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In silico prediction of anticonvulsant activity of *N*-(2,2,2-trichloro-1-hydroxyethyl) alkylcarboxamides

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ABSTRACT

With the use of the computer program PASS, we have predicted the anticonvulsant activity of chloral carboxamides - products of chloral condensation with carboxylic acid amides. All connections, which structures analysis being carried out, were obtained earlier, and the structures were taken from the SciFinder database. The analysis of acute toxicity in rats has been carried out at intravenous and oral routes of administration using the program GUSAR. Calculated LD_{50} values have been given for all structures. We have selected compounds leaders tested for compliance with Lipinski criteria.

KEY WORDS: PASS, GUSAR, Anticonvulsant, Toxic, LD_{50}, Chloral carboxamide.

1. INTRODUCTION

Epilepsy - is a chronic disorder associated with abnormal electrical activity in the brain that is characterized by recurrent, unprovoked seizures (Rowles and Olsen, 2012). Each clinical form of the disease has its own mechanism of development that is why the effectiveness of the treatment largely depends on properly selected antiepileptic therapy. Today, there is a significant arsenal of drugs for the treatment of epilepsy, but not all have the same specific activity and, in addition, have a number of side effects, which greatly complicates the process of treatment (Boldyreva, 2009). At the same time, 30% of epilepsy patients are characterized by pharmaco resistance (Pitkanen, 2010). Therefore, the relevance of new antiepileptic drugs search, having high therapeutic activity, low toxicity and without pronounced side effects is not in doubt.

From the literature, it is known that compounds possessing anticonvulsant activity often comprise amide, ureido or semicarbazono fragment in the structure (Zheng, 2014; Garrido-Acosta, 2016; Sameem, 2012; Kumar, 2013; Nikalje, 2012; Pandeya, 2013). Therefore, we selected chloral carboxamides, chloral hydrate condensation products with amides of carboxylic acids, as objects for study. Owing to their availability and poly functionality, they are successfully used in the synthesis of the heterocyclic compounds (Zadorozhnii, 2015; Drach, 1992), drugs, such as *Salubrinal*, and its analogs (Boyce, 2005; Matsuoka and Komoike, 2015; Liu, 2012).

In this study, using the PASS system (Filimonov, 2014), we have analyzed the anticonvulsant activity of *N*-(2,2,2-trichloro-1-hydroxyethyl) alkylcarboxamides, evaluated their acute toxicity in rats using GUSAR program (Lagunin, 2011). Selected compounds leaders have been tested for compliance with Lipinski criteria (Lipinski, 1997).

2. MATERIALS AND METHOD

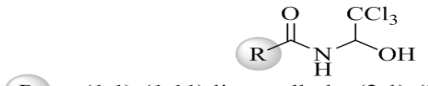
The computer system PASS (Prediction of Activity Spectra for Substances) (Sadym, 2002) is based on the concept of biological activity spectrum. It is considered as the whole complex of biological effects, which a substance is capable to produce under certain conditions of the interaction with biological objects, without taking into account the characteristics of specific experiments. The PASS program predicts the spectrum of biological activity of organic compounds on the basis of their structural formulas, that is, biological activity of a substance is considered as its internal property depending only on its structure.

The PASS system provides an estimate of "similarity / difference" of a testing compound towards the known biologically active substances. The results of prediction are presented as a list of possible types of activity with the calculated estimates of its presence (P_a) and absence (P_i), which have a value between 0 and 1. The higher the value (P_a) for the specific activity and the smaller the value (P_i), the greater is the probability of detection of the activity in the experimental conditions.

Using the PASS system we have analyzed the spectrum of biological activity of *N*-(2,2,2-trichloro-1-hydroxyethyl)alkylcarboxamides. The prediction has been prepared for individual structures, taken from the international database SciFinder. We have introduced the structures of compounds for biological activity prediction using the graphical editor Marvin Sketch at the official website. Then, these structures have been sent to the server as MNA-descriptors (Multilevel Neighborhoods of Atoms) (Filimonov, 2014; Sadym, 2002). The results of the prediction of biological activity spectrum have been visualized on the display and saved by "copy-paste".

