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SYNTHESIS AND STUDY OF HALOGENATED BENZYLAMIDES OF SOME ISOCYCLIC AND HETEROCYCLIC ACIDS AS POTENTIAL ANTICONVULSANTS

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Abstract: A series of potential anticonvulsants have been synthesized. There are eight fluorobenzylamides and three chlorobenzylamides of isocyclic or heterocyclic acids. Two not halogenated benzylamides were also synthesized to compare the effect of halogenation. The aim of the research performed was to evaluate whether halogenation of the mother structure is able to improve its anticonvulsant activity. The compounds were tested in Anticonvulsant Screening Project (ASP) of Antiepileptic Drug Development Program (ADDP) of NIH. Compound **1** showed MES ED_{50} = 80.32 mg/kg, PI = 3.16. Compound **7** showed CKM ED_{50} = 56.72 mg/kg. Compound **8** showed MES ED_{50} = 34.23 mg/kg and scPTZ ED_{50} > 300 mg/kg, PI = 8.53.Compound **13** showed 6Hz ED_{50} = 78.96, PI = 3.37. The results indicate that fluorination does not improve activity, whereas chlorination in our experiment even reduces it.

Keywords: anticonvulsants, chlorobenzylamides, fluorobenzylamides of isocyclic and heterocyclic acids

Many aromatic and heterocyclic acid benzylamides have been synthesized in search for new anticonvulsants (1-5). Some of them have been reported to be potent agents. Kohn et al. noticed significant role of benzyl fragment of these compounds (6, 7). They observed that electron-withdrawing substituents in benzyl moiety are able to increase anticonvulsant activity (8). The benzyl fragment could be also distinguished in the molecule of biphenyl, which derivatives are pharmacologically active affinity baits, chemical reactive units (9). The benzyl substituents change the hydrophobicity and molecular shape of the compounds, which determines their mechanism of action. Benzylamides of aromatic and heterocyclic acids are antagonists of excitatory amino acids. Up to now, no univocal data have been reported regarding the structure of the binding sites of the receptor. Therefore, a good way to obtain better anticonvulsants could be to modify the structure of the active compounds obtained earlier, which are mother compounds. Here, the purpose of the study was to evaluate if the incorporation of electron-withdrawing halogen substituent into the benzyl ring of previously obtained pharmacologically active compounds is able to improve the activity of the mother compounds. The design of new anticonvulsants can be assisted by comparison of the hydrophobicity and molecular shape of the synthesized halogenated compound with those properties of the mother compounds. Therefore, log P values of the partition coefficient between n-octanol and water of the compounds have been taken under consideration. As it was found previously, the optimal log P value of active benzylamide anticonvulsants ought to be > 0 and probably near to 3 (5). This scale is the best compromise between water and lipids partition of the designed anticonvulsants. Log P values of the halogenated compounds probably should not be excessively different from the values of the mother structures. Superimposing structures of halogenated compounds on the mother structures can, at least theoretically, let us evaluate if the receptor affinity of both is similar, thus providing additional information of structure elements crucial for phar-

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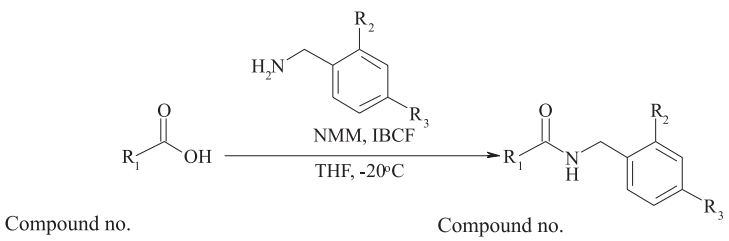
macological activity. The change of affinity could increase as well as decrease the pharmacological action of the new synthesized compounds in comparison to the mother structures.

