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STUDYING OF THE LIPOPHILICITY AND TOXICITY OF DIPHENYLACETAMIDE DERIVATIVES

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Abstract: Modern approach in the study of biologically active compounds includes the establishment of relationships between molecular structure, physicochemical properties and the behavior which studied compound can manifest in the biological medium. These examinantions are performed in the early stages of the design of future bioactive agent and require the knowledge of molecular descriptors that can point to its biological activity, including lipophilicity which occupies a key position. For the series of diphenylacetamide derivatives, lipophilicity is determined experimentally by thin-layer chromatography on reversed phase (RP TLC18 F254s), in mixtures of water and various organic modifiers and computationally, by using the relevant software packages. In order to estimate the potential acute toxicity of the tested diphenylacetamide derivatives, their effective concentrations, EC_{50}, on the selected test organisms have been determined. Experimentally determined lipophilicity (R_M^0 and m) is correlated with a standard measure of lipophilicity (log P), as well as with the selected parameters of toxicity. Thus it has been found that thin-layer chromatography on reversed phase can be used reliably for describing the lipophilicity and for the evaluation of the toxic effects of diphenylacetamide derivatives.

Keywords: diphenylacetamides, RP TLC, log P, toxicity.

1. INTRODUCTION

In recent decades, scientific studies have largely focused on the discovery, research and development of biologically active compounds. A modern design of a future bioactive agent is a complex process, and each phase requires a lot of time and costs [1]. Only 3% of the total number of research projects brings a new drug to the market, and for the production of 20 new drugs, the pharmaceutical industry invests about 50 billion dollars annually [2]. Clear definition of the properties of a future bioactive compound (desired effect, efficacy and potential toxicity) is the first step in the rationalization of the research. Also, the synthesis of a future drug precedes the establishment of qualitative and quantitative dependencies between its structure, physical-chemical properties and activities. Adequate bioavailability is one of the crucial properties of newly synthesized molecules for further study of their biological activity. Recognition of potentially biologically active compounds can be supported by the use of rules for good bioavailability, such as the Lipinski Rule of five and the Rule of Ghose [3–6]. According to the Lipinski Rule of five, a potentially biologically active compound should possess: molecular weight ≤ 500; number of hydrogen bond donors ≤ 5; the number of hydrogen bond acceptors ≤ 10 (2 · 5) and the value of the partition coefficient log $P \leq 5$. Similarly, the bioactive compound according to the Rule of Ghose should have: a molecular weight between 160–480; the values of the partition coefficient $-0.4 \leq \log P \leq 5.6$; the total number of atoms in the molecule within 20–70 and the molar refractivity in the range 40–130.

One of the key molecular descriptors which can point to the behavior of compounds in the biological medium is lipophilicity. It determines the passage of the compound through biological membranes, its solubility, absorption, distribution, metabolism, elimination and toxicity [7,8]. Lipophilicity is often defined by the partition coefficient, log P, which represents the concentration ratio of the compound in both phases of the saturated system 1-octanol/water [9,10]. The chromatographic parameters, RM0 and m, obtained by thin layer chromatography on reversed phase (RPTLC) are often applied as alternative measures of the lipophilicity [11–18]. For further examination in the design of a new drug, in addition to lipophilicity and good bioavailability, it is impor-

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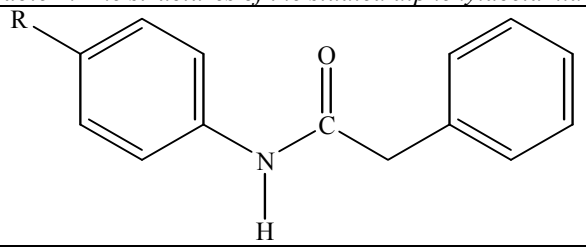
tant to predict its possible toxic effects to the society and the environment.

Bearing in mind the possibility of applying different acetamide as analgesics [19], antidepressants [20], anticonvulsants, [21] antivirotics [22], anthelmintics [23], insecticides [24] antimicrobial agens [25,26] and the anti-tumor drugs [27–29], the selected derivatives of diphenylacetamide were the subject of this paper. At first, it was first examined whether the studied diphenylacetamides fulfill the Lipinski Rule of five and Rule of Ghose. After that, their chromatographic parameters, R_M^0 and m, were determined by using RPTLC in water-acetic acid and water-dimethylsulfoxide (DMSO) systems. The possibility of applying the obtained chromatographic parameters of the studied diphenylacetamides as a measure of their lipophilicity and potential toxicity was tested by the correlation of R_M^0 and m with a partition coefficient, log P, as a standard criteria of lipophilicity, ie. with the selected parameters of acute toxicity by the linear regression method.