3. RESULTS AND DISCUSSION

All analytes have been divided into five groups depending on the nature of the alkyl moiety: a) linear alkyls; b) branched alkyls; c) alkyl halides; d) cycloalkyls; e) an alkyl radical containing moiety $CCl_3(HO)C$- (Fig.1). The probability of manifestation in anticonvulsant activity of test compounds equals 30.1% -91.8% (Tables.1-5).



R = **(1.1)-(1.11)** linear alkyls; **(2.1)-(2.9)** branched alkyls; **(3.1)-(3.19)** alkyl halides; **(4.1)-(4.13)** cycloalkyls; **(5.1)-(5.14)** $CCl_3(HO)C$- containing moiety.

Fig.1. General view of *N*-(2,2,2-trichloro-1-hydroxyethyl)alkylcarboxamides

Table.1. The results of prediction of anticonvulsant activity and acute toxicity of *N*-(2,2,2-trichloro-1-hydroxyethyl)alkylcarboxamides with linear structure of alkyl substituent

Compound	R	CAS Number	Anticonvulsant Activity		Toxic LD_{50} (mg/kg)	
			P_a	P_i	IV	Oral
1.1	CH_3-	5445-85-2	0.795	0.005	149.700	2669.000
1.2	CH_3CH_2-	34243-50-0	0.726	0.008	149.200	1990.000
1.3	$CH_3CH_2CH_2$-	34243-51-1	0.803	0.005	162.700	2043.000
1.4	$CH_3(CH_2)_4CH_2$-	875247-00-0	0.795	0.005	150.000	3107.000
1.5	$CH_3(CH_2)_5CH_2$-	56737-18-9	0.795	0.005	151.200	3252.000
1.6	$CH_3(CH_2)_6CH_2$-	304443-93-4	0.795	0.005	153.000	3397.000
1.7	$CH_3(CH_2)_8CH_2$-	66569-89-9	0.795	0.005	161.100	3334.000
1.8	$CH_3(CH_2)_9CH_2$-	100878-90-8	0.795	0.005	167.100	3676.000
1.9	$CH_3(CH_2)_{11}CH_2$-	302954-57-0	0.795	0.005	172.200	4053.000
1.10	$CH_3(CH_2)_{13}CH_2$-	56737-14-5	0.795	0.005	184.600	4090.000
1.11	$CH_3(CH_2)_{15}CH_2$-	102376-59-0	0.795	0.005	193.900	4274.000

Table.2. The results of prediction of anticonvulsant activity and acute toxicity of *N*-(2,2,2-trichloro-1-hydroxyethyl)alkylcarboxamides carboxamides with branched structure of alkyl substituent

Compound	R	CAS Number	Anticonvulsant Activity		Toxic LD_{50} (mg/kg)	
			P_a	P_i	IV	Oral
2.1	$(CH_3)_2CH$-	51361-16-1	0.838	0.005	135.800	1911.000
2.2	$(CH_3)_2CHCH_2$-	56737-13-4	0.806	0.005	153.400	1892.000
2.3	$C_2H_5(CH_3)CH$-	56737-20-3	0.756	0.007	135.500	1904.000
2.4	$(CH_3)_3C$-	16535-65-2	0.849	0.005	104.700	1615.000
2.5	$CH_3(CH_2)_3CH_2$-	857780-59-7	0.795	0.005	146.000	2957.000
2.6	$(C_2H_5)_2CH$-	55276-91-0	0.872	0.004	140.200	2049.000
2.7	$C_2H_5((CH_3)_2CH)CH$-	64037-69-0	0.876	0.004	118.500	3046.000
2.8	$C_4H_9(C_2H_5)CH$-	875247-72-6	0.910	0.004	108.500	3771.000
2.9	$(C_3H_7)_2CH$-	16535-66-3	0.918	0.004	117.200	3592.000