EXPERIMENTAL

Chemistry

All used acids: 3-oxocyclopentanecarboxylic acid, 2-oxocyclopentaneacetic acid, coumarin-3-carboxylic acid, isoquinoline-3-carboxylic acid, 1-cyclopentenecarboxylic acid, picolinic acid N-oxide, 5-methylfurancarboxylic acid, isoquinoline-1-carboxylic acid and furan-2-carboxylic acid were purchased from Aldrich. Other reagents as isobutyl chloroformate, N-methylmorpholine, benzylamine, 2-chlorobenzylamine, 2-fluorobenzylamine and 4-fluorobenzylamine were supplied by Merck. DMF and THF were from POCH Gliwice.[1]H NMR spectra were recorded on a Bruker DM 400 MHz spectrometer. Chemical shifts were measured as δ units (ppm) relative to tetramethylsilane. TLC was carried out on a 0.25 mm thickness silica gel plates (Merck Kieselgel 60 F-254). The spots were visualized in UV light or with 0.3% ninhydrin in EtOH (97 : 3). The solvent system used in TLC was $CHCl_3$/MeOH in different ratios. HPLC was performed on a Shimadzu chromatograph equipped with LC-10AT pump, SPD-10A UV spectrophotometer and a computer registrator/recorder (CHROMA POLLAB, Warszawa). The peaks were recorded at 210 nm. Elemental analysis was performed on an Elementar Analysensysteme GmbH – vario El III Element Analyzer. Melting points were determined in a Böetius apparatus.



1. R_1 = R_2 = H R_3 = H
2. R_1 = R_2 = H R_3 = H
3. R_1 = R_2 = Cl R_3 = H
4. R_1 = R_2 = Cl R_3 = H
5. R_1 = R_2 = Cl R_3 = H
6. R_1 = R_2 = H R_3 = F
7. R_1 = R_2 = F R_3 = H
8. R_1 = R_2 = F R_3 = H
9. R_1 = R_2 = F R_3 = H
10. R_1 = R_2 = H R_3 = F
11. R_1 = R_2 = H R_3 = F
12. R_1 = R_2 = H R_3 = F
13. R_1 = R_2 = H R_3 = F

Scheme 1. Synthesis of compounds **1**-**13**

Synthesis of amides

Compounds **1-13** were synthesized using the mixed anhydrides method of peptide synthesis (10). Suitable acid (10 mmol) was dissolved in DMF (15 mL) and THF (15 mL) was added. Next, N-methylmorpholine (10 mmol, 1.1 mL) was added and the mixture was stirred under nitrogen and chilled to -15°C. Isobutyl chloroformate (10 mmol, 1.3 mL) was added dropwise to keep the temperature below -15°C. Then, benzylamine or halogenated benzylamine (10 mmol) in THF was added in small portions and the reaction mixture was stirred at -15°C for 30 min, at room temperature for 1 h. The solution was concentrated *in vacuo* and the residue was dissolved in EtOAc (20 mL). This solution was washed with 20 mL portions of 1 M HCl, saturated $NaHCO_3$ solution and saturated NaCl solution, then dried with anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The obtained compounds were purified by crystallization with EtOAc/hexane or MeOH/Et_2O. All stages of the synthesis were controlled by TLC. The purity of the final compound was determined by HPLC and identity by ^{1}H NMR. The pathway for the synthesis of the obtained compounds is shown in Scheme 1.

Computer calculations

The HyperChem 4.5 (Hypercube, Inc.) program was used. The semiempirical method PM 3 was applied for a single point calculation. Geometry optimization was performed by the Polak-Ribiere algorithm. Afterward, the QSAR Properties module using atomic parameters derived by Ghose et al. (11) was applied to calculate log P values as a measure of the hydrophobicity of the optimized structures of the compounds. RMS Fit module was used for overlapping the molecular structures of the compounds.

