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STUDYING RETENTION BEHAVIOR, LIPOPHILICITY AND PHARMACOKINETIC CHARACTERISTICS OF N-SUBSTITUTED PHENYL-2-CHLOROACETAMIDES

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Abstract: The biological activity of compounds is mostly determined by its physical and structural characteristics. Among the many molecular descriptors that may indicate a potential biological activity of a compound, lipophilicity occupies the most important place. Since chloroacetamides show a variety of physiological activity, the task of this study was to investigate the potential biological activity of newly synthesized derivatives of selected N-substituted phenyl-2-chloroacetamides. Analysis was performed by thin layer chromatography on reversed phase (RP18 F254s TLC), and the mobile phase consisted of mixtures of water-acetic acid and water-dimethylformamide. By varying the volume fraction of organic modifier chromatographic retention constants, R_M^0, of the compounds were determined. Then R_M^0 were correlated with the software calculated partition coefficient, log *P*, as a standard measure of lipophilicity. Also, R_M^0 were correlated with selected pharmacokinetic parameters: intestinal absorption, *HIA*, the ability to bind to plasma proteins, PPB, and the distribution through the blood-brain barrier, BBB.

Keywords: R_M^0, log P, HIA, PPB, BBB.

1. INTRODUCTION

Modern scientific researches are largely based on studies of the newly synthesized molecules, especially those with potential biological activity. Particular attention was caused by numerous derivatives of amides, because even those with the simplest structures exhibit different activity in a biological medium. Phenylacetamide derivatives have found their applications in human and veterinary medicine, but also in the plant treatment. Acetanilide was the first known phenylacetamide derivative with analgesic and antipyretic properties, which is used in medicine under the name Antifebrin [1]. Recent studies have confirmed the previously discovered analgesic activity of phenylacetamides [2,3], and the existence of their antimicrobial [4,5], fungicidal [6,7], insecticidal [8] and antihelmintic activities [9]. In recent years, a lot of attention has been focused on investigating the application of newly synthesized phenylacetamide derivatives as potential anticonvulsant [10], antiarrhythmic [11], sodium channel blockers [12] and inhibitors of P-glycoprotein [13]. Some derivatives act as antipsychotics [14,15], but certainly, the biggest interest was sparked by acetamide derivatives, which inhibit the growth of tumor cells [16,17].

Detection, testing and development of future bioactive agents are parts of the complex scientific process, which carries a lot of risk, investment and time. The knowledge of the relationship between activities, structure and physicochemical properties of newly synthesized molecules enables early identification of potentially physiologically active substances. The selection of appropriate physicochemical parameters and their relationship with the predictors of activity is a long and very important part of the research. Quantitative Structure-Activity Relationship (*QSAR*), Quantitative Structure-Property Relationship (*QSPR*) and Quantitative Structure-Retention Relationship (*QSRR*) models make this comprehensive process easier. Lipophilicity is one of the most important molecular descriptors that affect the transport of compounds through biological system and the formation of complexes with receptors or biomolecules. In the pharmaceutical chemistry and environmental chemistry, it is widely used to predict the relationship between biological activity and

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chemical behavior of substances [18]. Lipophilicity can be determined by experimental and computational techniques. Because of its simplicity, reproducibility, cost and efficiency, thin-layer chromatography on reversed phase occupies a significant place in the determination of lipophilicity [19]. Chromatographic retention constant, R_M^0, as an alternative measure of lipophilicity, is widely applied in addition to standard measures of lipophilicity, partition coefficient, log *P* [20].

