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Article

Prediction of the Lipophilicity of Nine New Synthesized Selenazoly and Three Aroyl–Hydrazinoselenazoles Derivatives by Reversed-Phase High Performance Thin-Layer Chromatography

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Using reversed-phase high-performance thin-layer chromatography and a methanol–water mixture as the mobile phase, the lipophilicity of 12 new synthesized derivatives is studied. The first eight compounds have as a basic chemical structure aryliden–hydrazinoselenazoles, and the second group of the three compounds belongs to aroyl–hydrazinoselenazoles. The linear correlation between R_{Mw} and the methanol–water ratios showed high values for the correlation coefficient. The chromatographic hydrophobic index is determined by using the ratio $-R_{Mw}/S$, and the obtained values ranged between 99 and 73. A good linear correlation is obtained between R_{Mw} and the slope. The log *P* values are calculated using ACD/Labs Software. The matrices are formed with R_{Mw} and log *P* and are subjected to a principal component analysis (PCA). The best way to extract information from PCA is graphically, by plotting the obtained matrices. By analyzing the scores, the compounds can be grouped as follows: a group containing nine compounds, and a second one containing three compounds. Each group of compounds has the same basic chemical structure.

Introduction

The determination of the log *P* values of substances with potential biological activity by reversed-phase liquid chromatography (RP-LC) can, in principle, overcome the difficulties of the conventional "shake-flask" method as proposed by Boyce and Milborrow (1). As known, lipophilicity can be defined on the basis of the partition of a given compound between *n*-octanol and water. Fujita et al. (2) have proposed the *n*-octanol–water partition coefficient ($P_{o/w}$) as a standard measure of the hydrophobicity of substances. Log $P > 0$ characterizes hydrophobic substances soluble in the lipid phase, while log $P < 0$ typifies polar compounds soluble in the water phase. In the present study, all compounds showed log $P > 0$ and are, therefore, hydrophobic. By reversed-phase thin-layer chromatography (RP-TLC), the lydrophobic character of the studied compounds could be predicted.

The RP-TLC equation for a given compound is a linear relationship between the R_M values and the organic solvent concentrations in the mobile phase. The R_M values can be calculated using the following relation:

$$R_M = \log[(1/R_f) - 1] (3).$$

By extrapolating the values of R_M at zero percent organic solvent, the R_{Mw} value can be obtained. The correlations between log *P* and the extrapolated R_{Mw} is frequently linear for congeneric series. Many studies (4–9) have shown that the lipophilicity and the specific hydrophobic surface of a solute can be determined from the linear relationship between R_{Mw} and the concentration of the organic phase in the mobile phase. Numerous papers report the use of RP-LC to establish an octanol–water partition coefficients, with correlation coefficients (R^2) in the range of 0.5–0.999, depending on the applied column and compounds under investigation (10–14).

Pericic-Janjic et al. (15) have studied the chromatographic behavior of 12 newly synthesized thiazoles using TLC methods. The RF values of the thiazoles, using a normal phase (NP) and the RP-TLC systems, were investigated. The retention for different mobile-phase modifiers and different stationary phases was compared. The correlation between the retention of the compounds studied in NP, RP-TLC, and log *P* was examined. Log *P* was calculated only for the water–*n*-octanol mobile phase, and ranged between 2.33 and 5.94. Also, the chromatographic behavior of some β-adrenoreceptor antagonists has been studied by RP-HPTLC on C_{18} using acetonitrile (ACN) and dioxane as organic modifiers (16). A good correlation was obtained between R_{Mw} and the slope of the chromatographic equations. These retention constants showed a good correlation with log *P* of β-adrenoreceptor antagonists, and can be used as a measure of the lipophilicity of these compounds.

A series of functionalized 2-alkylidene-4-oxothiazolidines and 1, 2-ditioles have been studied by RP-TLC on C_{18} silica plates using MeOH, THF, and acetone as organic modifiers (17). The lipophilicity was calculated as a ratio between R_{Mw} and the slope (S) of chromatographic equations. The lipophilicity data are in good agreement with the calculated log *P* values.

