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RETENTION BEHAVIOR AND BIOLOGICAL ACTIVITY OF N-SUBSTITUTED-2-PHENYLACETAMIDE DERIVATES

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Abstract: Phenylacetamide derivatives are a group of compounds that exhibit a wide range of biological activities as analgetic, anticonvulsant, pesticide, cytostatic. It is well known that the biological activity and the field of activity of the substance are greatly dependent on its physical, chemical and structural properties. In this paper, we applied QSRR analysis (Quantitative Structure Retention Relationships), which is based on the prediction of biological properties of compounds based on their chromatographic retention behaviors. To that end, retention constants of investigated N-substituted-2-phenylacetamide were determined by reversed phase thin-layer chromatography, (HPTLC RP18 F_{254s}) in the presence of different volume fractions of *n*-propanol and tetrahydrofuran. The resulting data were correlated with molecular descriptors determined in different ways in order to establish the mathematical model that describes the relationship between retention properties and biological activities of investigated phenylacetamides.

Keywords: N-substituted-2-phenylacetamide, QSRR analysis, TLC, R_M^0.

1. INTRODUCTION

Amide derivatives have been the subject of many studies due to their broad spectrum of biological activities such as analgesic [1,2], anticonvulsant [3], fungicidal [4,5], cytostatic [6,7], and so on. The amide functional group, which from the chemical point of view represents a basic building block of proteins, is prone to build secondary bonds inside and outside of molecule. The existence of secondary chemical bonds of the amide groups and the presence of different functional groups in the amide molecule can significantly affect the chemical properties of the amide derivatives and hence their biological activity [8]. For these reasons, the knowledge of the behavior of the amide functional group, its physical, chemical and structural characteristics of both well-known and newly synthesized compounds may contribute to the correct prediction of the potential biological activity of the compound.

Parameters used to quantify the features of molecules are called descriptors. They are a result of logical and mathematical procedure which enables the conversion of chemical information encoded within a symbolic representation of molecules in a numeric value. To date over 5000 molecular descriptors have been defined [9]. There is an increasingly evident tendency to establish mathematical models that describe the required properties of molecules using the appropriate descriptors. The most well-known mathematical model is QSAR, which describes correlation between the structure of the molecule and its activity; another equally frequently used model is QSRR (Quantitative Structure Property Relationship), which has an ability of quantifying the relationship between the structure of the molecule and its chromatographic retention behavior.

One of the mostly used physicochemical parameters of molecule, which orders the activity of a bioactive compound is its lipophilicity. Lipophilicity of the molecule determines its transport through a biological system. It can affect the interaction between the compound and receptor or biomacromolecule. Usually, log *P* (the logarithm of the ratio of the concentrations of solute in a saturated 1-octanol-water system) is used as a standard measure of lipophilicity. The reversed-phase thin-layer chromatography (RP-TLC) belongs to one of the alternative methods for determining lipophilicity of molecules [27−29]. Experimentally obtained values of chromatographic retention parameter, R_M^0, by reversed-phase thin-layer chromatography is widely used as a measure of lipophilicity, instead of reference lipophilicity parameter, log *P*. Due to the simi-

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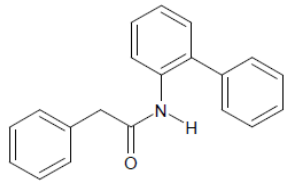
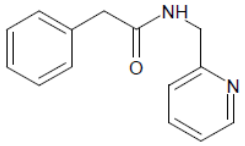
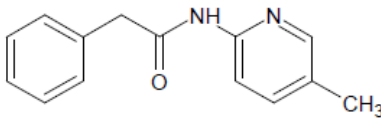
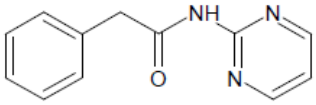
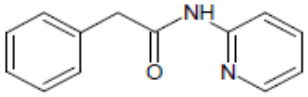
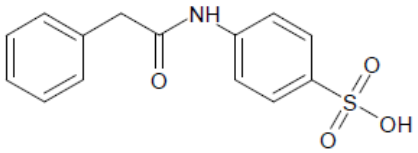
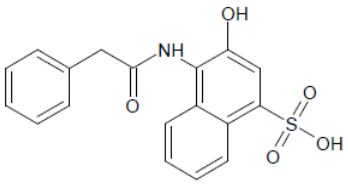
larity in intermolecular effects that determines the behavior of compounds in biological and chromatographic systems, retention constant is also widely used as a measure of lipophilicity [10−12].