Besides lipophilicity, the potential biological activity and effectiveness of compound depend on its pharmacokinetic properties. Absorption, distribution, metabolism, excretion and toxicity (ADMETox properties) of examined potentially bioactive compounds determine its path in the body. Good bioavailability is one of the preconditions for expression of compound's activity. Since most bioactive substances in the organism are taken orally, Human intestinal absorption, *HIA*, is the first indicator of good bioavailability. It represents the amount of active substance that is absorbed after its oral ingestion. If absorption is high (*HIA* > 80%), orally entered substance largely reaches the systemic circulation [21]. Another indicator of good bioavailability of compound is its tendency to bind to plasma proteins in living organisms. Ability to bind molecules to plasma proteins (plasma protein binding, *PPB*) expresses the ratio of compounds that bound to the protein and its total concentration. Only the unbound fraction of active substance is available for transport through the cell membrane and for interaction with pharmacological receptor. The bound fraction of bioactive molecules is a depot that is activated and releases a new portion of the substance when the free fraction is metabolized. A molecule with *PPB* > 90% is considered to have a high capacity to bind to plasma proteins. The possibility of passing potentially physiologically active compounds in the central nervous system, is defined by its distribution across the blood-brain barrier (Blood-brain barrier, *BBB*), i.e. ratio of the concentration of examined compound in the brain and its concentration in the blood. The values of the pharmacokinetic parameters suggest the possibility of application of the tested substance as a potential neurological medicine. According to the latest classification which used PreADMET, a compound easily crosses into the central nervous system if it has *BBB* > 2.0, whereas a compound with *BBB* values < 0.1 poorly passes the blood-brain barrier [22].

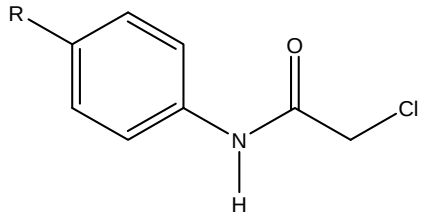
Applying thin-layer chromatography on reversed phase, HPTLC RP 18 F_{254s}, the effects of chemical structure of molecules and the influence of applied organic modifiers (acetic acid and dimethylformamide) on the retention behavior of selected N-substituted phenyl-2-chloroacetamide derivatives was investigated. The obtained chromatographic retention constants, R_M^0, are correlated with the standard criterion of lipophilicity, log *P*, and the relevant pharmacokinetic parameters, *HIA*, *PPB* and *BBB*. Establishing the connection between the chemical structure, retention behavior, lipophilicity and pharmacokinetic properties of newly synthesized derivatives of N-substituted phenyl-2-chloroacetamide presents a basis for further investigation of their potential biological activity.

2. EXPERIMENTAL

2.1. Chromatographic examination

The examined compounds (Table 1) were previously dissolved in ethanol (J.T.Baker, The Netherlands) at a concentration of 2 mg cm^{-3}. About 0.2 μl of created solutions were applied on the commercial chromatographic plates (HPTLC RP 18 F_{254s} Macherey–Nagel). Chromatograms were developed by one-dimensional ascending technique at 25 ^{0}C without previous saturation of the chamber atmosphere with solvent vapors: acetic acid (Zorka Pharma, Serbia) and dimethyl formamide (Fluka Chemika, Switzerland). Solvents were mixed with water: $\varphi_{(aa)}$ = 0.36 to 0.52, v/v and $\varphi_{(dmf)}$ = 0.36 to 0.52 v/v. Volume fraction of organic solvent in the mobile phase was varied in the amount of 4.00%. After development, chromatograms were dried in the air, and tge identification was performed by applying UV light wavelength λ = 254 nm, where dark spots appeared on the fluorescence basis. Three chromatograms were developed for both solvents.

Table 1. Structure of the N-substituted phenyl-2-chloroacetamides



Compound	Substituent
1.	- H
2.	-CH_3
3.	-Cl
4.	-Br
5.	-F
6.	-I

2.2. Processing of results

Obtained experimental data were processed by a computer program Origine 6.1., for the calculation of partition coefficients, log *P* program VCCLAB 2007 [23], was applied while the values of the pharmacokinetic parameters *HIA*, *PPB* and *BBB* were calculated using ChemSilico online programs [24].

3. RESULTS AND DISCUSSION

3.1. Retention behavior of the studied derivatives of N-substituted phenyl-2-chloroacetamide on reversed phase

Retention characteristics of N-substituted phenyl-2-chloroacetamides were examined by thin layer chromatography on reversed phases, HPTLC RP 18 F254s, in two organic solvents: amphiprotic acetic acid and aprotic dimethylformamide.

The chemical structure of molecules and the composition of the selected solvent mixtures have a strong influence on the efficiency in the chromatographic separation.