With increasing growth of alkyl chain, the probability of anticonvulsant activity is not changed (Table.1, Fig.2), but with increase of its branching - it increases significantly (Table.2, Fig.2). At the same time, when the length of alkyl chain increases, the estimated LD_{50} value increases for intravenous administration, that is the toxicity of a substance decreases (Fig.3), but with increase of its branching - LD_{50} value falls rapidly, i.e. the toxicity increases. Anticonvulsant drugs are mostly used orally. In the compounds analyzed having this route of administration the increase in molecular weight leads to the increase in LD_{50} value. LD_{50} value is slightly lower in the compounds with a branched alkyl moiety than in the compounds with a radical of normal structure (Fig.4).

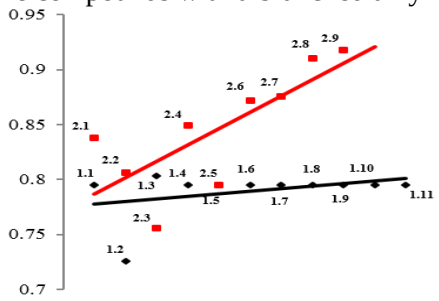


Fig.2. Probability of anticonvulsant activity of *N*-(2,2,2-trichloro-1-hydroxyethyl)alkylcarboxamides with linear (black) and branched (red) substituents structure

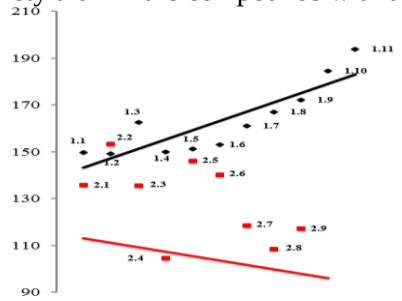


Fig.3. The estimated LD_{50} value in intravenous administration of *N*-(2,2,2-trichloro-1-hydroxyethyl)alkylcarboxamides with linear (black) and branched (red) substituents structure

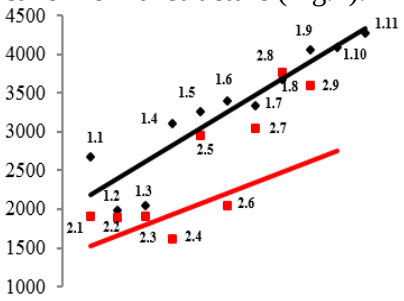


Fig.4. The estimated LD_{50} value in oral administration of *N*-(2,2,2-trichloro-1-hydroxyethyl)alkylcarboxamides with linear (black) and branched (red) substituents structure

Table.3. The results of prediction of anticonvulsant activity and acute toxicity of *N*-(2,2,2-trichloro-1-hydroxyethyl)carboxamides with an alkyl halide moiety

Compound	R	CAS Number	Anticonvulsant Activity		Toxic LD_{50} (mg/kg)	
			P_a	P_i	IV	Oral
3.1	FCH_2-	687-01-4	0.547	0.027	49.170	505.500
3.2	$ClCH_2$-	2755-35-3	0.525	0.030	55.980	1913.000
3.3	$BrCH_2$-	18271-90-4	0.641	0.014	44.890	1385.000
3.4	ICH_2-	121583-66-2	0.301	0.120	61.620	2075.000
3.5	Cl_2CH-	16535-70-9	0.333	0.100	64.660	2649.000
3.6	Br_2CH-	18271-91-5	0.339	0.096	67.480	2165.000
3.7	CF_3-	201990-14-9	0.584	0.021	100.700	1004.000
3.8	CCl_3-	18271-89-1	0.597	0.019	67.630	2064.000
3.9	$F_2(Ph)C$-	1017522-73-4	0.663	0.012	56.380	2493.000
3.10	$Cl_2(CH_3)C$-	24454-97-5	0.527	0.030	62.380	1726.000
3.11	$Cl_2(ClCH_2)C$-	24454-99-7	0.430	0.053	51.430	1033.000
3.12	$Cl_2(CN)C$-	10221-79-1	0.451	0.047	63.650	1647.000
3.13	$ClCH_2CH_2$-	24454-96-4	0.824	0.005	63.680	1730.000
3.14	$BrCH_2CH_2$-	134765-21-2	0.531	0.029	53.460	1473.000
3.15	$BrCH_2(Br)CH$-	24454-98-6	0.616	0.017	60.600	744.700
3.16	Cl_3CCH_2-	99848-08-5	0.687	0.010	146.800	1935.000
3.17	$BrCH_2CH_2CH_2$-	134765-22-3	0.506	0.034	50.980	1358.000
3.18	$BrCH_2(CH_2)_2CH_2$-	134765-23-4	0.496	0.037	49.800	975.500
3.19	$BrCH_2(CH_2)_3CH_2$-	134765-24-5	0.496	0.037	51.390	757.600

