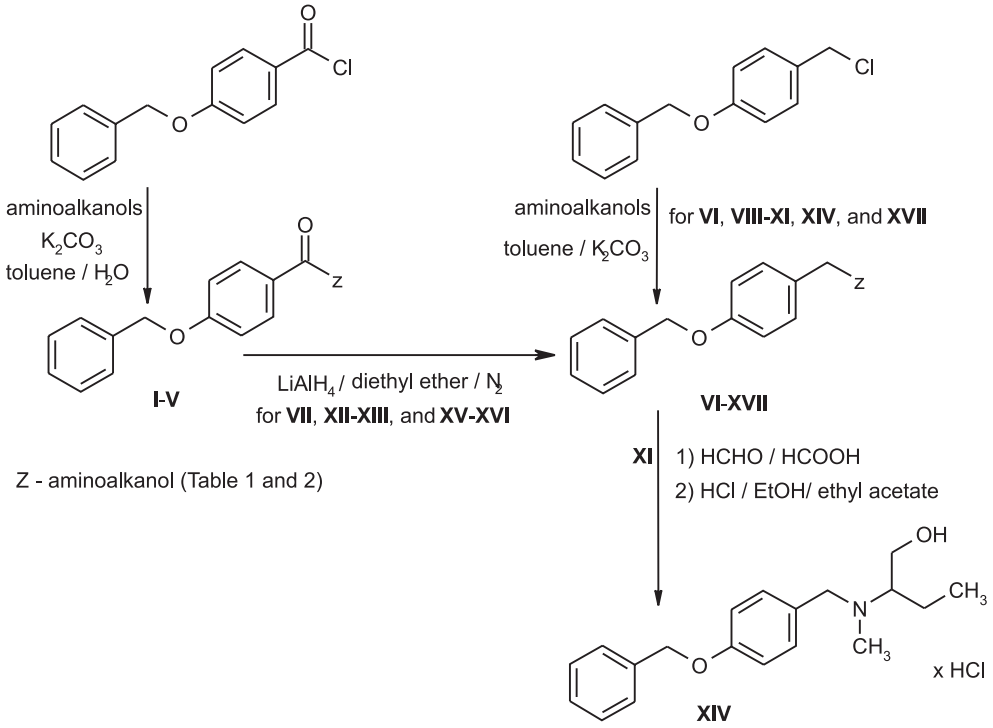
Chemistry

As a result of our investigations, we present the synthesis of the new aminoalkanol derivatives, that are based on the formula included in Tables 1, 2.

The synthesis of the appropriate alkanolamides **I-V** was carried out according to Scheme 1, by *N*-acylation of appropriate aminoalkanol with 4-(benzyloxy)benzoyl chloride in two-phase system (toluene / H_2O / K_2CO_3) according to well-known procedures (12). Yields of the reactions were within the range of 50-60%.

Two common methods were used in order to prepare **VI-XVII**. The first method was based on the reduction of the amides [**I-V**] to the appropriate amines [**VII, XII-XIII**, and **XV-XVI**] and the second one was *N*-alkylation of appropriate aminoalkanols by 4-(benzyloxy)benzyl chloride in the presence of anhyd. K_2CO_3 in toluene solution, which gave **VI**, **VIII-XI**, and **XVII** (yield 65 – 70%) (Scheme 1). The reduction of the amides was performed using $LiAlH_4$ in diethyl ether solution under nitrogen atmosphere at room temperature (yield 40-60%). The separated products [**VII, XII-XIII**, and **XV-XVI**] were purified with the use of planar circular chromatography (chromatotron), where the solid phase constituted silica gel 60 PF_{254} (Merck) and the liquid phase was $CHCl_3$ / CH_3OH (49 : 1, v/v), and then recrystallized from n-heptane. Change of the secondary amine group of **XI** into a tertiary one of **XIV** was performed by reductive *N*-methylation (HCHO / HCOOH) (Scheme 1). Some of the obtained amines were isolated and characterized as bases [**VI base**, **VIII base**, **XI-XIII**, and **XVII**] and their salts [**VI**, **VIII**, **XIa-XIIIa**, and **XVIIa**] or as bases [**VII**, **IX-X**, **XV**, and **XVI**] or as a hydrochloride [**XIV**]. The appropriate bases were converted into hydrochloride salts in ethyl acetate with an excess of EtOH saturated with HCl.