It can be seen in Table 2 that there is no marked difference in the retention of the same compound in applied organic solvents, in the same proportion in the mobile phase. The reason for this is a more pronounced interaction of the test substance with a more polar mobile phase in relation to its interaction with a less polar stationary phase.

Expectedly, stronger retention in an aprotic dimethyl formamide was observed for all tested compounds compared to amphiprotic acetic acid. A bigger difference in the retention behavior was observed between the various phenyl-chloroacetamide in the same solvent. This phenomenon can be explained by the influence of substituent's nature in the position 4 on the interaction of test compounds in the chromatographic analysis.

The decrease in polarity substituent bonded to a benzene ring leads to a greater retention compared to the unsubstituted molecule. In accordance with that, the compound 2, as the substituent of which is hydrophobic alkyl radical,-CH_3 is retained longer in the stationary phase. A similar phenomenon was registered during the bonding of halogen substituents to the basic molecule. Retention of molecules increases in the series F < Cl < Br < I (Table 2), which is explained by a difference between London dispersion interaction of the halogen atoms and non-polar stationary phase [25].

Table 2. Rf values of chloroacetamides on C-18 HPTLC stationary phase in the mobile phase which contained 40% organic solvent and 60% water

Substituent	R_f	
	acetic acid	dimethylformamide
H	0,562	0,529
CH_3	0,424	0,392
Cl	0,351	0,257
Br	0,326	0,220
F	0,543	0,433
I	0,264	0,182

3.2. Determination of lipophilicity of N-substituted phenyl-2-chloroacetamide experimentally

The lipophilicity of examined chloroacetamide was determined by reversed phase thin layer chromatography varying the volume fraction of the organic solvent, φ, in the mobile phase. Obtained R_f values gave R_M values for each composition of the mixture by equation (1):

$$R_M = \log (1/R_f - 1) \quad (1)$$

Using the linear regression method, based on equation (2) the following is determined: the intercept, R_M^0, slope, m, and the value of the correlation coefficient, r.

$$R_M = R_M^0 + m\varphi \quad (2)$$

Intercept, R_M^0, is a chromatographic retention constant, which is often used as a measure of compound's lipophilicity, while the slope corresponds to the chromatographic parameters that largely depends on the properties of the solute and its chemical structure (specific hydrophobic surface, the number of functional groups) and can also be used as an alternative measure of lipophilicity [26].

Chromatographic retention constant, R_M^0, should not depend on the nature of the organic solvent, because it represents the retention of substances in pure water. However, it can be seen in Table 3 that R_M^0 values for the same substance are different in both solvents, which was previously confirmed in practice [27].

Data from Table 3 show that the value of intercept, R_M^0, follow the value of the slope, m, for all tested derivatives in used solvents, which can be explained by the fact that both these chromatographic parameters depend on the same physico-chemical parameters [28]. With an aim of confirming this fact, the chromatographic retention constant, R_M^0, and the slope, m, are correlated.

It is evident in Figure 1 that linear relationship between these two chromatographic parameters in dimethylformamide was established. The same trend was observed in acetic acid. Equations of these relationships are given in Table 4.

Table 3. Chromatographic parameters R_M^0 equation, m, r and sd in applied solvents

Substituent	acetic acid				dimethylformamide			
	R_M^0	*m*	r	sd	R_M^0	*m*	r	sd
H	0,802	−2,350	0,990	0,031	0,414	−1,155	0,999	0,002
CH_3	1,316	−2,992	0,993	0,025	1,295	−2,888	0,985	0,037
Cl	1,412	−2,925	0,989	0,032	1,622	−2,950	0,988	0,033
Br	1,487	−2,928	0,995	0,022	1,730	−3,042	0,993	0,026
F	1,013	−2,770	0,992	0,026	1,084	−2,415	0,993	0,025
I	1,619	−2,935	0,996	0,018	1,881	−3,175	0,980	0,047