In *N*-(2,2,2-trichloro-1-hydroxyethyl)carboxamides with an alkyl halide moiety, with an increase in alkyl chain growth the probability of anticonvulsant activity is practically unchanged (Table.3, Fig.5). There is no clear dependence either from the nature of the halogen atom or their number as well. The LD_{50} value at intravenous route of administration with increase of alkyl chain also remains virtually unchanged (Fig.6), but bromine-containing structures are more toxic than chlorine and iodine-containing analogues (Table.3). At oral administration route, LD_{50} value of the analytes decreases with increase of alkyl chain (Fig.7).

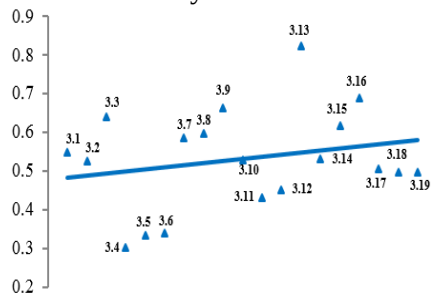


Fig.5. Probability of anticonvulsant activity of compounds (3.1)-(3.19)

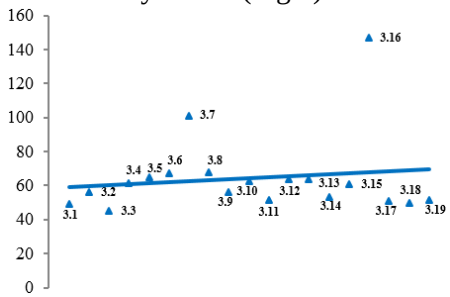


Fig.6. The estimated LD_{50} value in intravenous administration of compounds (3.1)-(3.19)

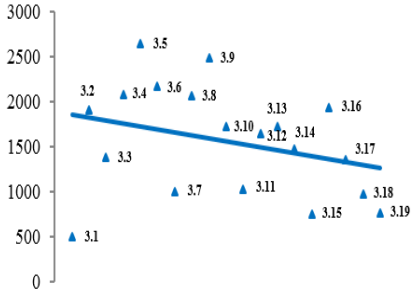
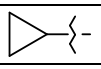
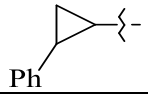
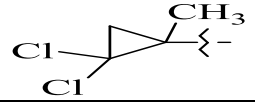
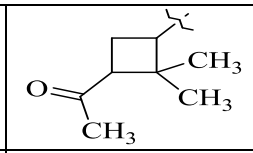
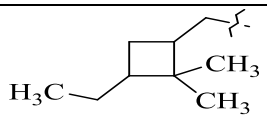
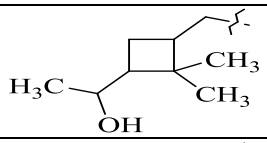
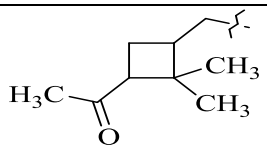
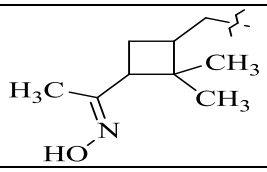
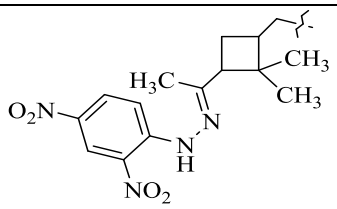
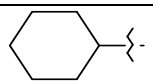
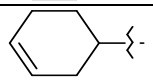
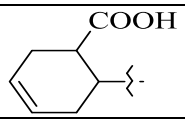
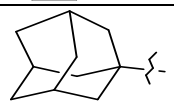