The aim of this study was to investigate the effect of the solvent and the substituents on retention, i.e. lipophilic properties of the given molecule and to determine whether the chromatographic retention constant of the investigated compounds can be used as a measure of their lipophilicity. To that end, the experimentally determined lipophilicity of N-substituted-2-phenylacetamides is correlated with the standard measure of liphophilicity, log *P*, which was determined mathematically. Examining, visualization of similarities and differences between chromatographically and mathematically obtained lipophilicity, also as a selection of the compounds based on the chemical properties of the functional groups were performed by linear regression analysis (LR) and multivariate analysis – Principal component analysis (PCA).

2. EXPERIMENTAL

The structures of the investigated compounds are presented in Table 1.

Table 1. Structures of the investigated N-substituted-2-phenylacetamides

The investigated compounds			
D_2		**D_{13}**	
D_4		**D_{15}**	
D_5		**D_{16}**	
D_{11}			

During the experimental determination of lipophilicity, on commercial RP TLC C_{18}/UV_{254} plates (Macherey-Nagel) aliquots of 0.2μL of 5% solutions of investigated compounds prepared in ethanol were spotted. The plates were developed in normal unsaturated chambers at 25^0C by ascending technique with aqueous solutions of two organic modifiers: n-propanol (φ = 0.32–0.50, v/v) and tetrahydrofuran (φ = 0.40−0.56, v/v). After development and drying, plates were examined under a UV light at λ = 254 nm as dark spots. At least three chromatograms were developed for each combination of solvent-solute and the average R_f values were calculated. The obtained experimental data were processed by software package Origin, version 6.1. Standard lipophilicity values, log *P*, were calculated using virtual Computational Chemistry Laboratory, VccLab 2007. Multivariate analysis was performed by Statistica v.12 software (StatSoft Inc., Tulsa, OK, USA).

3. RESULTS AND DISCUSSION

3.1 Determination of retention behavior of the investigated N-substituted-2-phenylacetamide derivatives using reversed phase thin layer chromatography

In order to determine lipophilicity of the tested N-substituted-2-phenylacetamide derivatives experimentally, chromatographic retention constants, R_M^0, of phenylacetamides were determined using thin-layer chromatography on reversed phase, RP 18 F254s HPTLC in the presence of different amount of one protic (*n*-propanol) and one aprotic solvent (tetrahydrofuran) in the mobile phase. Based on the experimentally determined R_f values for each composition of the mixture R_M values were calculated using the equation (1):

$$R_M = \log\left(\frac{1}{R_f} - 1\right) \quad (1)$$

Dependence R_M in the function of volume fraction of organic solvent is given by the equation (2):

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

The parameters of the given equation which were determined by linear regression: the value of intercept (R_M^0), slope of linear plots (m) and regression coefficients, (r) obtained for used organic solvents are presented in Table 2. The high values of regression coefficient confirm that linear relationships are valid in the chosen field of work for both organic modifiers.

Table 2. Parameters of chromatographic equations, R_M^0, m and r, in used solvents

Compounds	*n*-propanol			tetrahydrofuran		
	R_M^0	*m*	*r*	R_M^0	*m*	*r*
D2	1.919	−4.055	0.99	2.752	−4.468	0.95
D4	1.336	−3.137	0.99	2.269	−3.761	0.99
D5	1.076	−2.659	0.99	1.738	−2.865	0.99
D11	−0.686	−3.283	0.99	0.559	−1.920	0.99
D13	0.962	−2.431	0.99	1.048	−1.997	0.99
D15	0.634	2.103	0.99	0.827	−1.793	0.99
D16	−0.827	−0.300	0.96	−0.192	−1.459	0.99