2. EXPERIMENTAL

The solutions of the studied diphenylacetamides were prepared in ethanol in the concentration of 2mgcm^{-3} (J. T. Baker, The Netherlands). The structures of the studied derivatives are shown in Table 1, and their synthesis and characterization are described in the literature [30].

Table 1. The structures of the studied diphenylacetamides



derivative	R	derivative	R
1.	H	6.	Br
2.	CH_3	7.	F
3.	C_2H_5	8.	CN
4.	OH	9.	$COOCH_3$
5.	Cl	10.	$COCH_3$

Commercial plates HPTLC RP 18 F254s (Macherey-Nagel GmBH, Germany) were used as a stationary phase. After application about 0.2 μl of the solution of each tested compound, the chromatograms were developed 15 minutes in water-acetic acid mixtures (J. T. Baker, Netherlands) and water-dimethylsulfoxide (J.T. Baker, Netherlands). The volume fraction of the organic solvent in the mobile phase varied in the range $\varphi_{(dmso)}$ = 0.36-0.52 v/ v and $\varphi_{(sk)}$ = 0.36-0.52, v/ v. The development was carried out by a one-dimensional ascending technique at 25^{0}C without prior saturation of the atmosphere of the chromatographic chamber by the solvent vapor. After the development, the chromatograms were dried in the air, and the identification was carried out using a UV light of a wavelength λ = 254 nm, wherein on the fluorescent basis, the dark spots occured.

For each studied compound, the R_f values were calculated, and for each composition of the mixtures, R_M values were calculated by equation (1):

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

The linear dependence obtained by applying the equation (2) gave the intercept, R_M^0 and slope, m:

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

Intercept, R_M^0, represents the chromatographic retention constant, while the slope, m corresponds to the chromatographic parameter which largely depends on the specific hydrophobic surface of the solute [31]. In addition to R_M^0, the chromatographic parameter m can also be used as an alternative measure of lipophilicity.

The obtained experimental data were processed using the Origin 6.1 software. For the calculation of the partition coefficient, log P, the selected molecular descriptors and parameters of the toxicity, the software packages VCCLAB 2007, Molinspiration and PreADMET, respectively, were applied [32–34].

3. RESULTS AND DISCUSSION

3.1. The compliance of the studied diphenylacetamide with the rules of good bioavailability

Since many acetamide derivatives exhibit biological activity, the possibility of the existence of the tested diphenylacetamides' bioactivity has been studied theoretically, using the rules of good bioavailability – the Lipinski Rule of 5 and the Ghose's rule. For the analyzed diphenylacetamides, the values of molecular descriptors included in these rules are shown in Table 2 and Table 3.

Table 2. Selected molecular descriptors of the examined diphenylacetamides

R	MW	nON	nONHN	natoms	MR
H	211.26	2	1	29	62.88
CH_3	225.29	2	1	32	68.78
C_2H_5	239.33	2	1	35	73.38
OH	227.26	3	2	30	64.69
Cl	245.71	2	1	29	67.49
Br	290.16	2	1	29	70.57
F	229.25	2	1	29	63.29
CN	236.27	3	1	30	68.98
$COOCH_3$	269.30	4	1	35	75.13
$COCH_3$	253.30	3	1	34	74.13

MW- molecular weight; nON- number of hydrogen bond acceptor; nOHNH- number of hydrogen bond donor; natoms- the total number of atoms in molecule; MR- molar refractivity