Fig.7. The estimated LD_{50} value in oral administration of compounds (3.1)-(3.19)

Table.4. The results of prediction of anticonvulsant activity and acute toxicity of *N*-(2,2,2-trichloro-1-hydroxyethyl)carboxamides with a cycloalkyl moiety

Comp.	R	CAS Number	Anticonvulsant Activity		Toxic LD_{50} (mg/kg)	
			P_a	P_i	IV	Oral
4.1		344748-69-2	0.709	0.009	150.100	1942.000
4.2		1797983-63-1	0.808	0.005	74.630	1178.000
4.3		89571-63-1	0.272	0.139	74.820	1820.000

4.4		83324-77-0	0.620	0.017	81.550	1681.000
4.5		51249-40-2	0.596	0.020	85.580	1305.000
4.6		51249-41-3	0.356	0.085	60.920	1348.000
4.7		51249-39-9	0.558	0.025	60.870	1636.000
4.8		51249-45-7	0.419	0.057	101.600	1413.000
4.9		51249-46-8	0.502	0.035	46.350	694.700
4.10		56737-16-7	0.715	0.009	132.600	1713.000
4.11		300381-24-2	0.724	0.009	105.000	1985.000
4.12		90876-58-7	0.763	0.007	263.000	6085.000
4.13		295362-27-5	0.574	0.023	96.490	1985.000

The probability of anticonvulsant activity for *N*-(2,2,2-trichloro-1-hydroxyethyl)carboxamides with a cycloalkane moiety is virtually independent of the cycle value and the nature of the substituents in it (Table.4, Fig.8). The LD_{50} value, for both intravenous and oral routes of administration, with the increase in cycle size and complication of the substituents nature in it, synchronously increases (Fig.9, Fig.10).

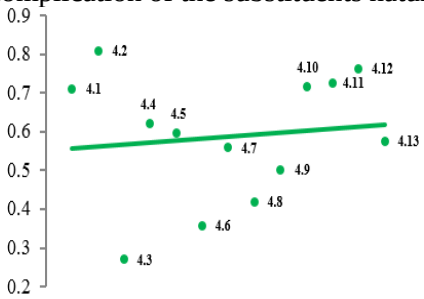


Fig.8. Probability of anticonvulsant activity of compounds (4.1)-(4.13)

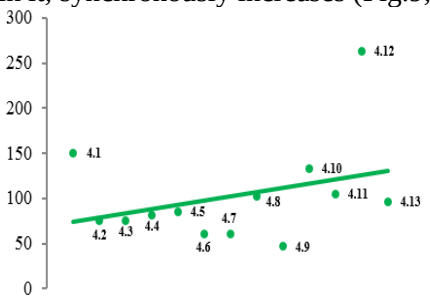


Fig.9. The estimated LD_{50} value in intravenous administration of compounds (4.1)-(4.13)