The appropriate enantiomers were recrystallized to constant rotation value [**II**, **III**, **V**] from



Scheme 1. Synthesis of the tested [4-(benzyloxy)benzoyl]- and [4-(benzyloxy)benzyl]-aminoalkanols [**I-XVII**].

toluene n-heptane (1 : 1) and [**XII-XIII**, **XVI**] from n-heptane. Recrystallization of racemates **I**, **IV** was performed from toluene / heptane (1 : 1, v/v), **VI**, **VIII, XIa-XIIIa, XIV** and **XVIIa** from a mixture of ethyl acetate / EtOH (3 : 1, v/v) and **VII, IX-XI, XV**, and **XVII** from n-heptane. The necessary 4-(benzyloxy)benzoyl and 4-(benzyloxy)benzyl chlorides were formerly prepared by heating the corresponding acid or alcohol, under reflux with thionyl chloride. The raw product was used in the amination process. The purity of **I-XVII** was checked by TLC using the developing systems: methanol / ethyl acetate (1 : 1, v/v) or methanol and all compounds were evaluated on the basis of elemental and spectral analyses (IR, ^{1}H-NMR). Moreover, COSY and HSQC spectra were taken in order to determine the structure of **XI**. The structures and calculated partition coefficient (Log $P_{comb.}$, Pallas 3.1.1.2) of **I-XVII** are summarized in Table 1 and 2.

All the obtained aminoalkanols with exception for **VI**, **VIII** and **XIV** (hydrochlorides) were tested in anticonvulsant screens as bases.

Pharmacology

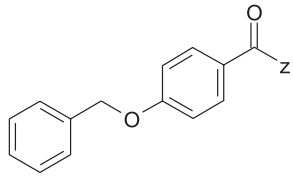
All compounds have been evaluated in preliminary pharmacological testing according to the ASP (NINCDS, Bethesda, MD, U.S.A). The procedures have been described formerly (13, 14). Phase I studies involved three tests: maximal electroshock-induced seizures (MES, mice, *i.p.*), subcutaneous pentylenetetrazole-induced seizures (ScMet, mice, *i.p.*), and neurological toxicity (TOX, mice, *i.p.*), which was measured by the rotorod test. The results of anticonvulsant assays are presented in Table 4.

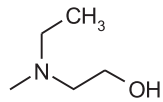
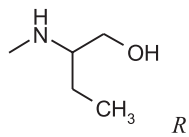
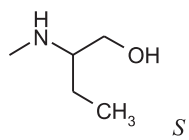
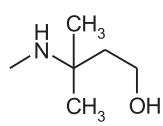
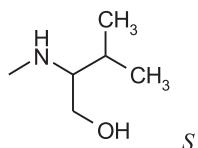
Selected compounds **II-III** and **V** were advanced to phase VIa in which they were tested for an oral activity in rats due to the ADD program. Phase VIa includes MES, ScMet and TOX screens. The results are presented in Table 5.

RESULTS AND DISCUSSION

As it is shown in Table 4, the protective activity in the MES test (mice, *i.p.*) was found for most of the tested compounds, including all tested amides [**I**-**V**]. Compounds **III** and **V** revealed activity at the dose of 100 mg/kg (100% and 67% activity, respectively) and they both were not toxic at the mentioned dose. Moreover, **I**, **II** and **IV** were also active in the ScMet test at the dose of 300 mg/kg (100%, 20% and 60% activity, respectively). Compounds **II** and **III** are enantiomers of formerly examined racemate

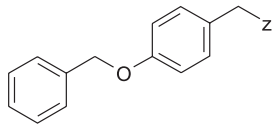
Table 1. Chemical structures, some physical data and Log $P_{comb.}$ of the tested 4-(benzyloxy)benzoyl derivatives [**I-V**] compared with known AEDs.



Compound	Z	Formula (M. w.) Melting point [°C] R_f Yield [α]	Log P_{comb} (Pallas 3.1.1.2)
CBZ *	-	-	3.30
VA **	-	-	2.61
I		$C_{18}H_{21}NO_3$ (299.37) 112-114 [a] 0.26 [b] 60%	2.03
II	 *R*	$C_{18}H_{21}NO_3$ (299.37) 144-146 [a] 0.78 [b] 50% $[\alpha]_{546}^{22.7} = +28.3^{o}$ [c] $[\alpha]_{589}^{20.5} = +28.2^{o}$ [c]	2.44
III	 *S*	$C_{18}H_{21}NO_3$ (299.37) 144-146 [a] 0.78 [b] 50% $[\alpha]_{546}^{22.7} = -27.3^{o}$ [c] $[\alpha]_{589}^{20.5} = -27.0^{o}$ [c]	2.44
IV		$C_{19}H_{23}NO_3$ (313.38) 120-122 [a] 0.73 [b] 60%	2.96
V	 *S*	$C_{19}H_{23}NO_3$ (313.38) 128-130 [a] 0.77 [b] 60% $[\alpha]_{589}^{18.5} = -25.7^{o}$ [c] $[\alpha]_{546}^{20} = -30.0^{o}$ [c]	2.68

***** Carbamazepine; ** Valproic Acid; [a] toluene/heptane (1:1); [b] CH_3OH; [c] c = 2%, CH_3OH.

Table 2. Chemical structures, some physical data, and Log $P_{comb.}$ of the synthesized 4-(benzyloxy)benzyl derivatives [**VI-XVII**].