Table 3. Software obtained log P values of diphenylacetamides

R	AClog *P*	Alog *P*	Mlog *P*	milogP	*kowwin*	Clog *P*	Xlog P_3
H	2.86	2.65	3.11	2.92	2.81	2.70	3.07
CH_3	3.18	3.14	3.36	3.37	3.35	3.20	3.43
C_2H_5	3.54	3.59	3.61	3.84	3.85	3.73	3.86
OH	2.57	2.38	2.54	2.44	1.98	2.03	2.71
Cl	3.48	3.31	3.63	3.60	3.45	3.67	3.69
Br	3.56	3.40	3.76	3.73	3.70	3.82	3.76
F	2.92	2.86	3.51	3.08	3.01	3.10	3.17
CN	2.68	2.53	2.72	2.68	2.90	2.73	2.78
$COOCH_3$	2.84	2.51	2.97	3.09	3.04	3.14	2.92
$COCH_3$	2.79	2.39	2.97	2.82	2.49	2.61	2.75

The data shown in Table 2 and Table 3 indicate that all the tested diphenylacetamide derivatives theoretically fulfill the requirement of good bioavailability in the organism, and thus have a predisposition for the biological activity. Also, based on the data in Table 3, it can be seen that different values of the partition coefficient, log *P* are obtained for the same compound. The existing differences can be explained by using different mathematical methods within the software package. By comparing the calculated partition coefficient, it is notable that the highest values are obtained for derivatives with –Br and $–C_2H_5$ as the less polar substituents, and the lowest for the compound with the most polar –OH group.

3.2. The determination of lipophilicity of diphenylacetamide derivatives using RPTLC

Given the similarities in the intermolecular interactions which determine the chromatographic and biological behavior of the compounds, for the studied diphenylacetamides, chromatographic parameters, R_M^0 and *m*, were determined by using RPTLC in two organic modifiers- acetic acid and dimethylsulfoxide (Table 4).

The validity of the linear dependence between the retention factor, R_M, and the volume fraction of the organic modifier, φ, in the selected field of experimental work is confirmed by the high values of the regression coefficient, r.

From Table 4 it is noticeable that the value of the slope, *m*, follows the same trend of changes as the value of intercept R_M^0, for all the investigated derivatives in both applied organic modifiers. It was assumed that both chromatographic parameters are dependent on the same physical-chemical parameters, and with this aim they were correlated by the linear regression method. The equations of the obtained linear R_M^0-*m* dependencies are given in Table 5.

The results from Table 5 show that slightly higher dependence was obtained in dimethylsulfoxide.

Table 4. The parameters of the chromatographic equations R_M^0, m, r obtained in the applied organic modifiers

R	modifier					
	acetic acid			DMSO		
	R_M^0	*m*	r	R_M^0	*m*	r
H	1.613	-3.302	0.998	1.705	-3.435	0.999
CH_3	1.840	-3.503	0.999	1.991	-3.715	0.998
C_2H_5	2.106	-3.713	0.999	2.270	-3.931	0.998
OH	1.155	-2.818	0.999	1.255	-3.105	0.996
Cl	2.005	-3.649	0.998	2.134	-3.815	0.998
Br	2.095	-3.703	0.999	2.200	-3.893	0.999
F	1.795	-3.455	0.998	1.890	-3.609	0.999
CN	1.251	-2.951	0.996	1.365	-3.194	0.999
$COOCH_3$	1.355	-3.057	0.999	1.514	-3.316	0.999
$COCH_3$	1.301	-3.002	0.996	1.419	-3.240	0.996

Table 5. Equations of R_M^0- m relationships of the examined diphenylacetamides in used modifiers

Modifier	equations	r	P
DMSO	$R_M^0 = -2.509-1.215m$	0.999	< 0.0001
acetic acid	$R_M^0 = -1.944-1.084m$	0.998	< 0.0001

3.3. The correlation of experimentally and mathematically obtained lipophilicity parameters

In order to confirm that the chromatographic parameters, R_M^0 and *m*, can be used as alternative lipophilicity criteria of the tested diphenylacetamides, they were correlated with the software obtained partition coefficient, log *P*, as the standard measure of lipophilicity by linear regression.

The dependence of the chromatographic parameters R_M^0 and *m* obtained in the acetic acid from the partition coefficient, Clog *P*, are shown in Figure 1 and Figure 2, respectively.

Figure 1 and Figure 2 show the linear dependence between the software obtained lipophilic parameter Clog *P* and the chromatographic parameters R_M^0 and *m* obtained in acetic acid. From the linear dependence obtained in acetic acid derivatives with polar substituents, which is not observed in the case of dimethylsulfoxide. Table 6 shows the correlation matrix obtained as a result of the linear regression between the experimentally and mathematically obtained parameters of lipophilicity.