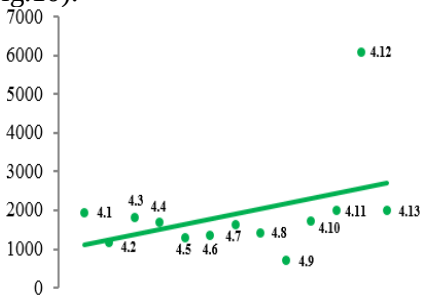
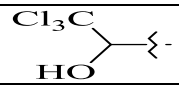
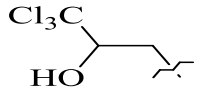
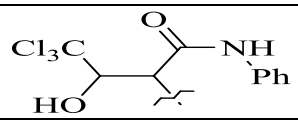
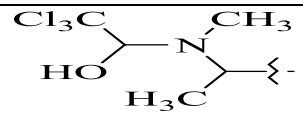
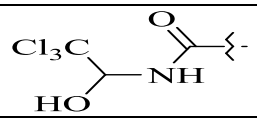
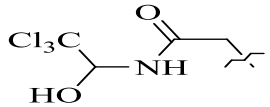
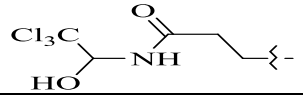
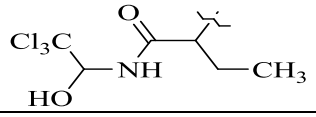
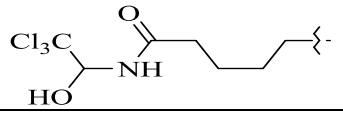
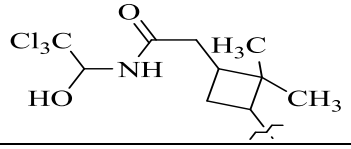
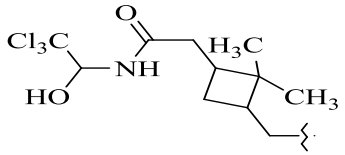
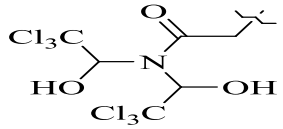
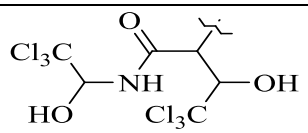
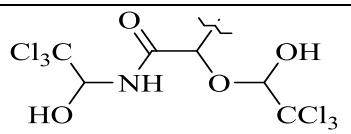


Fig.10. The estimated LD_{50} value in oral administration of compounds (4.1)-(4.13)

Table.5. The results of prediction of the anticonvulsant activity and acute toxicity of *N*-(2,2,2-trichloro-1-hydroxyethyl)carboxamides containing $CCl_3(HO)C$- group in the alkyl moiety

Comp.	R	CAS Number	Anticonvulsant Activity		Toxic LD_{50} (mg/kg)	
			P_a	P_i	IV	Oral
5.1		91493-05-9	0.646	0.014	95.630	2432.000
5.2		90724-40-6	0.638	0.014	145.900	2957.000
5.3		75456-99-4	0.588	0.021	181.200	4752.000
5.4		117508-89-1	0.649	0.013	251.900	2437.000
5.5		75457-07-7	0.669	0.011	117.300	2462.000
5.6		859199-12-5	0.687	0.010	218.700	2895.000
5.7		856065-67-3	0.752	0.007	239.000	3806.000
5.8		75457-01-1	0.763	0.007	189.100	4122.000
5.9		75457-01-1	0.742	0.008	212.400	3219.000
5.10		73600-17-6	0.368	0.368	143.400	2611.000
5.11		79926-54-8	0.555	0.025	120.300	3816.000
5.12		55668-54-7	0.683	0.010	195.300	3553.000
5.13		859197-56-1	0.679	0.011	160.700	3809.000
5.14		55276-93-2	0.894	0.004	67.670	2731.000

The probability of anticonvulsant activity for *N*-(2,2,2-trichloro-1-hydroxyethyl)carboxamides containing $CCl_3(HO)C$- group in the alkyl moiety with complication of the structure is slightly increased (Table.5, Fig.11). In this case, the LD_{50} value in intravenous route of administration decreases, and in oral one - increases (Fig.12, Fig.13).