In order to understand the relationship between the S and the intercept (R_{Mw}) of the linear TLC equations, R_{Mw} can be considered as a measure of the repartition of the compound between two phases: a non-polar stationary phase and a polar (methanol–acetonitrile–water) mobile phase in RP-TLC. A new chromatographic hydrophobic index (φ_0) was introduced as a measure of the lipophilic character of compounds in RP-HPLC (18). The φ_0 values obtained with two different solvents (methanol or acetonitrile) showed an excellent correlation with each other (19). Significant correlations were obtained between the φ_0 values and log P_{ow} ($\varphi_0 = -\log k_w/S$). The relationship between the chromatographic hydrophobic indices and the solute descriptors, obtained by using several RP-HPLC methods, was investigated (20).

The hydrophobicity and specific hydrophobic surface area of 12 commercially available pesticides were determined by

chromatographic methods. PCA provided that the hydrophobicity parameters determined by RP-HPLC and RP-TLC are slightly different, and the compounds could not be distinguished according to their hydrophobicity parameter (21).

Gocan et al. (22) studied the prediction of the lipophilicity of some plant growth stimulators (amidoesters of ethanolamine and maleic and succinic acid derivatives) by RP-TLC, and the relationship between S and R_{Mw} of the TLC equations was established. A good correlation was obtained between log P vs. R_{Mw} and S. On the basis of these relationships, it was established that both series of the compounds are two congeneric series.

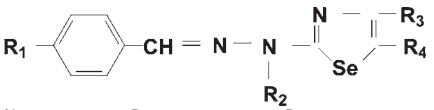
Mannhold et al. (23) used experimental values for R_{Mw} and 17 calculated descriptors of log P for molecular lipophilicity for investigating by multivariate analysis 159 compounds, with simple structures as well as more complex drug molecules. PCA of the entire database exhibits a clustering of chemical groups corresponding to chemical similarity. The acrylanilide derivatives were investigated by RP-TLC using acetone and methanol as the organic modifiers (24). The chromatographic parameter, R_{Mw}, and S values related to the molecular lipophilicity and to the specific hydrophobic surface area of the analytes were calculated. The relationships between the chromatographic parameters and the physicochemical characteristics were calculated by PCA, cluster analysis (CA), and a stepwise linear regression analysis. The CA calculation indicated the highest similarities between metalaxyl and furalaxyl, as well as between oxadixyl and RE26745.

Hydrophobicity of some pyridinium aldoximes were experimentally determined using RP-TLC and an aqueous–organic mobile phase (25). The hydrophobicity was estimated by using the R_{Mw} values obtained by extrapolating R_M to a zero organic phase in the eluent. The lipophilicities of the 18 ring-substituted phenol and aniline derivatives were determined by TLC (26). The chromatographic system consisted of alumina and silica as a thin-layer support impregnated with 2.5% and 10% paraffin oil in *n*-hexane in a combination with water–methanol in various percents as the mobile phase. The degree of impregnation exerts a greater impact on the retention than the character of the support. Not only are hydrophobic forces in the retention mechanism implicated, but also various steric and polarity parameters have significant influence.

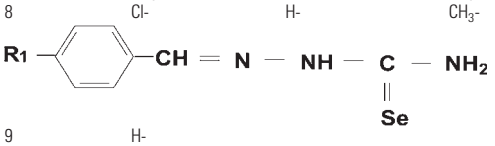
Experimental

The structures of the 12 new synthesized derivatives are presented in Table I. The first group of compounds (1–8 and 12) have the basic chemical structure belonging to aryliden–hydrazino-selenazoles, while the second group (9–11) have the basic chemical structure belonging to aroyl–hydrazinoselenazoles. Considering the anticancer activity obtained with the reference antineoplastic compound (doxorubicin) on both prostate DU145 and hepatocarcinoma HepG2 cancer cell lines, some of the compounds can be considered as promising anticancer candidates. Compounds 1, 2, 4, 6, 7, 8, and 11, showed 100% inhibition of DU145 proliferation at 25 μg/mL. Total inhibition (at 25 μg/mL) of HepG2 proliferation was also recorded with 1, 2, 4, 6, 8, and 11 (27, 28).