From the results presented in Table 2 it is evident that the retention behavior of the investigated N-substituted-2-phenylacetamide derivatives is influenced by the nature of the substituent *R* related to the nitrogen atom of the amide group, as well as the used organic modifier. Because of this there is different interaction that occurs between applied organic modifier and the investigated amides during chromatographic analysis. Two kinds of interactions are dominant in the case of investigated phenylacetamides: hydrophobic interactions of substituent *R* with the non-polar stationary phase and polar interactions of the amide group with mobile phase. For all investigated compounds, as expected, stronger retentions were detected in the presence of aprotic, non polar tetrahydrofuran compared to protic *n*-propanol. From the retention data in Table 2 it can be seen that the nature of the substituent related to the nitrogen atom of the amide group has much bigger influence on the retention behavior of the compounds compared to the selected organic solvent. That the compounds, which differ by the type of substituent, have different retention in the same solvent can be explained by the influence of the nature of the substituent related to the nitrogen atom of the amide group on the possibility of molecule to form intermolecular interactions. The obtained results for phenylacetamide derivatives are typical for chromatographic retention behavior in reversed phase thin layer chromatography. Increased nonpolarity of substituent leads to extended staying molecule in non polar stationary phase, and thus to stronger retention. In the case of investigated phenylacetamides the highest retention, in both used solvents were registered for compound D2. The obtained results are in line with the expectations, given that this compound has the least polar substituent, diphenyl group. The lowest retention and the fastest movement through the chromatographic system were observed in the case of D16, which as a substituent has the most polar SO_3H group. Compounds D4 and D5 differ in the presence of one CH_3 in the pyrimidine ring. The introduction of additional alkyl groups in the molecule phenylacetamides as expected leads to an increased retention of compounds with respect D4 to D5. The opposite effect is observed in the case

when non polar CH_2 group is introduced between the pyridine ring and the rest of the molecule (D13 molecule compared to D5). The same phenomenon, reduction of retention, only much more intense, is registered when introducing additional nitrogen heteroatom in the pyridine ring (D15 compared to D5).

3.2. Determination of lipophilicity of N-substituted-2-phenylacetamide derivatives using mathematical methods

Today, in addition to experimental techniques, determination of lipophilicity of newly synthesized compounds, is increasingly performed by various mathematical methods based on the structure of the compounds. Table 3 shows, the values of partition coefficient, log*P*, of N-substituted-2-phenylacetamides calculated using different mathematical methods in the software package VccLab [13].

As data presented in Table 3 show, obtained values for partition coefficient, log*P*, as standard measures of lipophilicity, differ from each other for the same compound. This fact can be explained by different ways of calculating. Although the obtained values log*P*, differ from each other, they should be in good correlation, as they describe one and the same phenomenon – distribution of a given compound in the system of 1-octanol-water. Table 4 shows the correlation matrix of log *P* values obtained by using different mathematical methods.

It is evident from the data presented in Table 4, that there is a good agreement between partition coefficients obtained by various computational methods. The highest correlation was observed between milog*P* and AClog*P*, while the lowest was registered in the case of xlog*P* and *kowwin*.

Table 3. Values of partition coefficient, log P, obtained by mathematical methods

Compounds	AClog*P*	AB/log*P*	milog*P*	Alog*P*	Mlog*P*	*kowwin*	xlog*P*
D2	4.55	4.47	4.67	4.17	4.33	4.01	3.61
D4	2.50	2.37	2.47	2.52	2.69	2.73	2.32
D5	2.27	1.96	2.02	2.04	2.43	2.18	2.20
D11	1.34	1.85	0.73	2.25	2.35	0.35	2.34
D13	1.68	1.29	1.45	1.93	1.61	1.53	1.60
D15	1.67	1.54	1.52	1.39	1.75	1.54	1.31
D16	0.46	0.34	−0.09	1.61	2.01	−0.35	1.81

Table 4. The correlation matrix of log P values obtained by using different mathematical methods.

	AClog*P*	ABlog*P*	milog*P*	Alog*P*	Mlog*P*	*kowwin*	xlog*P*
AClog*P*	1.00	0.97	0.99	0.90	0.88	0.96	0.82
ABlog*P*		1.00	0.96	0.93	0.92	0.89	0.88
milog*P*			1.00	0.87	0.85	0.98	0.77
Alog*P*				1.00	0.96	0.76	0.96
Mlog*P*					1.00	0.74	0.97
kowwin						1.00	0.65
xlog*P*							1.00

3.3. Correlation of lipophilic parameters obtained experimentally and by theoretical calculations

Comparing the data presented in Table 2 and Table 3 it is evident that the value of the retention constant and partition coefficients for the same compounds follow a similar trend. The highest value of partition coefficient as well as in the chromatographic analysis was registered in the case of compound D2, and the lowest value in the majority cases was obtained for compound D16, which is also consistent with the experimental data. In order to establish the dependence between standard measures of lipophilicity, log *P* calculated in different ways and experimentally determined lipophilicity (chromatographic retention constants, R_M^0), these two values were correlated using a linear regression analysis and multivariate analysis-principal component analysis (*PCA)*. Chemometrics access has an increasing application in interpreting lipophilicity of organic compounds based on their retention parameters,

while one the most frequently used methods is principal components analysis [14−18].