Pharmacology

All the synthesized compounds (**1-13)** were evaluated qualitatively in anticonvulsant identification system (ASP) – 6 Hz 32 mA and TOX tests. Compounds **1**, **2** and **5**-**13** were evaluated also in MES test (Table 3). The MES and TOX tests were performed in mice after *i.p*. administration, according to the method described by Krall et al. (12). The minimal clonic seizure (6 Hz 32 mA) test was used to assess compound's efficacy against electrically induced seizures but using a lower 6 Hz frequency and longer duration time – 3 s. The test was accomplished by the Barton et al. method (13). This test was performed, because some compounds ineffective in standard MES or scPTZ tests still have anticonvulsant activity *in vivo*. All the synthesized compounds (**1**-**13**) were evaluated qualitatively also in rats after *i.p*. and *p.o*. administration in MES and TOX tests (Table 4). The tests were performed according to the method of Krall et al. (12). Some

Table 1. Physical and analytical data of the synthesized compounds.

Compound No.	Formula	M.w.	M.p. °C	log. P*
1	$C_{13}H_{15}NO_2$	217.26	87-89	1.95
2	$C_{14}H_{17}NO_2$	231.30	101-102	2.35
3	$C_{17}H_{13}ClN_2O$	296.71	110-111	3.84
4	$C_{17}H_{12}ClNO_3$	313.75	186-188	3.19
5	$C_{17}H_{13}ClN_2O$	296.75	133-134	3.84
6	$C_{13}H_{14}FNO$	219.26	111-114	2.74
7	$C_{13}H_{14}FNO$	219.26	86-87	2.74
8	$C_{13}H_{11}FN_2O_2$	246.24	123-124	1.21
9	$C_{14}H_{16}FNO_2$	249.30	123-125	2.49
10	$C_{14}H_{16}FNO_2$	249.30	107-108	2.49
11	$C_{13}H_{12}FNO_2$	233.25	74-76	0.91
12	$C_{17}H_{13}FN_2O$	280.30	68-70	3.47
13	$C_{12}H_{10}FNO_2$	219.22	119-120	1.35

HPLC purity of the all compounds was 100%. The elemental analyses were within ± 0.4% of the theoretical value. * Hydrophobicity of the compounds is expressed as log P value calculated by a computational method.

Table 2. ^{1}H NMR spectra in $CDCl_3$ of the synthesized compounds.