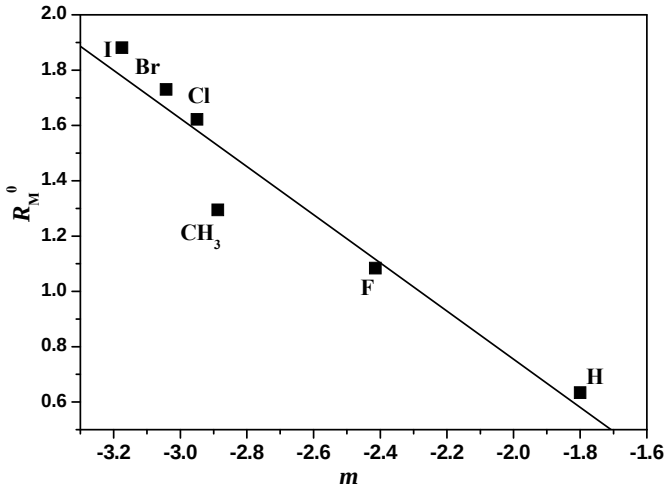


Figure 1. Dependence of intercept, R_M^0, on the slope, m, in dimethylformamide

Table 4. Equations of relationships between retention parameters, intercept, $R_M^0$and slope, m, in applied solvents

solvent	equation	r	Sd
acetic acid	$R_M^0 = - 1{,}840 – 1{,}106\ m$	0,861	0,176
dimethylformamide	$R_M^0 = - 0{,}986 – 0{,}871\ m$	0,965	0,137

Higher correlation of these two chromatographic parameters is obtained in dimethylformamide compared to acetic acid (Table 4).

The values of correlation factor, r, indicate that in observed modifiers the values of the slope, m, can be used as descriptors for the evaluation of lipophilicity, and consequently for the biological activity of the newly synthesized compounds.

3.3. Determination of the lipophilicity of N-substituted phenyl-2- chloroacetamides by computation method

Besides experimental methods for determining the lipophilicity mathematical methods are often used. In this study, partition coefficient, log *P*, of N-substituted phenyl-2-chloroacetamide derivatives were calculated as standard measure of lipophilicity. Obtained values of the log *P* are shown in Table 5.

Data from Table 5 indicate that the values of partition coefficient log *P* differ from each other although they relate to the same compound. The differences can be explained by using different mathematical methods within the software package. Regardless of the differences, log *P* values should be in high correlation with each other, since they represent the same properties of the molecule, its distribution in the system 1-octanol-water, respectively, lipophilicity. As a result, obtained log *P* values of these molecules were compared (Table 6).

Table 5. log P values of the N-substituted phenyl-2-chloroacetamide obtained by calculation

Compound	Alog *P*s	AClog *P*	Alog *P*	Mlog *P*	*kowwin*	Xlog *P*	log *P*ch.s.
1.	1,73	1,77	1,70	1,95	1,68	1,83	1,64
2.	1,87	2,08	2,18	2,25	2,23	1,99	2,31
3.	1,69	1,66	1,68	1,68	2,32	1,67	1,86
4.	2,39	2,38	2,36	2,52	2,57	2,26	2,59
5.	2,42	2,47	2,44	2,66	1,88	2,32	2,79
6.	2,00	1,83	1,90	2,37	2,85	1,73	1,91

Table 6. Correlation matrix of different log P values obtained by computation method

	Alog *P*s	AClog *P*	Alog *P*	Mlog *P*	*kowwin*	Xlog *P*	log $P_{ch.s.}$
Alog *P*s	1,000	0,948	0,767	0,910	−	0,843	0,941
AC log *P*		1,000	0,902	0,915	−	0,959	0,977
Alog *P*			1,000	0,871	−	0,934	0,871
Mlog *P*				1,000	−	0,845	0,869
kowwin					1,000	0,348	0,266
Xlog *P*						1,000	0,901
log $P_{ch.s.}$							1,000

According to data from Table 6, the best agreement is obtained when Alog *P*s and log *P*ch.s are correlated, while a linear dependence was not observed in the correlation values *kowwin* with other log *P* values. This phenomenon can probably be explained by the fact that all of the calculated values of log *P*, except the *kowwin*, were obtained by the method, which takes into account the contribution of individual fragments in the molecule [29]. The value *kowwin* was obtained by the method that is based on the impact and the contribution of the individual atoms in the molecule [30].