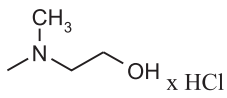
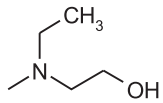
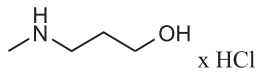
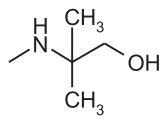
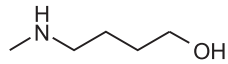
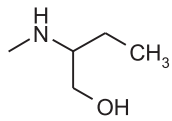
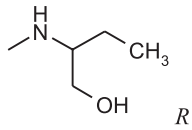
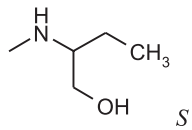
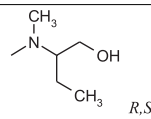
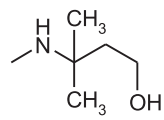
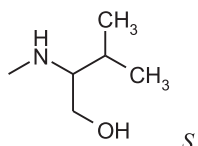
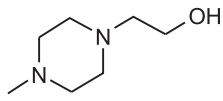
Compound	Z	Formula (M. w.) Melting point [°C] R_f Yield [α]	Log P_{comb} (Pallas 3.1.1.2)
VI		$C_{17}H_{22}NO_2Cl$ (307.82) 97-99 [a] 0.33 [b] 90% **Base:** $C_{17}H_{21}NO_2$ (271.36) 48-50 [c] 0.37 [b] 60%	2.53
VII		$C_{18}H_{23}NO_2$ (285.38) 35-37 [c] 0.40 [b] 70%	2.97
VIII		$C_{17}H_{21}NO_2Cl$ (307.81) 155-157 [a] 0.42 [b] 40% **Base:** $C_{17}H_{20}NO_2$ (271.35) 64-65 [c] 0.24 [b] 40%	2.50
IX		$C_{18}H_{23}NO_2$ (285.37) 95-96 [c] 0.31 [b] 60%	3.10
X		$C_{18}H_{23}NO_2$ (285.38) 41-43 [c] 0.26 [b] 60%	2.88
XI	 *R,S*	$C_{18}H_{23}NO_2$ (285.38) 71-73 [c] 0.40 [b] 65% **XIa (hydrochloride):** $C_{18}H_{24}NO_2Cl$ (321.85) 132-134 [a] 0.71 [b] 90%	2.86

Table 2. cont.

Compound	Z	Formula (M. w.) Melting point [°C] R_f Yield [α]	Log P_{comb} (Pallas 3.1.1.2)
XII	 *R*	$C_{18}H_{23}NO_2$ (285.38) 85-86 [c] 0.37 [b] 65% $[\alpha]_{589}^{22.7}$ = -15.1° [d] $[\alpha]_{546}^{24.1}$ = -15.0° [d] **XIIa (hydrochloride):** $C_{18}H_{24}NO_2Cl$ (321.85) 169-171 [a] 0.71 [b] 90% $[\alpha]_{546}^{24.1}$ = +2.1° [d]	2.86
XIII	 *S*	$C_{18}H_{23}NO_2$ (285.38) 86-87 [c] 0.37 [b] 70% $[\alpha]_{589}^{22.7}$ = +16.0° [d] $[\alpha]_{546}^{24.1}$ = +14.50° [d] **XIII a (hydrochloride):** $C_{18}H_{24}NO_2Cl$ (321.85) 169-171 [a] 0.71 [b] 85% $[\alpha]_{546}^{24.1}$ = -2.0° [d]	2.86
XIV	 *R,S*	HCl $C_{19}H_{26}NO_2Cl$ (335.92) 116-118 [a] 0.31 [b] 90%	3.14
XV		$C_{19}H_{25}NO_2$ (299.42) 53-55 [c] 0.35 [b] 65%	3.41
XVI	 *S*	$C_{19}H_{25}NO_2$ (299.42) 48-50 [c] 0.43 [b] 70% $[\alpha]_{589}^{17.0}$= + 4.82° [d] $[\alpha]_{546}^{20}$= + 3.0° [d]	3.19
XVII		$C_{20}H_{26}N_2O_2$ (326.44) 73-75 [c] 0.33 [b] 60% **XVIIa (Dihydrochloride):** $C_{20}H_{28}N_2O_2Cl_2$ (399.37) 236-238 [a] 0.38 [e] 90%	2.44

[a] ethyl acetate/EtOH (3:1, v/v); [b] CH_3OH/ethyl acetate (1:1, v/v); [c] n-heptane; [d] c = 1%, CH_3OH; [e] CH_3OH.