Table I
1-8 and 12 Aryliden-Hydrazino-Selenazoles and 9-11 Aroyl–Hydrazino- Selenazoles

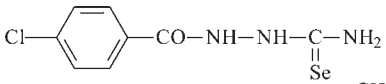


No	R_1	R_2	R_3	R_4
1	Cl-	H_3C-CO-	C_6H_5-	H-
2	Cl-	H-	CH_2Cl-	H-
3	Cl-	H_3C-CO-	CH_3-	H-
4	CH_3-O-	H-	C_6H_5-	H-
5	CH_3-O-	H_3C-CO-	CH_3-	H-
6	CH_3-O-	H_3C-CO-	C_6H_5-	H-
7	CH_3-O-	H-	CH_3-	H-
8	Cl-	H-	CH_3-	-CO_2-C_2H_5

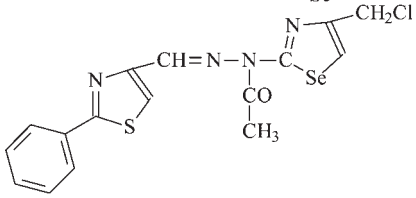


9	H-
10	CH3O-

11



12



RP-HPTLC

The RP-HPTLC was performed on silica gel plates (10 × 10 cm) RP-18WF254s, and methanol, as the mobile phase, was purchased from Merck (Darmstadt, Germany). The compounds' solutions were prepared in methanol (1 mg/mL), and 2 μL per spot were applied to the starting line. Before development, the chamber was saturated with the mobile phase (methanol–water) for 30 min. All developments were performed at room temperature. The migration distance of the eluent, between start and front, was 8 cm in all cases. Concentrations of the mobile phase (methanol–water) in different proportions between 50% to 70% with 5% increments were used. Detection was done by fluorescence quenching in UV light at λ = 254 nm.

For each solute at least three chromatograms were developed, and the R_f values were averaged. The R_M values were calculated by the classical formula:

$$R_M = \log[(1/R_f) - 1]$$

for each compound in each RP-HPTLC system:

$$R_M = {}_{RMw} + SX \qquad \text{Eq.1}$$

Where X is the concentration (%, v/v) of methanol in the mobile phase. The correlations showed good linearity, usually $R^2 > 0.99$. Taking into account Equation 1, R_{Mw} is a theoretical value (calculated) from the R_M values extrapolated to zero methanol concentration.

Computational methods

The log *P* values of selenazoly and aroyl–hydrazinoselenazoles derivatives from Table I were calculated using ACD/Lab Software (Toronto, Canada) (29). The character of the polarity surface plays an important role in establishing the hydrophobicity value (30). ACD/Log *DB* calculates an accurate Log *P* (octanol–water partition coefficient) for the neutral form of a molecule, in most cases with an accuracy of ± 0.3 Log *P* units or better. The calculation is based on an algorithm which uses the ACD/Log *P* database, containing one or more experimental Log *P* values for over 3600 structures with 500 different functional groups (31). The prediction is based on both atomic [Alog *P* (32)] and fragment (group, clog *P*, etc.) contributions. The program breaks the molecule into fragments, sums these constant fragment values, and uses structure dependent correction values taken from Hanch and Leo's database to predict Log *P* for several organic molecules (33).

Results and Discussion

The R_{Mw} value was obtained by an extrapolated to zero methanol concentration and S, respectively, of the linear relationship (1). A good linear correlation was found between R_M and *X*, characterized by high values for the correlation coefficient, R^2 (over 0.99). The results obtained for R_{Mw}, *S*, R^2, and φ_0 are shown in Table II.

The experimental values of the hydrophobic chromatographic index, can be calculated as:

$$\varphi_0 = -\log k_w'/S.$$

The isocratic retention factors, log *k*', for RP-HPLC are similar to the retention factor, R_M, for TLC. In RP-HPTLC, the chromatographic hydrophobic index is expressed by:

$$\varphi_0 = -R_{Mw}/S.$$

The results obtained for the compounds studied by RP-HPTLC are presented in Table II. The hydrophobic chromatographic index can be considered as a measure of the lipophilic character of compounds in RP-LC (18). The relationship between R_{Mw} and *S* is described by the following equation (where $R^2 = 0.8771$):