Correlation results obtained by using linear regression analysis for one of the calculated lipophilicity Alog *P* and chromatographic retention constants, R_M^0, are presented in Figure 1 obtained in propanol and in Figure 2 obtained in tetrahydrofuran as a modificator.

As it -can be seen in Figure 1, in *n*-propanol, linear dependence of these two parameters which describe lipophilicity was registered. The most polar compounds D11 and D16 can be registered, which therefore were not taken into account during the correlation. In the case when chromatographic constants are determined in tetrahydrofuran as a modifier, it can be observed that investigated compounds are grouped into two entities. One group formed compounds which have aromatic rings (D16, D11 and D2) as a substituent – *R* and the other group contains phenylacetamide derivatives that have heterocyclic group (D4, D5, D13 and D15) as substituent. Compounds which as a substituent –*R* have aromatic rings form one group (2, 9 and 11), while the second group contains phenylacetamide derivatives that have heterocyclic group as substituent (1, 3 − 8 and 10). A similar distribution of compounds was registered in the case of all determined log *P* values. The correlation matrix, obtained for correlation between various log *P* and R_M^0 obtained in n-propanol and tetrahydrofuran using linear regression analysis is presented in Table 5.

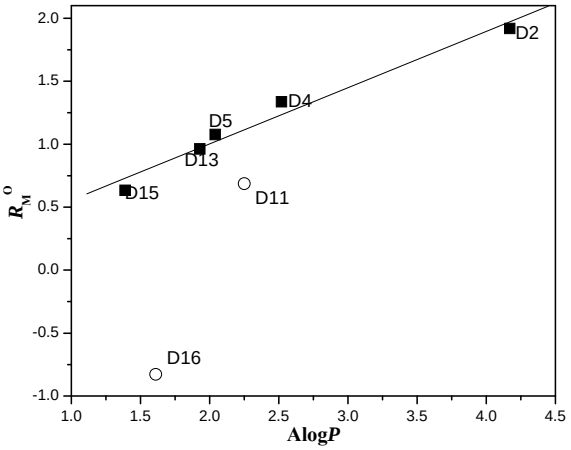


Figure 1. Relationships between Alog P and R_M^0, in propanol

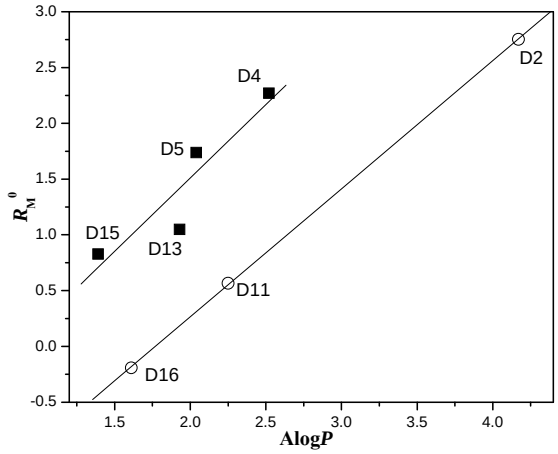


Figure 2. Relationships between Alog P and R_M^0, in tetrahydrofuran

The results presented in Table 5 confirm that good linear relationships exist between retention constants R_M^0 obtained by reversed-phase thin chromatography and standard measure of lipophilicity, log *P*. Higher correlation was registered in the case when tetrahydrofuran was used as a modifier than in the case of *n*-propanol. In tetrahydrofuran, for compound with aromatic substituents in all cases very good correlation between these two lipophilic parameters was obtained. While for compounds with heterocyclic substituents, correlation R_M^0 with AClog*P*, *kowwin* and milog*P* slightly stands out.

Obtained good linear relationships between chromatographic retention constants, R_M^0, in both modifiers and partition coefficients, log *P* as a standard measure for lipophilicity of the examined compounds confirm that the retention constants, R_M^0 obtained by thin-layer chromatography on reversed phase can be successfully used as a measure of lipophilicity of the newly synthesized derivatives N-substituted-2-phenylacetamides.

The correlation of investigated parameters of lipophilicity in addition to the method of linear regression was also obtained applying one multivariate method- principal component analysis (PCA).