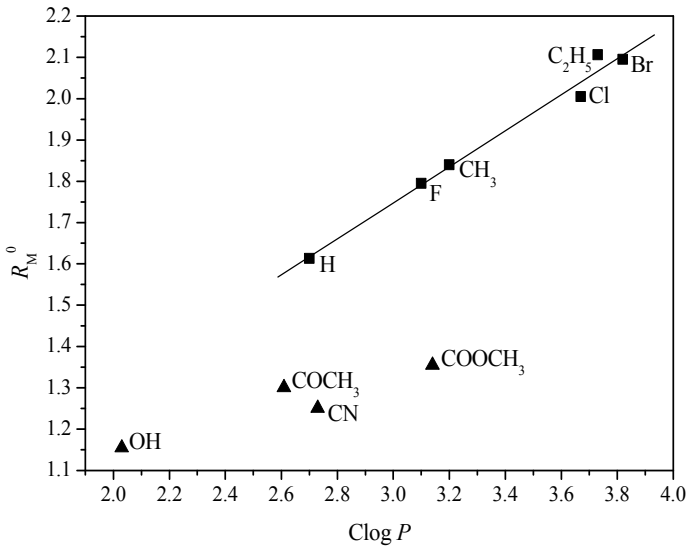


Figure 1. Dependence of chromatographic retention constant R_M^0 determined in acetic acid from Clog P

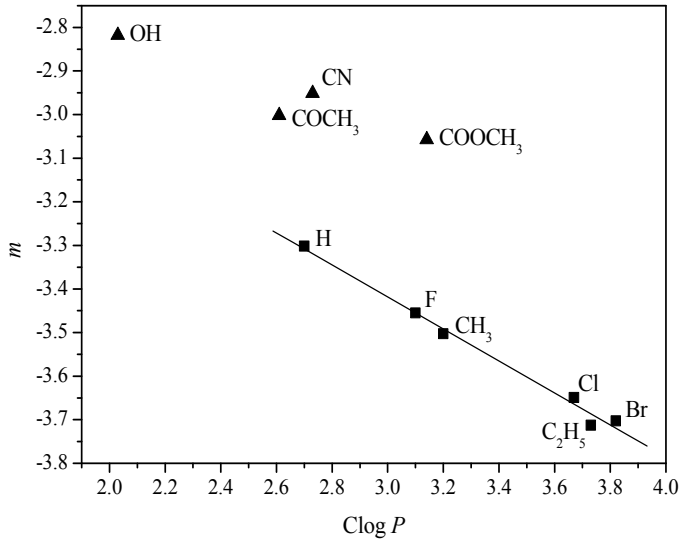


Figure 2. Dependence of chromatographic parameter m determined in acetic acid from Clog P

Table 6. Statistical parameters for the obtained R_M^0-log P and m-log P dependence

log *P*	R_M^0	r	P	*m*	r	P
AClog *P*		0.956	< 0.0001		0.963	< 0.0001
Alog *P*		0.972	< 0.0001		0.977	< 0.0001
Mlog *P*		0.967	< 0.0001		0.966	< 0.0001
milog *P*	DMSO	0.958	< 0.0001	DMSO	0.964	< 0.0001
kowwin		0.906	0.0003		0.911	0.0002
Xlog P_3		0.982	< 0.0001		0.985	< 0.0001
Clog *P*		0.911	0.0002		0.918	0.0002
AClog *P*		0.962	0.0021		0.968	0.0016
Alog *P*		0.971	0.0012		0.972	0.0011
Mlog *P*		0.919	0.0050		0.918	0.0050
milog *P*	acetic acid	0.978	0.0007	acetic acid	0.979	0.0006
kowwin		0.965	0.0018		0.962	0.0022
Xlog P_3		0.972	0.0012		0.974	0.0010
Clog *P*		0.992	< 0.0001		0.995	< 0.0001

Based on the statistical parameters shown in Table 6 (r and P), it can be seen that, on average, better relationships of partition coefficients were established with the chromatographic parameters determined in DMSO. Among partition coefficients, the best agreement with the R_M^0 and m showed Xlog P_3 and the weakest partition coefficient *kowwin*.

The obtained linear R_M^0-log *P* and *m*-log *P* dependence indicate the reliable applicability of thin layer chromatography on reversed phase for determination of lipophilicity of the selected diphenylacetamide derivatives.