$$R_{Mw} = -86.07\ S + 0.006 \qquad \text{Eq.2}$$

Table II

R_{Mw}, Slope, and Hydrophobic Index (φ_0) Determinated Values

Nr. Compound	TLC			
	R_{Mw}	*S*	R^2	$\varphi_0 = -R_{Mw}/S$
1	3.49	−0.038	0.9831	92
2	2.63	−0.030	0.9949	87
3	2.00	−0.024	0.9794	84
4	2.17	−0.024	0.9817	91
5	1.63	−0.019	0.9826	86
6	2.68	−0.030	0.9913	91
7	1.57	−0.018	0.9813	88
8	3.57	−0.040	0.9949	90
9	2.73	−0.035	0.9981	77
10	3.00	−0.031	0.9823	98
11	2.83	−0.029	0.9938	99
12	2.32	−0.032	0.9795	73

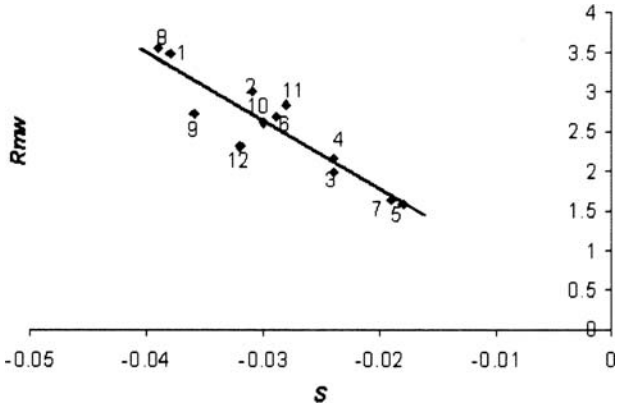


Figure 1. Relationship between RMw and S for 12 selenazoly.

Table III

R_{Mw} Experimental Values and Calculated Values log*P*

Nr. compound	R_{MW}	ACD/LogP	ALogP	xlogP	clogP	ACD/logD at pH	
						4.5	7.4
	1	2	3	4	5	6	7
1	3.48	4.41	4.26	4.94	4.05	3.89	3.89
2	2.62	3.34	3.37	4.07	3.76	3.33	3.33
3	1.99	3.11	3.05	3.23	2.22	1.31	1.31
4	2.17	4.20	3.61	4.84	4.79	4.12	4.12
5	1.62	2.48	2.37	2.52	1.42	0.61	0.61
6	2.68	3.78	3.60	4.23	3.25	3.19	3.19
7	1.57	2.90	2.38	3.12	2.96	2.01	2.01
8	3.56	4.90	4.61	4.92	5.16	4.89	4.89
9	2.73	0.47	0.92	2.48	1.91	–	–
10	3.00	0.60	0.90	2.40	1.83	–	–
11	2.83	1.49	1.73	2.72	2.35	–	–
12	2.32	0.33	0.77	2.13	0.54	–	–

The equation describes the correlation between the chromatographic parameter and the slope for a series of 12 compounds belonging to the selenazoly and aroyl–hydrazinoselenazoles derivatives. The φ_0 values are in agreement with their chemical molecular structures and with the chromatographic parameters, R_{Mw}. The chromatographic index for the studied compounds ranges from 73 to 99, indicating high hydrophobicity. Figure 1 represents an arrangement of the compounds in an increasing order of their hydrophobicity of selenazoly and aroylhydrazinoselenazoles derivatives.

The principal component analysis (PCA) is a technique useful to "summarize" all of the information contained in the x-matrix (Table III) in a form that is understandable by a simple performance. Table III presents various calculated lipophilicity descriptors, log *P*, for all 12 compounds corresponding of the R_{Mw} values experimentally determined.

The PCA works by decomposing the x-matrix as a product of two smaller matrices, which are called loadings and scores matrices. The best way to extract information from the PCA is graphically, by plotting the matrices to obtain 2D scores and loadings plots.