Compound	Chemical shift in δ (ppm) in *CDCl$_3$*
1	2.11-2.27 (m, 3H), 2.31-2.64 (m, 4H), 2.84-2.92 (m, 1H CH), 4.46 (d, *J* = 5.0 Hz 2H, CH_2), 5.90 (s 1H, NH), 7.26-7.35 (m, 4H).
2	1.35-1.81 (m, 4H), 2.08-2.19 (m, 2H), 2.38-2.46 (m, 1H, CH), 4.45-4.60 (m, 2H), 7.22-7.37 (m, 8H).
3	4.83 (d, *J* = 5 Hz, 2H, CH_2), 7.22-7.26 (m, 2H, 2×CH), 7.38-7.41 (m, 1H, CH) 7.52-7.56 (m, 1H, CH), 7.69-7.79 (m, 2H, 2×CH), 7.87 (t, *J* = 4.1 Hz, 2H, 2×CH) 8.48 (d, *J* = 5.7 Hz, 1H, CH), 8.79 (s, br, 1H, NH), 9.57 (d, *J* = 8.6 Hz, 1H, CH).
4	4.75 (d, *J* = 7.5 Hz, 2H, CH_2), 7.22-7.26 (m, 2H), 7.35-7.46 (m, 5H), 7.64-7.70 (m, 3H), 8.39 (s, 1H, CH), 9.29 (s, br, 1H, NH).
5	4.83 (d, *J* = 4.7 Hz, 2H, CH_2), 7.20-7.26 (m, 2H, 2×CH), 7.40 (d, *J* = 9 Hz, 1H,CH), 7.50 (d, *J* = 9 Hz, 1H, CH), 7.71 (t, *J* = 6.0 Hz, 1H, CH), 7.75 (t, *J* = 6.0 Hz, 1H, CH),7.98-8.06 (m, 2H, 2xCH), 8.64 (s, 1H, CH), 8.69 (s br, 1H, NH), 9.16 (s, 1H, CH).
6	1.94-2.04 (m, 2H, CH_2), 2.45-2.55 (m, 4H), 4.47 (d, *J* = 4.8 Hz, 2H, CH_2), 5.88 (s br, 1H, NH), 6.56 (t, *J* = 5.0Hz, 1H, CH), 7.00 (t, *J* = 6.5 Hz 2H, CH_2), 7.25-7.29 (m, 2H).
7	1.94-2.03 (m, 2H, CH_2), 2.45-2.59 (m, 4H, 2×CH_2), 4.54 (d, *J* = 5.0, 2H, CH_2), 5.97 (s br, 1H, NH), 6.55 (t, *J* = 6.5, 1H, CH), 7.08 (q, 2H, 2xCH), 7.23-7.30 (m, 1H, CH), 7.37 (t, *J* = 6.0, 1H, CH).
8	4.74 (d, *J* = 5.4 Hz, 2H, CH_2), 7.0-7.13 (m, 2H, 2×CH), 7.22-7.29(m, 1H, CH), 7.36-7.48 (m, 3H, 3×CH), 8.24 (d, *J* = 6.0 Hz, 1H, CH), 8.46 (d, *J* = 5.5 Hz, 1H, CH), 11.6 (s br, 1H, NH).
9	1.33-1.44 (m, 1H), 1.48-1.60 (m, 1H), 1.67-1.83 (m, 3H), 2.11-2.19 (m, 2H), 2.40-2.49 (m, 1H), 2.80-2.89 (m, 1H), 3.45 (s br, 1H), 4.48-4.69 (m, 2H, CH_2), 6.99-7.12 (m, 2H), 7.20-7.27 (m, 1H), 7.39-7.44 (m, 1H).
10	1.33-1.50 (m, 2H), 1.61-1.75 (m, 3H), 2.05-2.18 (m, 2H), 2.43 (q, *J* = 2 Hz, 1H), 2.71-2.81 (m, 1H), 3.44 (s br, 1H, NH), 4.46 (q, 2H, CH_2), 6.98 (t, *J* = 1.Hz, 2H, CH_2), 7.26-7.35 (m, 2H).
11	2.32 (s, 3H, CH_3), 4.56 (d, *J* = 5.5 Hz, 2H, CH_2), 6.09, 6.10 (dd, *J* = 0,6 Hz, 0.6 Hz, 1H, CH), 6.59 (s br, 1H, NH), 6.98-7.06 (m, 4H), 7.26-7.34 (m, 2H).
12	4.71 (d, *J* = 7.7 Hz, 2H, CH_2), 7.03 (t, *J* = 6.0 Hz, 2H, 2×CH), 7.35-7.40 (m, 2H), 7.68-7.81 (m, 2H), 8.01 (t, *J* = 5 Hz, 2H, 2×CH), 8.57 (s br, 1H, NH), 8.65 (s, 1H, CH), 9.14 (s, 1H, CH).
13	4.58 (d, *J* = 6.0 Hz, 2H, CH_2), 6.50-6.52 (m, 1H, CH), 6.64 (s br, 1H, NH), 7.00-7.06 (m, 2H, 2×CH), 7.14 (d, *J* = 3.7 Hz, 1H, CH), 7.29-7.34 (m, 2H, 2×CH), 7.42 (d, *J* = 1.5 Hz, 1H, CH).