The data matrix for PCA was formed in a way that rows (cases) correspond to the investigated phenylacetamide derivatives, whereas the columns (variables) correspond to the lipophilicity calculated in different ways. PCA is able to decompose the original retention data matrix into loading (retention data) and score (investigated compounds) vectors [19], whereby new variables are obtained, the so-called principal components, PC. The newly formed principal component, PC, represents a linear combination of the original variables. During the analysis more principal components are obtained. The first principal component (PC1) should account for a maximum of the total variance, the second PC

should be uncorrelated with the first one and should account for maximum residual variance, and so on until the total variance is accounted for. Other principal components are formed on the same principle, as long as the total variance is calculated. In this way elimination of redundant information is achieved as well as a big reduction of the volume of experimental data.

By applying PCA on the variables (lipophilicity determined in different ways), principal components are obtained, whose interdependence indicates the distribution (clustering) of investigated parameters of lipophilicity on the basis of their similarity. Figure 3 shows dependence of the first two principal components.

Table 5. Correlation matrix between log P determined by theoretical calculations and chromatographic parameters R_M^0 obtained in n-propanol and tetrahydrofuran

log*P*	R_M^0		
	n-propanol	*tetrahydrofuran*	
	without D11 and D16	Heterocyclic -*R*	Aromatic -*R*
ABlog*P*	0.94	0.94	0.99
AClog*P*	0.95	0.99	0.99
Alog*P*	0.99	0.93	0.99
kowwin	0.97	0.99	0.99
milog*P*	0.95	0.98	0.99
Mlog*P*	0.95	0.96	0.99
xlog*P*	0.98	0.97	0.99

In Figure 3, two specific groups of lipophilic parameters can be registered and appearance of one outlier. The first group is characterized by negative values of PC1 and positive values of PC2 and includes the following lipophilicity parameters: AClog*P*, milog*P*, *kowwin* and R_M^0 determined in tetrahydrofuran. In contrast, the second group includes lipophilic parameters both principal components of which are negative: ABlog*P*, Alog*P*, Mlog*P* and xlog*P*. Lipophilic parameter, R_M^0 measured in *n*-propanol appears as outlier. The obtained result for grouping parameters of lipophilicity suggests that the retention constant, R_M^0 determined in tetrahydrofuran is in better agreement with the standard criterion of lipophilicity than retention constants determined in *n*-propanol. The best agreement is achieved between parameters of lipophilicity that formed the same group, which is fully consistent with the results obtained in linear regression analysis.

Application of PCA on the tested phenylacetamide makes it possible to analyze their distribution on the basis of similarities and differences in their chemical structure (lipophilicity). Usually, in chromatographic analysis, a description of the total variance of 98% is required and generally accepted [20], what was achieved in the case of studied phenylacetamides, with two principal components (PC1 86,83% и PC2 11,22%). The resulting correlation of these two principal components of tested compounds is shown in Figure 4.

As it can be seen in Figure 4, the first principal component has the capability of classification of the compounds on the basis of their lipophilicity: the most lipohilic compound has the most negative value of PC1 (D2), while the most positive value of PC1 is registered in the case of the compound with the most polar group, D16. Similar occurrence was registered earlier also in the case of substituted phenylacetamide derivatives [18]. It is evident that the first two PCs performed almost a perfect classification of the compounds based on the nature of the substituent related to the nitrogen atom of the amide group. The existence of two groups of compounds could be registered. One group consists of compounds with both principal components negative and these are phenylacetamides with aromatic substituents (D16, D11 и D2), while in the second group separated compounds, unlike the first, have positive second principal components. The results are almost completely identical with those obtained using the linear regression analysis.