3.4. The correlation of chromatographic parameters R_M^0 and *m* with selected parameters of toxicity

In addition to its positive effects, the application of the newly synthesized bioactive compound is conditioned by its negative effects on the ecosystem. In order to evaluate the potential toxicity of the studied diphenylacetamides, values of the effective concentration, EC_{50}, $mgkg^{-1}$, as acute toxicity criteria for the selected organisms (Algae, Daphnia, Medaka and Minnow) were calculated using the software package preADME (Table 7).

Table 7. Software calculated values of EC_{50} of studied diphenylacetamide for the selected organisms

R	Algae	Daphnia	Medaka	Minnow
H	0.100	0.184	0.048	0.046
CH_3	0.058	0.109	0.018	0.024
C_2H_5	0.039	0.058	0.005	0.012
OH	0.078	0.197	0.057	0.047
Cl	0.045	0.075	0.009	0.014
Br	0.038	0.059	0.006	0.011
F	0.078	0.149	0.032	0.022
CN	0.084	0.143	0.032	0.034
$COOCH_3$	0.071	0.161	0.040	0.046
$COCH_3$	0.078	0.189	0.054	0.060

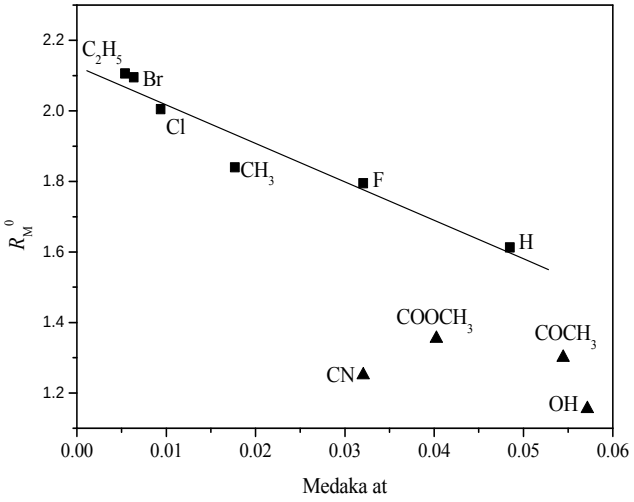


Figure 3. Dependence of chromatographic retention constant R_M^0 determined in acetic acid from Medaka at

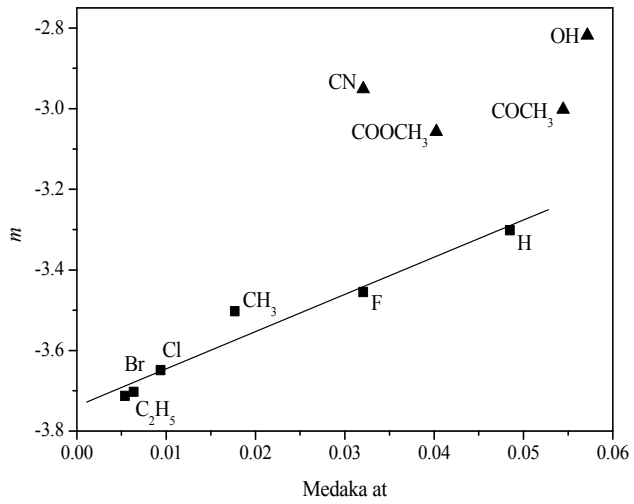


Figure 4. Dependence of chromatographic parameter m determined in acetic acid from Medaka at

Figure 3 and Figure 4 show that R_M^0-Medaka at and *m*-Medaka dependence obtained in acetic acid are linear. Also, it is evident that the compounds with polar substituents deviate from this dependence, which is also noticed in the case of dimethylsulfoxide. The correlation matrix obtained as a result of linear regression analysis between the chromatographic parameters (R_M^0 and *m*) and the EC_{50} values of the studied derivatives for the selected test organisms are shown in Table 8.