Table 3. The IR and ^{1}H NMR spectral data of **I**, **IV-XI**, and **XIV-XVII**.

Compd.	IR (KBr, cm^{-1}) ν=OH and/or NH ν=C=O	^{1}H NMR (δ ppm)
I	3400 1616	1.18 (t, *J* = 7 Hz, 3H, -CH_2-$C\underline{H}_3$), 3.35 – 3.45 (m, 2H, -$C\underline{H}_2$-CH_3), 3.62 – 3.72 (m, 2H, N-$C\underline{H}_2$-CH_2-OH), 3.82 – 3.94 (m, 3H, N-CH_2-$C\underline{H}_2$-OH and OH), 5.15 (s, 2H, Ar-$C\underline{H}_2$-O), 6.98 (d, *J* = 8.5 Hz, 2H, C2,C6-C_6H_4), 7.30 – 7.45 (m, 7H, Ar: 5H, C_6H_5, 2H, C3,C5-C_6H_4)
IV	3331, 1636	1.51 (s, 6H, -$C(CH_3)_2$), 1.88 (t, *J*=5,6 Hz, *J*=5.3 Hz, 2H, $C\underline{H}_2$-CH_2-OH), 3.90 (t, *J*=5.4 Hz, 2H, CH_2-$C\underline{H}_2$-OH), 5.07 (s, 2H, Ar-$C\underline{H}_2$-O), 6.93 (d, *J*=9.0 Hz, 2H, C2,C6–C_6H_4) 7.34-7.40 (m, 6H, Ar, N-H), 7.70 (d, *J*=9Hz, 2H, C3,C5–C_6H_4)
V	3304 1631	1.01 (dd, *J*=5.6 Hz, *J*=5.5 Hz, 6H, -$CH(C\underline{H}_3)_2$), 1.97-2.06 (m, 1H, -$C\underline{H}(CH_3)_2$), 2.43 (s, 1H, -OH), 3.76-3.89 (m, 2H, -$C\underline{H}_2$-OH), 3.91-3.96 (m, 1H, $C\underline{H}$-CH_2-OH), 5.11 (s, 2H, Ar-$C\underline{H}_2$-O), 6.27 (d, *J*=7.95 Hz, 1H, N-H), 6.99 (d, *J*=2.05 Hz, 2H, C2,C6-C_6H_4), 7.33-7.44 (m, 5H, Ar), 7.74 (d, *J*=2.05 Hz, 2H, C3,C5-C_6H_4)
VI	3167	2.25 (s, 3H, N-CH_3), 2.62 (t, *J* = 5.5 Hz, 2H, N-CH_2-), 3.54 (s, 2H, Ar-$C\underline{H}_2$-N), 3.65 (t, *J* = 5.5 Hz, 2H, -$C\underline{H}_2$-OH), 5.09 (s, 2H, Ar-$C\underline{H}_2$-O), 6.97 (d, *J* = 8.5 Hz, 2H, C2,C6 – C_6H_4) 7.22 – 7.49 (m, 7H, Ar: 5H, C_6H_5, 2H, C3,C5-C_6H_4)
VII	3343, 3163	1.09 (t, *J* = 7 Hz, 3H, -CH_3), 2.59 (q, *J* = 7 Hz, 2H, -$C\underline{H}_2$-CH_3), 2.67 (t, *J* = 5.5 Hz, 2H, N-CH_2-), 3.59 (t, *J* = 5.5 Hz, 2H, -$C\underline{H}_2$-OH), 3.60 (s, 2H, Ar-$C\underline{H}_2$-N), 5.09 (s, 2H, Ar-$C\underline{H}_2$-O), 6.97 (d, *J* = 8.5 Hz, 2H, C2,C6 – C_6H_4), 7.23 – 7.49 (m, 7H, Ar: 5H, C_6H_5, 2H, C3,C5-C_6H_4)
VIII	3335	1.76 (m, 2H, -CH_2-$C\underline{H}_2$-CH_2-), 2.84 (t, *J*=7.5 Hz, 2H, NH-$C\underline{H}_2$-CH_2-CH_2-), 3.44 (t, *J*=6.0 Hz, 2H, -CH_2-$C\underline{H}_2$-OH), 3.99 (s, 2H, C_6H_4-$C\underline{H}_2$-NH), 5.11 (s, 2H, C_6H_5-$C\underline{H}_2$-O), 6.98-7.47 (m, 10H: 9H-Ar: C_6H_5 and C_6H_4, 1H, N$\underline{H}$)
IX	3331, 3298	($CDCl_3$) 1.15 (s, 6H, -$C(CH_3)_2$), 2.20 (br s, 2H, N$\underline{H}$, O$\underline{H}$), 3.34 (s, 2H, C_6H_4-$C\underline{H}_2$), 3.62 (s, 2H, $C\underline{H}_2$-OH), 5.05 (s, 2H, C_6H_5-$C\underline{H}_2$), 6.93 (d, *J*=8.8 Hz, 2H, C2,C6-C_6H_4), 7.25 (d, *J*=8.8 Hz, 2H, C3,C5-C_6H_4), 7.27-7.45 (m, 5H, C_6H_5)