3.4. Correlation of lipophilicity parameters obtained experimentally and by calculation

Considering that chromatographic retention constant, R_M^0, describes the overall effect of the intermolecular interaction of the compounds with the stationary and the mobile phase, it was confirmed that it can be used as a measure of lipophilicity [31]. In order to confirm these facts, the experimentally determined lipophilicity of the examined novel N-substituted phenyl-2-chloroacetamide determined by reversed phase thin layer chromatography, R_M^0, is correlated with the software calculated partition coefficient, log *P*, as the standard measure of lipophilicity. Figure 2 shows dependence of partition coefficient, log *P*ch.s. and retention constant, R_M^0, obtained in acetic acid and dimethylformamide.

The existence of linear dependence between these two parameters of lipophilicity in both of applied solvent can be seen in Figure 2. Data in Table 7 shows that the best correlation was obtained for correlation between log *P*ch.s. and R_M^0 in acetic acid, and the weakest is registered between Alog *Ps* and R_M^0 in the same solvent. High values of correlation factor, r, give an indication of the possibility of using retention constant, R_M^0, as a measure of lipophilicity.

Table 7. Correlation matrix of different log P values and chromatographic retention constants, R_M^0

log *P*	R_M^0	
	acetic acid	dimethylformamide
AC log *P*	0,958	0, 958
Alog *P*	0,932	0,932
Alog *P*s	0,853	0,897
kowwin	0,976	0,963
log $P_{ch.s.}$	0,977	0,973
Mlog *P*	0,902	0,956
Xlog *P*	0,895	0,889

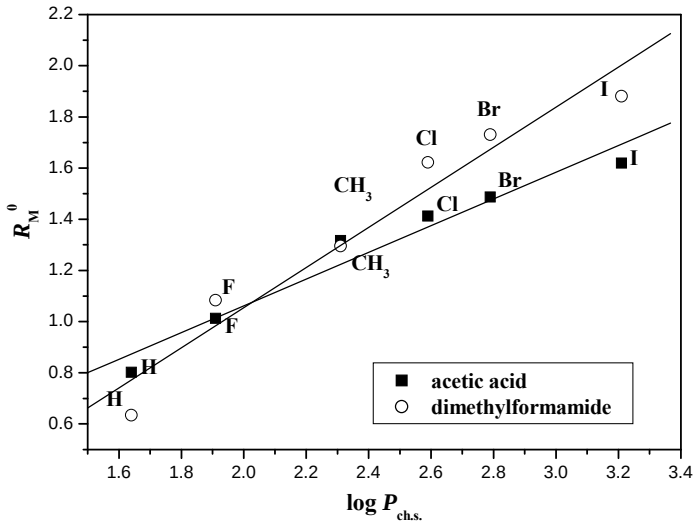


Figure 2. Correlation between R_M^0 and log Pch.s, in both used solvents

3.4. Correlation of chromatographic retention constant, R_M^0, with predictors of biological activity

For predicting potential biological activity of a molecule it is important to know its pharmacokinetic properties. Three important pharmacokinetic predictors: *HIA, PPB* and BBB are calculated for investigated chloroacetamide derivatives by applying a software program Chemsilico [24] and their values are shown in Table 8.

As presented in Table 8, the tested chloroacetamide derivatives have a predisposition for high intestinal absorption (*HIA* > 90), which causes their good bioavailability in the organism. Furthermore, these molecules show a relatively high affinity of binding to plasma proteins (45 < *PPB* < 91), which suggests slow and long-term distribution in the organism. Based on BBB values of the investigated molecules, it can be assumed that they have high absorption (0.20 < *BBB* < 0.58) in the central nervous system, which gives them a relatively good primary properties of potentially neurologically active substances.

Table 8. Pharmacokinetic parameters HIA, PPB and BBB of examined chloroacetamide derivatives

Compound	*HIA*	*PPB*	*BBB*
1.	94,60	45,46	0,20
2.	93,20	79,38	0,31
3.	92,40	80,00	0,42
4.	91,80	84,80	0,47
5.	94,30	63,51	0,24
6.	90,20	91,06	0,58

In order to establish dependency between the experimentally determined lipophilicity of the tested compounds and mentioned important pharmacokinetic parameters, a correlation between chromatographic retention constant, R_M^0, and calculated values of *HIA*, *PPB* and *BBB* was performed.