Table 8. Correlation matrix obtained for R_M^0-EC_{50} and m-EC_{50} dependence

toxicity parameter	R_M^0	r	P	*m*	r	P
Algae at	DMSO	0.982	0.0005	DMSO	0.989	0.0002
Daphnia at		0.989	0.0002		0.992	< 0.0001
Medaka at		0.978	0.0007		0.986	0.0003
Minnow at		0.935	0.0050		0.942	0.0050
Algae at	acetic acid	0.974	0.0010	acetic acid	0.981	0.0005
Daphnia at		0.983	0.0004		0.988	0.0002
Medaka at		0.966	0.0017		0.975	0.0010
Minnow at		0.944	0.0046		0.949	0.0038

The statistical parameters in Table 8 show that slightly better R_M^0-EC_{50} and the *m*-EC_{50} dependence were obtained in the case of dimethylsulfoxide. Besides, data in Table 8 confirm the assumption that the chromatographic parameters R_M^0 and *m*, of examined diphelyacetamide derivatives, obtained by thin-layer chromatography on reversed phase, can be used to estimate their environmental toxicity.

4. CONCLUSION

The selected derivatives of diphenylacetamide have been studied with the aim of predicting the existence of their biological activity using the rules of good bioavailability (the Lipinski Rule of 5 and the Ghose's rule), by determining their lipophilicity (experimentally and mathematically) and assessing their toxicity.

By applying thin-layer chromatography on reversed phase in the presence of two organic modifiers (acetic acid and dimethylsulfoxide), chromatographic parameters R_M^0 and *m* of the studied diphenylacetamide derivatives were determined. Satisfactory correlations of chromatographic parameters R_M^0 and *m* were established with software obtained partition coefficient, log *P*, as the standard measure of lipophilicity, as well as with a software obtained EC_{50} values of examined derivatives for various test organisms (Algae, Daphnia, Medaka and Minnow) by linear regression. The validity of the obtained linear dependence was confirmed by the values of statistical parameters (r and P).

All the obtained results confirm that the chromatographic parameters R_M^0 and *m* can be reliably applied to describe lipophilicity and to evaluate the ecotoxicity of the studied diphenylacetamides.

5. ACKNOWLEDGEMENTS

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6. REFERENCE

[1] S. M. Paul, D. S. Mytelka, C. T. Dunwiddie, C. C. Persinger, B. H. Munos, S. R. Lindborg, A. L. Schacht, *How to improve RD productivity: The pharmaceutical industry's grand challenge*, Nature Reviews Drug Discovery, Vol. 9 (2010) 203–214.

[2] D. W. Borhani, D. E. Shaw, *The future of molecular dynamics simulations in drug discovery*, Journal of Computer-Aided Molecular Design, Vol. 26 (2012) 15–26.

[3] A. K. Ghose, V. N. Viswanadhan, J. J. Wendoloski, *A knowledge-based approach in designing combinatorial or medicinal chemistry libraries for drug discovery. 1. A qualitative and quantitative characterization of known drug databases,* Journal of Combinatorial Chemistry, Vol. 1 (1999) 55–68.

[4] C. A. Lipinski, *Lead- and drug-like compounds: The rule-of-five revolution*, Drug Discovery Today Technologies, Vol. 1 (2004) 337–341.

[5] D. R. M. Moreira, D. S. Santos, R. F. D. Espírito Santo, F. E. D. Santos, G. B. de Oliveira Filho, A. C. L. Leite, M. B. P. Soares, C. F. Villarreal, *Structural improvement of new thiazolidinones compounds with antinociceptive activity in experimental chemotherapy-induced painful neuropathy*, Chemical Biology and Drug Design, Vol. 90 (2017) 297–307.

[6] A. Galano, *Computational-aided design of melatonin analogues with outstanding multifunctional antioxidant capacity*, RSC Advances, Vol. 6 (2016) 22951–22963.

[7] X. Liu, B. Testa, A. Fahr, *Lipophilicity and its relationship with passive drug permeation*, Pharmaceutical Research, Vol. 28 (2011) 962–977.

[8] S. Münch, J. Wohlrab, R.H.H. Neubert, *Dermal and transdermal delivery of pharmaceutically relevant macromolecules*, European Journal of Pharmaceutics and Biopharmaceutics, Vol. 119 (2017) 235–242.

[9] T. Fujita, J. Iwasa, C. A. Hansch, *A new substituent constant, π, derived from partition coefficients*, Journal of the American Chemical Society, Vol. 86 (1964) 5175–5180.

[10] A. Leo, C. Hansch, D. Elkins Partition coefficients and their uses, Chemical Review, Vol. 71 (1971) 525–616.