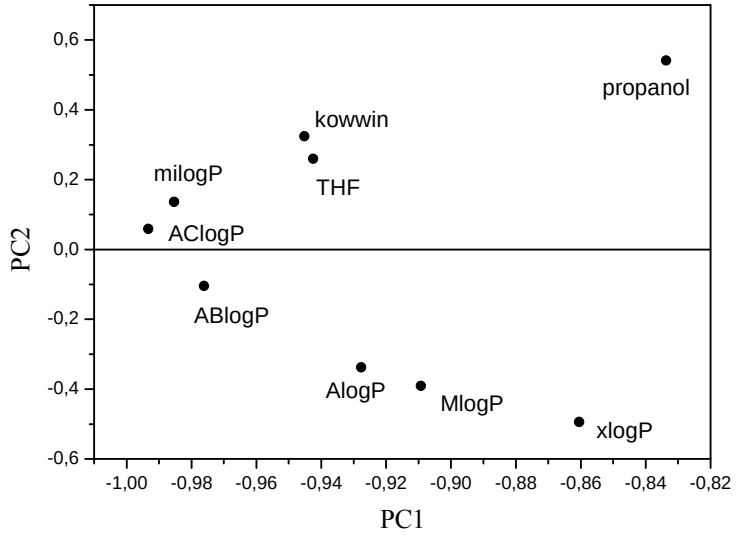


Figure 3. Loading plots as a result of PCA

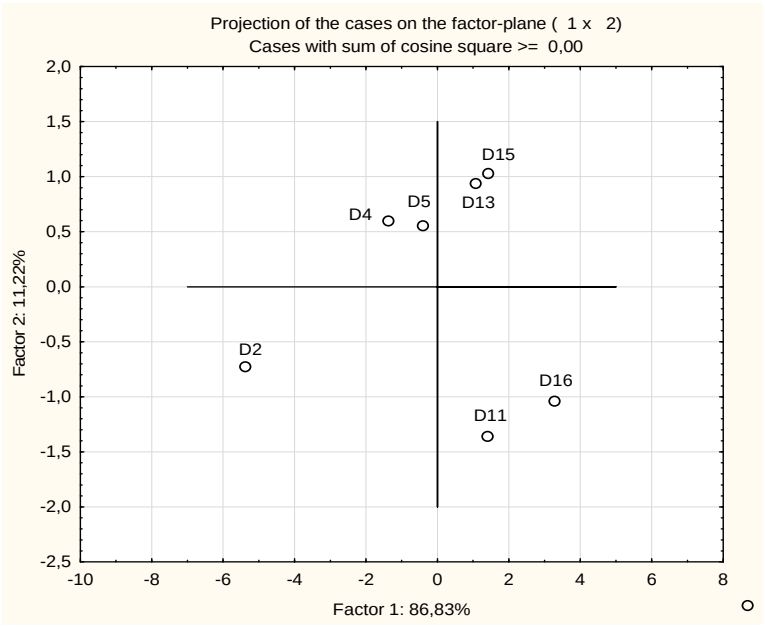


Figure 4. Score plots as a result of PCA

4. CONCLUSION

A group of newly synthesized N-substituted-2-phenylacetamides were investigated in order to determine their lipophilicity. Lipophilicity of derivatives of N-substituted-2-phenylacetamide was investigated in two ways, experimentally, applying thin-layer chromatography on reversed phase and by using software packages. The obtained results indicate that the chemical nature of the substituent related to the nitrogen atom of the amide group has a greater effect on retention of investigated derivatives than the selected organic solvent. Experimentally obtained R_M^0 as a measure of lipophilicity was compared with partition coefficient, log *P*, as a standard measure of lipophilicity by using classic linear regression analysis and principal component analysis. Both applied methods indicate that retention constants determined in tetrahydrofuran are in better correlation to the standard measure of lipophilicity than those obtained in *n*-propanol. The best agreement is obtained with AClog*P*, *kowwin* and milog*P*. This fact indicates that chromatographic retention constants, R_M^0, obtained by reversed phase thin layer chromatography can be used as a measure of lipophilicity of investigated N-substituted-2-phenylacetamides, respectively, to predict their potential biological activity.

5. ACKNOWLEDGEMENTS

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РЕТЕНЦИОНЕ ОСОБИНЕ И БИОЛОШКА АКТИВНОСТ ДЕРИВАТА N-СУПСТИТУИСАНИХ-2-ФЕНИЛАЦЕТАМИДА

Сажетак: Деривати фенилацетамида спадају у групу једињења која испољавају широк спектар билошке активности као што су аналгетска, антиконвулзивна, пестицидна, цитостатичка. Познато је да биолошка активност и поље деловања неке супстанце у великој мјери зависе од њених физичких, хемијских и структурних особина. У данашње вријеме све више се уочава тежња за успостављањем математичких модела који повезују ове особине молекула. У овом раду примијењена је QSRR анализа (Quantitative Structure Retention Relationships), која се заснива на предвиђању биолошких особина једињења на основу њиховог хроматографског ретенционог понашања. У том циљу одређене су ретенционе константе, R_M^0, испитиваних деривата N-супституисаних-2-фенилацетамида танкослојном хроматографијом на обрнутим фазама (HPTLC RP18 F_{254s}) у присуству различитих запреминских удјела *n*-пропанола и тетрахидрофурана. Добијене вриједности R_M^0 су корелисане са различитим молекулским дескрипторима у циљу успостављања математичког модела који описује везу између ретенционих особина и биолошке активности испитиваних фенилацетамида.

Кључне ријечи: N-супституисани-2-фенилацетамиди, QSRR анализа, TLC, R_M^0.

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