The dependence of the chromatographic retention constant, R_M^0, obtained in acetic acid and dimethylformamide, on the calculated pharmacokinetic parameters *HIA*, *PPB* and *BBB* are shown in Figure 3a, Figure 3b and Figure 3c, respectively.

It can be seen in Figure 3a, Figure 3b and Figure 3c that the dependence of chromatographic retention constants, R_M^0 on selected pharmacokinetic predictors *HIA*, *PPB* and *BBB*, is linear in both applied solvents. This fact is confirmed by the value of the coefficient of correlation (Table 9).

Data in Table 9 suggest the possibility of using R_M^0, in the evaluation of pharmacological properties of the newly synthesized molecules in the modern design of bioactive substances.

Table 9. Correlation factors of linear dependence between chromatographic retention constant, R_M^0, and pharmacokinetic parameters

solvent	*HIA*	*PPB*	*BBB*
acetic acid	0,940	0,987	0,945
dimethylormamide	0,932	0,970	0,952

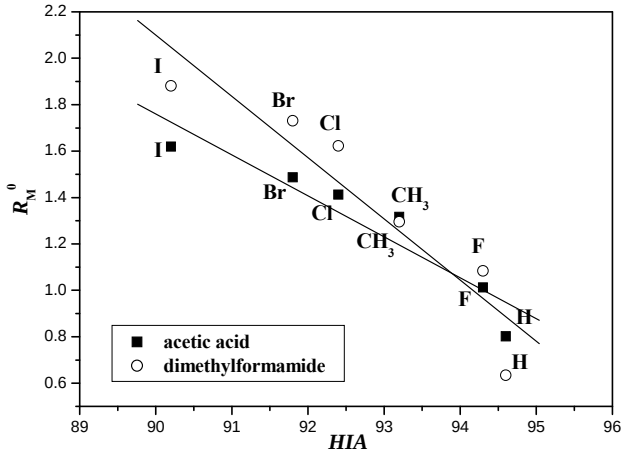


Figure 3a. Dependence between R_M^0 and HIA in both applied organic solvents

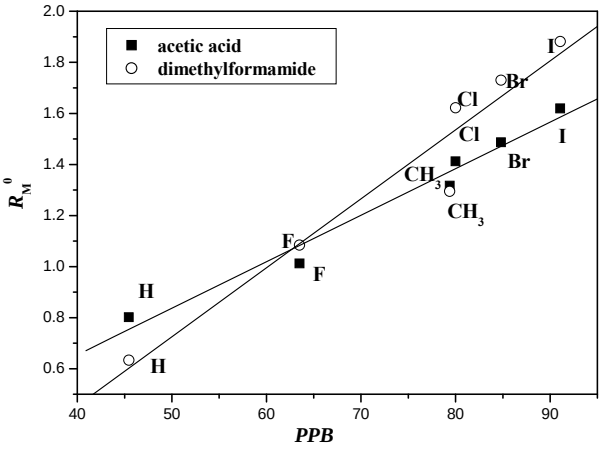


Figure 3b. Dependence between R_M^0 and PPB in both applied organic solvents

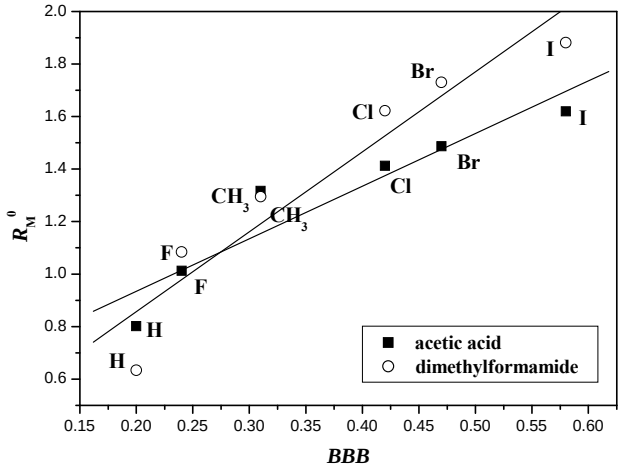


Figure 3c. Dependence between R_M^0 and BBB in both applied organic solvents

4. CONCLUSION

Newly synthesized derivatives of substituted N-phenyl-2-chloroacetamide were investigated with an aim of predicting their potential biological activity. One of the most important indicators of the potential biological activity is lipophilicity of a compound.