[11] H. Kalász, B. Benko, Zs. Gulyás, K. Tekes, *Lipophilicity determination using both TLC and calculations*, Journal of Liquid Chromatography and Related Technologies, Vol. 32 (2009) 1342–1358.

[12] R. D. Naşcu-Briciu, C. Sârbu, *Lipophilicity of oils and fats estimated by TLC*, Journal of Separation Science, Vol. 36 (2013) 1317–1326.

[13] Đ. Vaštag, S. Apostolov, B. Matijević, J. Nakomčić, A. Marinković *Retention behavior and biological activity of N-substituted-2-phenylacetamide derivates*, Contemporary Materials, Vol. V−1 (2014) 124–132.

[14] S. Apostolov, Đ. Vaštag, B. Matijević, J. Nakomčić, A. Marinković, *Studying of retention behavior, lipophilicity and pharmacokinetic characteristics of N-substituted phenyl-2-chloroacetamides*, Contemporary Materials, Vol. V−1 (2014) 101–110.

[15] L. R. Jevrić, S. O. Podunavac-Kuzmanović, J.V. Švarc-Gajić, S. Z. Kovačević, B. Ž. Jovanović, *RP-HPTLC retention data in correlation with the In-silico ADME properties of a series of s-triazine derivatives*, Iranian Journal of Pharmaceutical Research, Vol. 13 (2014) 1203–1211.

[16] Gy. Vastag, S. Apostolov, B. Matijević, S. *Petrović, Establishing dependence between different lipophilic parameters, of new potentially biologically active N-substituted-2-phenylacetamide derivatives by applying multivariate methods*, Journal of Chromatographic Science, Vol. 53 (2015) 312–319.

[17] T. Djaković Sekulić, G. Vastag, K. Tot, J. Tot, A. Lazić, *Quantitative structure-retention relationships modeling and multivariate data analysis of lipophilicity data of new spirohydantoin derivatives,* Journal of Planar Chromatography - Modern TLC, Vol. 29 (2016) 281–286.

[18] M. Dąbrowska, M. Starek, Ł. Komsta, P. Szafrański, A. Stasiewicz-Urban, W. Opoka, *Assessment of the chromatographic lipophilicity of eight cephalosporins on different stationary phases*, European Journal of Pharmaceutical Sciences, Vol. 101 (2017) 115–124.

[19] J.S. Rogers, S.J. Rehrer, N.R. Hoot, *Acetylfentanyl: An Emerging Drug of Abuse*, Journal of Emergency Medicine, Vol. 50 (2016) 433–436.

[20] L. P. Guan, B. Y. Liu, Y. C. Quan, L. Y. Yang, X. H. Zhen, S.H. Wang, *Synthesis and evaluation of phenyliminoindolin-containing phenylacetamide derivatives with the antidepressant and anticonvulsant effects*, Medicinal Chemistry, Vol. 12 (2016) 786–794.

[21] D. Kadadevar, K. C. Chaluvaraju, M. S. Niranjan, C. Sultanpur, S. K. Madinur, M. Nagaraj, Hegde, M. Smitha, K. Chakraborty*, Synthesis of N-(substituted phenyl)-2 [5- phenyl-2H-1, 2, 4-triazol-3ylamino] acetamide as anticonvulsant*, International Journal of ChemTech Research, Vol. 3 (2011) 1064–1069.

[22] D. A. Babkov, A. L. Khandazhinskaya, A. O. Chizhov, G. Andrei, R. Snoeck, K. L. Seley-Radtke, M.S. Novikov, *Toward the discovery of dual HCMV-VZV inhibitors: Synthesis, structure activity relationship analysis, and cytotoxicity studies of long chained 2-uracil-3-yl-N-(4-phenoxyphenyl)acetamides*, Bioorganic and Medicinal Chemistry, Vol. 23 (2015) 7035–7044.

[23] R. Sawant, D. Kawade, *Synthesis and biological evaluation of some novel 2-phenyl benzimidazole-1-acetamide derivatives as potential anthelmintic agent*, Acta Pharmaceutica, Vol. 61 (2011) 353–361.

[24] T. Seenivasagan, L. Guha, *Forced egg retention induced by diethyl-phenylacetamide diminishes the fecundity and longevity of dengue vectors*, Journal of Vector Borne Diseases, Vol. 52 (2015) 309–313.