X	3287	1.60 – 1.73 (m, 4H, – CH_2- CH_2-), 2.69 (t, *J* = 5.5 Hz, 2H, N-CH_2-), 2.97 (br s, 2H, NH and OH), 3.59 (t, *J* = 5.5 Hz, 2H, -$C\underline{H}_2$-OH), 3,73 (s, 2H, Ar- $C\underline{H}_2$-N), 5.05 (s, 2H, Ar-$C\underline{H}_2$-O), 6.93 (d, *J* = 8.5 Hz, 2H, C2,C6-C_6H_4), 7.22 – 7.44 (m, 7H, Ar: 5H, C_6H_5, 2H, C3,C5-C_6H_4)
XI	3263	0.96 (t, *J* = 7.4 Hz, 3H, -CH_3), 1.53 (m, 2H, -$C\underline{H}_2$-CH_3), 2.19 (br s, 2H, OH and NH), 2.65 (m, 1H, NH-$C\underline{H}$), 3.31 (dd, J_2 = 10.6 Hz, J_3 = 6.4 Hz, 1H, -$C\underline{H}_2$-OH), 3.65, (dd, J_2 = 10.6 Hz, J_3 = 4.0 Hz, 1H, -$C\underline{H}_2$-OH), 3.70 (d, *J* = 12.8 Hz, 1H, Ar-$C\underline{H}_2$-N), 3.78 (d, *J* = 12.8 Hz, 1H, Ar-$C\underline{H}_2$-N), 5.10 (s, 2H, Ar-$C\underline{H}_2$-O), 6.98 (d, *J* = 8.5 Hz, 2H, C2,C6-C_6H_4), 7.23 – 7.49 (m, 7H, Ar: 5H, C_6H_5, 2H, C3,C5-C_6H_4)
XIV	3231	0.83 (t, *J*=7,2 Hz, 3H, -CH_2-$C\underline{H}_3$), 1.22-1.42 (m, 2H, -$C\underline{H}_2$-CH_3), 2.66-2.69 (s, 3H, N-$C\underline{H}_3$), 2.78-3.16 (m, 2H, Ar-$C\underline{H}_2$-N), 3.16-3.78 (m, 2H, Ar-$C\underline{H}_2$-N), 3.75-3.98 (m, 1H, CH), 4.12-4.36 (m, 2H, $C\underline{H}_2$-OH), 5.11 (s, 2H, Ar-$C\underline{H}_2$-O), 5.49 (br s, 1H, OH), 7.05 (d, *J*=8.70 Hz, 2H, C2,C6-C_6H_4), 7.28-7.46 (m, 5H, C_6H_5), 7.52 (d, *J*=8.7, 2H, C3,C5-C_6H_4), 10.06-10.45 (br s, 1H, NH^+)
XV	3276	1.25 (s, 6H, -$C(CH_3)_2$), 1.64 (t, *J*=5,5 Hz, 2H, $C\underline{H}_2$-CH_2-OH), 3.69 (s, 2H, Ar-$C\underline{H}_2$-NH), 3.87 (t, *J*=5.5 Hz, 2H, CH_2-$C\underline{H}_2$-OH), 5.04 (s, 2H, Ar-$C\underline{H}_2$-O), 6.92 (d, *J*=8.7 Hz, 2H, C2,C6–C_6H_4), 7.20-7.41 (m, 7H, Ar: 5H, C_6H_5, 2H, C3,C5-C_6H_4)
XVI	3293, 3165	0.94 (dd, *J*=6.7 Hz, *J*=6.9 Hz, 6H, -$CH(C\underline{H}_3)_2$), 1.83-1.90 (m, 1H, -$C\underline{H}(CH_3)_2$), 2.24 (s, 1H, OH), 2.44-2.49 (m, 1H, NH), 3.34-3.40 (m, 1H, NH-$C\underline{H}$), 3.61-3.80 (m, 4H, Ar-$C\underline{H}_2$, $C\underline{H}_2$-OH), 5.06 (s, 2H, Ar-$C\underline{H}_2$-O), 6.94 (d, *J*=8.5 Hz, 2H, C2, C6-C_6H_4), 7.24-7.45 (m, 7H, Ar: 5H, C_6H_5, 2H, C3,C5-C_6H_4)
XVII	3412, 3232	2.57 (t, *J* = 5.5 Hz, 2H, N-$C\underline{H}_2$-CH_2-OH), 2.51 – 2.68 (m, 8H, piperazine), 3,49 (s, 2H, Ar-$C\underline{H}_2$-N), 3.63 (t, *J* = 5.5 Hz, 2H, N-CH_2-$C\underline{H}_2$-OH), 5.09 (s, 2H, Ar-$C\underline{H}_2$-O), 6.97 (d, *J* = 8.5 Hz, 2H, C2,C6-C_6H_4), 7.24 – 7.49 (m, 7H, Ar: 5H, C_6H_5, 2H, C3,C5-C_6H_4)