In this paper, the aforementioned molecular descriptor was determined experimentally and by calculation. Since the behavior of a compound in a biological medium depends on its physical, chemical, and structural characteristics, by using thin layer chromatography on reversed phase retention properties of selected chloroacetamide derivative were studied. Tests were performed on a C18 RP-F254s stationary phase, and two organic solvents were used as modifiers: acetic acid and dimethyl formamide. It was found that the retention behavior of these molecules is largely dependent on the chemical characteristics of the substituents at position 4, and in a smaller degree on the applied organic solvents.

Between the retention parameter, R_M, and volume fraction of the solvent, φ, a linear dependence in both organic solvents was established and on that basis the values of chromatographic retention constant, R_M^0, were calculated, which are assumed as a measure of lipophilicity. The experimentally determined lipophilicity, R_M^0, is correlated with the values of the standard measures lipophilicity log *P* previously calculated by software, whereby a good linear relationship was determined in both of applied solvent.

In addition to lipophilicity, the physiological activity of a compound is conditioned by its pharmacokinetic properties, so three important pharmacokinetic parameter, intestinal absorption, *HIA*, the ability to bind to plasma proteins, *PPB*, and the distribution of the blood-brain barrier, the *BBB* were calculated using the software package. The obtained values confirmed that the tested compounds may be used as potential pharmacokinetic agents. In the cor-

relation chromatographic retention constant, R_M^0, with each of these predictors a linear dependence in both applied solvent was established .

A high agreement of chromatographic retention constant, R_M^0, obtained in acetic acid and dimethylformamide, with the calculated lipophilicity log *P*, and with calculated pharmacokinetic calculation predictors *HIA*, *PPB* and the *BBB* makes the thin layer chromatography on reversed phase a reliable method for determining the lipophilicity, the assessment of the pharmacokinetics, and consequently possible predicting the biological activity of the studied substituted N-phenyl-2-chloroacetamide derivatives. In this way, by simple experimental technique an opportunity can be provided for the identification of potentially biologically important compounds among a number of structurally related derivatives and long-term steps in the design process of the future bioactive substances can be reduced.

5. ACKNOWLEDGEMENTS

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ПРОУЧАВАЊЕ РЕТЕНЦИОНОГ ПОНАШАЊА, ЛИПОФИЛНОСТИ И ФАРМАКОКИНЕТИЧКИХ ОСОБИНА N-СУПСТИТУИСАНИХ ФЕНИЛ-2-ХЛОРОАЦЕТАМИДА

Сажетак: Биолошка активност једињења у највећој мјери условљена је његовим физичким и структурним карактеристикама. Међу бројним молекулским дескрипторима који могу да укажу на потенцијалну биолошку активност неког једињења, липофилност заузима најзначајније мјесто. С обзиром на разноврсну физиолошку активност хлороацатемида, задатак овог рада је био проучавање потенцијалне биолошке активности одабраних новосинтетисаних деривата N-супституисаних фенил-2-хлороацетамида. Испитивање је вршено примјеном танкослојне хроматографије на обрнутим фазама (TLC RP18 F_{254s}), при чему су мобилну фазу чиниле смјеше:

вода − сирћетна киселина и вода – диметил − формамид. Варирањем запреминског удјела органског модификатора, одређене су хроматографске ретенционе константе, R_M^0, испитиваних једињења. Добијене вриједности R_M^0 корелисане су са софтверски израчунатим подионим коефицијентом, log *P*, као стандардним мјерилом липофилности и одабраним фармакокинетичким параметрима: цријевна апсорпција, *HIA*, способност везивања за протеине плазме, *PPB*, и расподјела кроз крвно-мождану баријеру, *BBB*.

Кључне ријечи: R_M^0, log *P, HIA*, *PPB*, *BBB*.