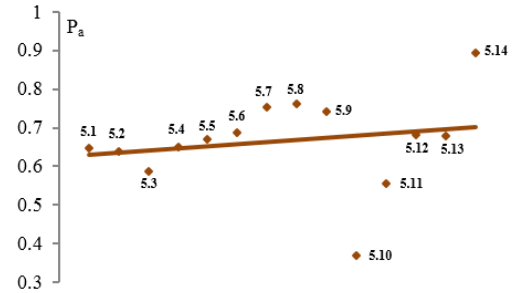


Fig.11. Probability of anticonvulsant activity of compounds (5.1)-(5.14)

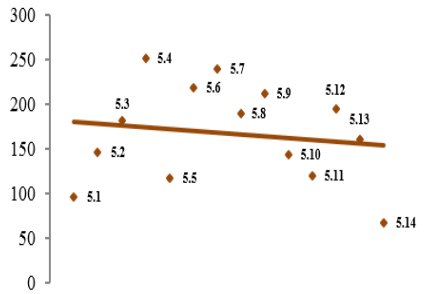


Fig.12. The estimated LD_{50} value in intravenous administration of compounds (5.1)-(5.14)

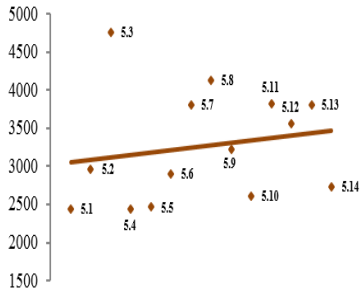


Fig.13. The estimated LD_{50} value in oral administration of compounds (5.1)-(5.14)

Compounds leaders were assigned to the structures having the probability of anticonvulsant activity more than 80%. Of all the compounds studied, eleven structures will have the greatest probability of anticonvulsant activity (Fig. 14): (1.3), (2.1), (2.2), (2.4), (2.6), (2.7), (2.8), (2.9), (3.13), (4.2), (5.14). For compounds (2.8) and (2.9), the probability of anticonvulsant activity is over 90%.

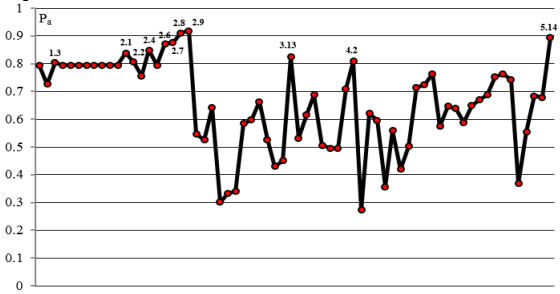


Fig.14. The choice of the compounds leaders of the studied structures

The compounds leaders have been tested for compliance with Lipinski criteria using Molinspiration web resource. All compounds meet the criteria, except (5.14), which has a molecular weight greater than 500 (Table.6).

Table.6. The test of the compounds leaders for compliance with Lipinski criteria

Entry	Compound	Mr	logP	Rot.Bond	H_{donor}	$H_{acceptor}$
1	1.3	234.51	2.05	4	2	3
2	2.1	234.51	1.73	3	2	3
3	2.2	248.54	2.26	4	2	3
4	2.4	248.54	2.64	3	2	3
5	2.6	262.56	2.74	5	2	3
6	2.7	276.59	3.74	5	2	3
7	2.8	290.62	3.80	7	2	3
8	2.9	290.62	3.86	7	2	3
9	3.13	254.93	1.49	4	2	3
10	4.2	308.59	2.82	4	2	3
11	5.14	560.26	2.07	9	5	8

4. CONCLUTION

In this work, using the PASS system, we have predicted biological activity spectrum of *N*-(2,2,2-trichloro-1-hydroxyethyl)alkylcarboxamides and showed their prospects as potential anticonvulsants. The dependence of the probability of anticonvulsant activity of side-radical R has been built. For the structures analyzed, evaluation of acute toxicity in rats has been carried out using GUSAR program. We have selected the compounds leaders having the probability of anticonvulsant activity more than 80%. The structures of the compounds leaders have been tested for compliance with Lipinski criteria.

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