Table 4. Anticonvulsant activity of the tested compounds [**I-XVII**] (mice, i.p.).

Compd.	Dose mg / kg	MES [a]		ScMet [a]		Neurotoxicity [b]	
		0.5 h	4 h	0.5 h	4 h	0.5 h	4 h
I	30	-	-	-	-	-	-
	100	1/3	-	-	-	-	-
	300	1/1	-	1/1	-	4/4	-
II	30	-	-	-	-	-	-
	100	-	-	-	-	-	-
	300	1/1	-	-	1/5	-	-
III	30	-	-	-	-	-	-
	100	3/3		-	-	-	-
	300	1/1	1/1	-	-	-	-
IV	30	-	-	-	-	-	-
	100	-	-	-	-	-	-
	300	-	-	3/5	-	1/4	-
V	30	-	-	-	-	-	-
	100	2/3	-	-	-	-	-
	300	1/1	-	-	-	2/4	-
VI	30	-	-	-	-	-	-
	100	3/3	-	-	-	2/8	-
	300	|	-	|	|	3/4	-
VII	30	-	-	-	-	-	-
	100	3/3	-	-	-	3/8	
	300	|	|	|	|	4/4	|
VIII	30	-	-	-	-	-	-
	100	3/3	1/3	-	-	7/8	2/4
	300	|	|	|	|	4/4	|
IX	3	-	|	|	|	1/4	|
	10	-	|	|	|	-	|
	30	1/1	-	-	-	1/4	-
	100	3/3	3/3	-	-	8/8	1/4
	300	|	|	|	|	4/4	|
X	30	-	-	1/5	-	-	-
	100	3/3	-	2/5	1/1	6/8	-
	300	|	|	|	|	4/4	-
XI	3	-	|	|	|	-	|
	10	-	|	|	|	-	|
	30	1/1	-	-	-	-	-
	100	3/3	3/3	-	-	8/8	-
	300	|	|	|	|	4/4	|
XII	30	-	-	-	-	-	-
	100	3/3	1/3	-	-	7/8	-
	300	|	|	|	|	4/4	|
XIII	3	-	|	|	|	-	|
	10	-	|	|	|	-	|
	30	1/1	-	|	|	1/4	-
	100	3/3	3/3	|	|	8/8	1/4
	300	|	|	|	|	4/4	|
XIV	30	-	-	-	1/5	2/4	-
	100	3/3	3/3	-	-	8/8	3/4
	300	|	|	|	|	4/4	|
XV	3	-	|	|	|	-	|
	10	-	|	|	|	-	|
	30	1/1	-	-	-	-	-
	100	|	1/1	|	|	8/8	2/2
	300	|	|	|	|	4/4	|
XVI	3	-	|	|	|	-	|
	10	-	|	|	|	-	|
	30	1/1	-	-	-	-	-
	100	2/2	2/2	|	-	8/8	1/3
	300	|	|	|	|	4/4	|
XVII	30	-	-	-	-	-	-
	100	3/3	-	-	-	-	-
	300	1/1	|	-	|	4/4	|

[a] Number of animals protected / number of animals tested; [b] number of animals exhibiting toxicity / number of animals tested in the rotorod test; | indicates that the compound was not tested in the particular case; - indicates that the compound was not active or toxic in the particular case.