[25] B. Li, X. Lin, Y. Zhang, D. Zhang, Y. Xiao, F. Lin, *Synthesis and characterization of novel N-phenylacetamide bearing 1,2,4-triazole derivatives as potential antimicrobial agents*, Chemical Research in Chinese Universities, Vol. 33 (2017) 70–73.

[26] J. H. Tailor, P. C. Patel, G. M. Malik, *Synthesis, characterization and antimicrobial activity of 2-(11-oxodibenzo [b,f][1,4]thiazepin-10(11H)-yl)-N (substituted phenyl) acetamide derivatives*, Indian Journal of Chemistry - Section B Organic and Medicinal Chemistry, Vol. 53B (2014) 1263–1268.

[27] V. S. Bhadauria, V. Sravanthi, S. Kumar, D. Das, E. De Clercq, D. Schols, H. Tokuda, S. S. Karki, *Synthesis and cytotoxic evaluation of some 2-{4-[(2-oxo-1,2-dihydro-3h-indol-3-ylidene)methyl] phenoxy}-N-phenylacetamide*, Acta Poloniae Pharmaceutica - Drug Research, Vol. 74 (2017) 137–145.

[28] A. Aliabadi, A. Mohammadi-Farania, S. Seydikangarshahib, F. Ahmadia, *Discovery of 2-(1,3-dioxoisoindolin-2-yl)-n-phenylacetamide derivatives as probable 15-lipoxygenase-1 inhibitors with potential anticancer effects*, Farmacia, Vol. 65 (2017) 268–274.

[29] S. Ihmaid, H. E. A. Ahmed, A. Al-Sheikh Ali, Y. E. Sherif, H. M. Tarazi, S. M. Riyadh, M. F. Zayed, H. S. Abulkhair, H. S. Rateb, *Rational design, synthesis, pharmacophore modeling, and docking studies for identification of novel potent DNA-PK inhibitors*, Bioorganic Chemistry, Vol. 72 (2017) 234–247.

[30] V. D. Janković, D. Ž. Mijin, S. D. Petrović, *Conformations of N-(4-substituted phenyl)-2-phenylacetamides*, Book of abstracts, 6th International Conference on Fundamental and Applied Aspects of Physical Chemistry, Belgrade, 2002, 117–119.

[31] G. L. Biagi, A. M. Barbaro, A. Sapone, M. Recanatini, *Determination of lipophilicity by means of reversed-phase thin-layer chromatography I. Basic aspects and relationship between slope and intercept of TLC equations*, Journal of Chromatography A, Vol. 662 (1994) 341–361.

[32]http://www.vcclab.org (September 2013).

[33]http://www.molinspiration.com (May 2017).

[34]https://preadmet.bmdrc.kr/ (June 2017).

ПРОУЧАВАЊЕ ЛИПОФИЛНОСТИ И ПРОЦЕНА ТОКСИЧНОСТИ ДЕРИВАТА ДИФЕНИЛАЦЕТАМИДА

Сажетак: Савремени приступ у проучавању биолошки активних једињења обухвата успостављање зависности између структуре молекула, физичко-хемијских својстава и понашања које изучавано једињење може испољити у неком биолошком медијуму. Ова испитивања се врше у раним фазама дизајна будућег биоактивног агенса и захтевају познавање молекулских дескриптора који могу указати на његову биолошку активност, међу којима липофилност заузима кључно место. За серију деривата дифенилацетамида, липофилност је одређена експериментално, применом танкослојне хроматографије на обрнутим фазама (RP TLC18 F_{254s}), у смешама воде и различитих органских модификатора, као и рачунски, применом релевантних софтверских пакета. У циљу процене потенцијалне акутне токсичности испитиваних деривата дифенилацетамида, одређене су вредности њихове ефективне концентрације, $EC_{50,}$ на одабране тест организме. Експериментално одређена липофилност (R_M^0 и m) је корелисана са стандардним мерилом липофилности (log P), као и са одабраним параметрима токсичности, при чему је утврђено да се танкослојна хроматографија на обрнутим фазама може поуздано користити за описивање липофилности и процену токсичних ефеката деривата дифенилацетамида.

Кључне речи: дифенилацетамиди, RP TLC, log P, токсичност.