Table 3. Anticonvulsant identification. Qualitative tests in mice, *i.p.*

Compound No.	MES, 0.5 h		TOX, 0.5 h		6 Hz, 0.5 h	
	mg/kg	prot./used	mg/kg	prot./used	mg/kg	prot./used
1	100	3/4	300	6/8	300	4/4
2	300	4/4	300	3/8	100	2/4
3	ND	ND	100	0/4	100	1/4
4	ND	ND	100	0/4	100	0/4
5	300	0/4	300	1/8	300	0/4
6	300	4/4	300	0/8	300	4/4
7	100	4/4	300	7/8	100	2/4
8	300	4/4	300	1/8	300	3/4
9	300	0/4	300	0/8	300	2/4
10	300	4/4	300	8/8	300	4/4
11	100	2/4	300	6/8	100	3/4
12	100	1/4	300	0/8	300	3/4
13	300	4/4	300	0/8	100	2/4

MES = maximal electroshock seizure test. 6Hz = psychomotor minimal clonic seizure test, model 32 mA (ASP).TOX = neurological toxicity rotorod test. ND = not determined.

Table 4. Anticonvulsant identification. Qualitative tests in rats.

Compound No	*p.o.*, MES, 0.5 h		*p.o.*, TOX, 0.5 h.		*i.p.*, MES, 0.5 h		*i.p.*, TOX. 0.5 h	
	mg/kg	prot./used	mg/kg	prot./used	mg/kg	prot./used	mg/kg	prot./used
1	30	1/4	30	0/4	30	0/4	30	0/4
2	30	0/4	30	0/4	30	0/4	30	0/4
3	ND	ND	ND	ND	ND	ND	ND	ND
4	ND	ND	ND	ND	ND	ND	ND	ND
5	30	0/4	30	0/4	30	1/4	30	0/4
6	30	0/4	30	0/4	30	0/4	30	0/4
7	ND	ND	ND	ND	ND	ND	ND	ND
8	ND	ND	ND	ND	ND	ND	ND	ND
9	30	0/4	30	0/4	30	0/4	30	0/4
10	30	1/4	30	0/4	30	0/4	30	0/4
11	30	0/4	30	0/4	30	0/4	30	0/4
12	30	0/4	30	0/4	30	0/4	30	0/4
13	30	0/4	30	0/4	30	1/4	30	0/4

MES = maximal electroshock seizure test. TOX = behavioral positioned sense test. prot. = protected. ND = not determined.

Table 5. ED_{50} values.

Compound No.	Test	ED_{50} mg/kg	TD_{50} mg/kg	Time (h)	PI
1	MES*	80.32		0.25	3.16
	TOX		253.89	0.25	
7	CKM**	56.72		0.5	
8	MES***	34.23		0.25	8.53
	TOX		291.86	0.25	
	sc PTZ	300		0.25	
13	6 Hz****	78.96		0.5	3.37
	TOX		266.05	24.0	

MES = maximal electroshock test. TOX = neurological toxicity test. TD_{50} value determined from the rotorod test. PTZ = pentetrazole. PI = TOX TD_{50}/MES ED_{50} or TOX TD_{50}/6Hz ED_{50}. *Quantitative, mouse (*i.p.*) test (14). ** Quantitative corneal kindled mouse (CKM) test (15).*** Quantitative, mouse (*p.o.*) test (14). ****Quantitative, mouse 6Hz 32 mA (*i.p.*) test (13).

compounds were chosen for further examination. They were tested quantitatively in mice in MES and TOX tests according to the method of Swinyard et al. (14). ED_{50} values of these compounds were determined by the White method (15) and are given in Table 5. The biological responses of compounds **1**, **7**, **8** and **13** are given in Tables 6-9. Moreover, the evaluation of compounds **1** and **7** was accomplished in the pilocarpine induced status prevention test (ASP) using the method of Racin et al. (16). In this test, the compounds were assessed for evaluation of potential activity against nerve agents using the pilocarpine model of epilepsy as the introductory screen. The compound tested was administered to rat *i.p.*. Then, a challenge dose of pilocarpine was administered to observe the treatment effects of the compound. The outcome measures are determined in protected or non-protected animals. The obtained results are given in Table 10.

RESULTS

A series of halogenated benzylamides of heterocyclic and isocyclic acids was synthesized (**1**-**13**).