Table 5. Anticonvulsant activity of the compounds tested in phase VIa in rats, *i.p.* [II-III] and rats, *p.o.* [III, V].

Compound	Test	Dose mg/kg	Time in hours				
			0.25	0.5	1.0	2.0	4.0
II (*i.p.*)	MES [a]	30	–	–	–	–	–
	ScMet [a]	50	–	–	1/4	–	–
	TOX [b]	50	–	–	–	–	–
III (*p.o.*)	MES [a]	30	–	–	1/4	1/4	–
	TOX [b]	30	–	–	–	–	–
III (*i.p.*)	MES	30	2/4	1/4	–	2/4	–
	TOX	30	–	–	–	–	–
V (*p.o.*)	MES	30	–	1/4	1/4	–	–
	TOX	30	–	–	–	–	–

[a] and [b] see Table 3.

(12). Isomer **III** (*S*) is more active in the MES test than racemate and **II** (*R*), which gave 100% anti-MES activity in the dose of 300 mg/kg. Of all the tested amides **III** seems the most promising, 100% active in MES without neurotoxicity at the tested doses.

Among the tested amines, the most active in the MES test (mice, *i.p.*) were **IX**, **XI**, **XIII,** and **XV-XVI** as they produced 100% activity at the dose of 30 mg/kg at 0.5 h. Of all the compounds, neurotoxicity was observed for **IX** and **XIV** at the dose of 30 mg/kg, at 0.5 h and it was not revealed for any substance at 300 mg/kg at 4 h after administration. The racemate **XI** and its enantiomer **XIII** (*S*) were more active in the MES test (100% protection at 30 mg/kg) than **XII** (*R*) (100% protection at 100 mg/kg). However, the enantiomer **XIII** exhibited larger neurotoxicity than its isomer **XII** and the parent compound **XI**. Substitution of a secondary amine [**XI**] gave **XIV** and did not increase the anticonvulsant activity in MES, however, **XIV** was active in ScMet. Protective activity in the MES without neurotoxicity was shown for **XI** and **XV-XVI** (at the dose of 30 mg/kg) and **III**, **V**, and **XVII** (at the dose of 100 mg/kg). **X** was also active in the ScMet (40% protection for 0.5 h and 100% protection for 4 h at the dose of 100 mg/kg). **XIV** was active in the ScMet 4 h after administration (20% protection) in the dose of 30 mg/kg. At this stage it seems that among the amines **[VI-XVII] XI**, **XV**, and **XVI** are the most promising compounds, active in the MES at the dose of 30 mg/kg and non-toxic at the doses up to 100 mg/kg.

Compounds **II**, **III**, and **V** were advanced to the phase VIa (rats) where **III** and **V** revealed 25% activity in MES (at 1 and 2 h after *p.o.* administration for the former and at 0.5 and 1 h after *p.o.* administration for the latter) and **II** was active in ScMet (25% activity at 1 h after *i.p.* administration). **III** was also tested in rats, *i.p.* (30 mg/kg), where it revealed 50% activity at 0.25 h, 25% activity at 0.5 h and 50% activity at 2 h without neurotoxicity. Activity after 1.5 h interval implies that it might be a metabolite to be active in this case. None of the substances exhibited neurotoxicity in rats, *p.o.* at the mentioned dose. The results are presented in Table 5.

Comparing the activity and neurotoxicity between amides tested [**I-V**] and published previously (12) and their amine analogues [**VI-XVII**], the achieved results of the preliminary anticonvulsant tests suggest that the aminoalkanol derivatives [**VI-XVII**] are slightly more active in MES and more neurotoxic comparing to their alkanolamide analogues. On the contrary, the amides reveal stronger anti-ScMet activity. As both groups of the compared derivatives (i.e. aminoalkanols and alkanolamides) reveal anti-Mes and/or anti-ScMet activity, there exist strong premises for further research in the field of anticonvulsant activity within both these groups.

As far as the calculated partition coefficient is considered, its values for compounds **I-XVII** were in the range 2.03-2.96 [for amides **I-V**] and 2.44-3.41 [for amines **VI-XVII**] which correspond to the Log $P_{comb.}$ of carbamazepine (CBZ) and valproic acid (VA) (3.30 and 2.61, respectively) (15). Moreover, compounds which were advanced to Phase VIa, i.e. **II**, **III**, and **V** exhibited Log $P_{comb.}$ 2.44, 2.44, and 2.68, respectively, which is similar to Log $P_{comb.}$ of the mentioned AEDs, predicting comparable penetration through blood-brain barrier.