Physico-chemical data of the synthesized compounds are given in Tables 1 and 2, the results of preliminary pharmacological tests in Tables 3–10. Compound **1** showed MES ED_{50} = 80.32 mg/kg, PI = 3.16. Compound **7** showed in quantitative corneal kindled mouse test CKM ED_{50} = 56.72 mg/kg. Compound **8** showed MES ED_{50} = 34.23 mg/kg and scPTZ ED_{50} = 300 mg/kg, PI = 8.53. Compound **13** showed 6Hz ED_{50} = 78.96, PI = 3.37.

DISCUSSION

A series of isocyclic and heterocyclic acids benzylamides were previously obtained in search for new effective anticonvulsants (1-5). Preliminary anticonvulsant identification tests (ASP) allow to define the structure elements of this group of compounds conditioning pharmacologically advantageous properties. It was found that 5-membered

Table 6. Biological response of **1** (mice *i.p.*).

Test	Time (h)	Dosage (mg/kg)	Protected/used
MES	0.25	50	0/8
MES	0.25	75	4/8
MES	0.25	100	6/8
MES	0.25	150	8/8
scPTZ	0.25	255	2/8
TOX	0.25	150	0/8
TOX	0.25	225	2/8
TOX	0.25	260	3/8
TOX	0.25	300	8/8

MES = maximal electroshock test. TOX = neurological neurotoxicity test. PTZ = pentetrazole.

Table 7. Biological response of **7** (corneal kindled mouse).

Test	Time (h)	Dosage (mg/kg)	Protected/used
CKM	0.5	25	0/8
CKM	0.5	50	3/8
CKM	0.5	65	5/8
CKM	0.5	100	8/8

CKM = corneal kindled mouse.

Table 8. Biological response of **8** (mice *p.o.*).

Test	Time (h)	Dosage (mg/kg)	Protected/used
MES	0.25	10	0/8
MES	0.25	30	4/8
MES	0.25	50	5/8
MES	0.25	70	8/8
scPTZ	0.25	300	0/8
TOX	0.25	150	1/8
TOX	0.25	200	1/8
TOX	0.25	300	3/8
TOX	0.25	500	8/8

MES = maximal electroshock test. TOX = neurological neurotoxicity test. PTZ = pentetrazole.

Table 9. Biological response of **13** (6 Hz, mice, *i.p*).

Test	Time (h)	Dosage (mg/kg)	Protected/used
6Hz	0.50	35	1/8
6Hz	0.50	65	4/8
6Hz	0.50	85	4/8
6Hz	0.50	150	6/8
6Hz	0.50	250	4/4
TOX	24.0	150	1/8
TOX	24.0	210	1/8
TOX	24.0	300	3/8
TOX	24.0	500	8/8

MES = maximal electroshock test. TOX = neurological neurotoxicity test. PTZ = pentetrazole

Table 10. Pilocarpine-induced status test in rats. Response data.

Compound No.	Dosage (mg/kg)	Time	Protected/used
1	400	0.0	0/7
7	400	0.0	0/8

structure of acid is especially useful. Substituents of the ring, presence of heteroatoms or double bonds do not have a decisive influence upon the activity. However, among the benzylamides of 6-membered acids and bicyclic 6-membered acids there were also some compounds with poor anticonvulsant activity. Electron-withdrawing groups on benzylamide site are able to increase the anticonvulsant activity. Therefore, it was decided to halogenate some previously obtained most active structures. Also there were obtained six fluorinated benzylamides of isocyclic 5-membered acids (**6**, **7**, **9**, **10**, **11 and 13**) and one fluorinated benzylamide of 6-membered heterocyclic acid (**8**). Also there were obtained one fluorinated (**12**) and three chlorinated (**3**, **4**, **5**) benzylamides of bicyclic 6-membered acid. It was decided to synthesize two new benzylamides of isocyclic acid (**1**, **2**) and to fluorinate them (**9**, **10**) for comparison of the activity. All the synthesized compounds were screened in qualitative tests (ASP): in mice, *i.p*. (MES, 6 Hz 32 mA, TOX) (Table 3) and in rats, *p.o*. and *i.p*. (MES, TOX) (Table 4). On the basis of the preliminary results some compounds (**1**, **7**, **8** and **13**) were put to further tests. There were performed the following tests (ASP): ED_{50} values determination (Table 5), biological response determination (Tables 6-9), pilocarpine-induced status, and response data (Table 10). The results lead to the conclusion that the fluorination of the active mother structure does not improve anticonvulsant activity (similar activity of compounds **6**-**13** and mother compound (N-oxidepicolinic acid benzylamide (2), 1-cyclopentenecarboxylic acid benzylamide (4), 2-furoic acid benzylamide (4), 5-methyl-2-furoic acid benzylamide (4), 3-isoquinolinecarboxylic acid benzylamide (4), 2-oxocyclopentaneacetic acid benzylamide (**2**)). All the obtained fluorinated compounds show strong anticonvulsant activity and low neurotoxicity. On the other hand chlorination of the mother compounds yields derivatives of decreased activity or not active at all (high activity of mother compound - 3-isoquinolinecarboxylic acid benzylamide (4) and lack of activity of compounds **4** and **5**). The important property of the structure related to biomolecular interaction is hydrophobicity of the compound. Its pertinent value assures a better transmembrane transport, protein binding and receptor affinity of the compound. The values of log P of the synthesized halogenated compounds reported in Table 1 approach the values of the mother compounds: (1-cyclopentenecarboxylic acid benzylamide – 2.60 (4), 3-cyclopentenecarboxylic acid benzylamide – 2.54 (4), cyclopentanocarboxylic acid benzylamide – 2.80 (4), 2-furoic acid benzylamide – 1.21 (5), 5-methyl-2-furoic acid benzylamide – 0.77 (5), 3-isoquinolinecarboxylic acid benzylamide – 3.33 (5), 2-oxycyclopentaneacetic acid benzylamide – 2.35 (**2**). This confirms relations

among the hydrophobicity and anticonvulsant activity of the compounds. However, it does not explain the difference between the activity of fluorinated and chlorinated structures. The molecular shape is the major factor contributing to the receptor affinity. The test of structure overlapping was performed to study the space relations between the halogenated derivatives and the active mother compounds. The optimized structures of the synthesized halogenated compounds were superimposed on the mother structures. Generally, a good superimposing was observed. It suggests that the receptor affinity of the mother and the newly synthesized compounds is similar and therefore, pharmacological activity is also similar, which was confirmed by the results of pharmacological tests. However, there is no explanation at the moment of difference between activity of fluorinated and chlorinated structures. Among the synthesized and tested compounds the most promising are **1**, **7**, **8** and **13**. The PI values of these compounds is enclosed in limits 8.53 and 3.16. For comparison – PI values of known anticonvulsant drugs: valproic acid is 6.0 (MES ED_{50} = 425.1 mg/kg, TD_{50} = 243.0), phenobarbital is 6.7 (MES ED_{50} = 9.1 mg/kg, TD_{50} = 6.7 mg/kg). What deserves particular attention is very low neurotoxicity of these four compounds, similar to valproic acid, but much lower than phenobarbital (**1** – TD_{50} = 253.89 mg/kg, **7** – TD_{50} = 312.04 mg/kg, **8** – TD_{50} = 291.86 mg/kg and **13 -** TD_{50} = 266.05 mg/kg) (Table 5). High anticonvulsant activity and low neurotoxicity also show biological response of these compounds (Table 6-9). Considering the structure-activity relationship it is worth observing that three promising compounds are derivative of 5-membered acids (**1**, **7**, **13**) and three (**7**, **8**, **13**) are fluorinated benzylamides. This observation is worth consideration in the course of new anticonvulsant designing.

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