EXPERIMENTAL

Chemistry

Melting points are uncorrected and were determined using a Büchi SMP-20 apparatus. Analyses of C, H, N were within +/- 0.4% of the theoretical values. The IR spectra were recorded on a Jasco FT / IR 410 spectrometer. The ^{1}H-NMR spectra were recorded in $CDCl_3$ with a Varian Mercury-VX 300 NMR spectrometer at 29°C. Chemical shifts were referenced against solvent lock signal. Standard Varian pulse sequences were used for 2D experiments. Analytical TLC was carried out on precoated plates (silica gel, 60 F-254 Merck) using the solvent system (methanol / ethyl acetate (1:1, v/v)); spots were visualized with UV light. Measurements of optical rotation ($[\alpha]_{589}$ and $[\alpha]_{546}$) were carried out using Jasco DIP-1000 (λ = D (589 nm)) and Polamat A (Carl Zeiss, Jena) (λ = 546). Enantiomeric 2-amino-1-butanols ($[\alpha]^{20}_{546}$: (*R*) = -11.25°; (*S*) = +11.15°) were obtained earlier (11). The reagent: 4-(benzyloxy)benzylalcohol was purchased from Lancaster, other reagents and solvents were commercially available materials of reagent grade. The theoretical values of log $P_{comb.}$ (partition coefficient) of synthesized structures and comparative AEDs were calculated with the use of PALLAS 3.1.1.2 program.

General procedure for synthesis of I-V:

A mixture of 0.01 mole of appropriate aminoalkanols with 0.025 mole K_2CO_3 in 15 cm^3 of water and 15 cm^3 of toluene was cooled to 10-12°C. After cooling, a solution of 0.011 mole of 4-(benzyloxy)benzoyl chloride in 30 cm^3 of dry toluene was added under vigorous stirring at 10-12°C for 0.5 h. Then the reaction mixture was heated at 50°C and then left to cool down. The precipitated amide deposit was filtered off, stirred with a 10% solution of $NaHCO_3$, and after drying recrystallized from a mixture of toluene/heptane (1:1, v/v).

General procedure for synthesis of VII, XII-XIII, and XV-XVI:

A solution of 0.002 mole of appropriate [4-(benzyloxy)benzoyl]-aminoalkanol in dried and fresh distilled diethyl ether was cooled to 0°C under nitrogen. Then 1.2 cm^3 of 1 M solution of $LiAlH_4$ was added dropwise and the mixture was stirred for 12 h at room temperature. The reaction was quenched by adding 2 cm^3 of 15% NaOH. The organic phase was separated, the residue was extracted with diethyl ether, and dried over K_2CO_3, filtered and the solvent was removed in vacuum. The obtained compounds [**VII**, **XII-XIII**, and **XV-XVI**] were purified using planar circular chromatography (chromatotron) and recrystallized from n-heptane.

General procedure for synthesis of VI, VIII-XI, and XVII:

A mixture of 0.01 mole of an appropriate aminoalkanol with 0.01 mole of 4-(benzyloxy)benzyl chloride in 30 cm^3 of toluene was refluxed in the presence of 0.01 mole of K_2CO_3 for 6 h. Inorganic salts were filtered off from the hot mixture and washed with hot toluene (5 cm^3). The solvent was distilled off from the filtrate under reduced pressure. After addition of n-heptane (for bases) or ethanol saturated with HCl (for hydrochlorides) to the residue, the mixture was refluxed and cooled. The crystals formed were collected by filtration and dried. Recrystallization from n-heptane (for bases) gave **VI base**, **VIII base, IX-XI**, and **XVII** and from ethanol with small amount of acetone gave **VI**, **VIII**, **XIa**, and **XVII**.

Pharmacology

Initial evaluations for anticonvulsant activity were carried out by the ASP, which consisted of initial evaluations of anticonvulsant activity and included Phase I and VIa tests procedures. These screens were performed either in male Carworth Farms no. 1 (CF 1) mice (18-25 g) or male Sprague-Dawley rats (100-150 g). In the phase I studies which deal with qualitative assay, all the compounds were tested for activity in MES and ScMet tests as well as in the rotorod screen for TOX. The examined compounds were suspended in 0.5% aq. methylcellulose and were administered at three dosage levels (30, 100 and 300 mg/kg) with anticonvulsant activity noted 0.5 and 4 h after *i.p.* administration in mice. Phase VIa was a similar qualitative evaluation to the Phase I evaluation, but the test drug was examined for an oral activity in the rats utilizing the three screens noted previously. The details of these procedures have been published (13, 14). The Phase I and VIa tests results are listed in Table 4 and 5, respectively.

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