In order to get an overview of data, one should look at the scores plot of the two most important principal components (PCs) (Figure 2A). These plots represent the relative position of the objects in the two dimensional space of the principal

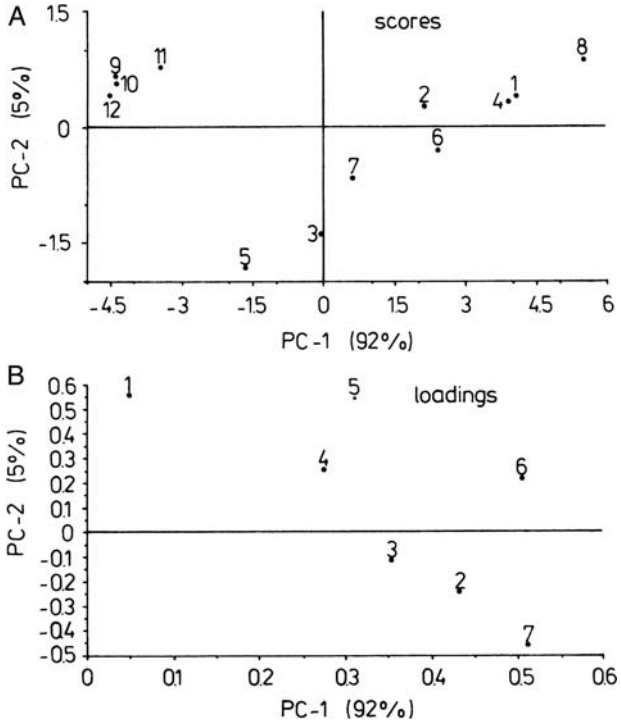


Figure 2. Scores (A) and loading (B) for 12 new selenazoly obtained by PCA methods.

components. The loadings define the size of the contribution of each original variable to the PCs. In addition, the loadings plot will provide an overview of the importance of the original variables (Figure 2B). PCA was performed to explore and visualize the similarities and differences among the compounds.

By analyzing the scores figure (Figure 2A), the following was found: the compounds from the first group (1–8) (acetylated hydrazinoselenazoles and hydrazinoselenazoles), are arranged in the right part, constituting one straight line, while the second group of compounds (9–12), are arranged in the left part. The compounds (9, 10, 11, and 12) form a cluster. These compounds have very similar R_{Mw}, A log *P*, and x log *P*, which mean they have very close *n*-octanol–water repartition coefficients (Table III).

In analyzing the scores (Figure 2A), one straight line between the compounds (1–8) may be found, described by the following equation (where: n = 1–8 and $R^2 = 0.8895$):

$$PC - 2 = 0.364(PC - 1) - 1.111 \quad \text{Eq.3}$$

The correlation between R_{Mw} and log *P* can be expressed by using an equation similar to the Collander equations (34) (where: n = 1–8 and $R^2 = 0.7596$):

$$ACDLog\,P = 0.940\,R_{Mw} + 1.326 \quad \text{Eq.4}$$

Furthermore, when Log *P* as a function of R_{Mw} was calculated, for the linear R^2, it was found to be a value of 0.7596 for ACD-Log *P*. This value is not good enough to draw the conclusion that all compounds form a congeneric series. Therefore, only the compounds that fit very well on a straight line were selected (namely, those showing a very small standard deviation for the slope) and the following equations were found (where: $n = 3, 6, 4, 1$ and $R^2 = 0.9999$ for Equation 5 and $n = 3, 6, 4, 1$ and $R^2 = 0.8518$):

$$PC - 2 = 2.319(PC - 1) + 3.1607 \quad \text{Eq.5}$$

$$ALog\,P = 0.684\,R_{Mw} + 1.861 \quad \text{Eq.6}$$

In this case, the compounds (1, 3, 4, and 6) have the same chemical basic structure, which explains the formation of a congeneric series with good correlation correlation (R^2) values (Equations 5 and 6). Also, analyzing the scores from Figure 2A, the compounds (5, 7, and 2) from the first group (1–8), are arranged in straight line in the middle part of the figures with a good linear R^2, as is shown Equation 7. The correlation between Alog *P* and R_{Mw} was done using the same argument mentioned herein. A very high R^2 of 0.9974 was obtained. In this circumstance, the compounds 5, 7, and 2 formed a congeneric series (Where: n = 5, 7, 2 and $R^2 = 0.8908$ for equation 7 and n = 5, 7, 2 and $R^2 = 0.9974$ for Equation 8).

$$PC - 2 = -0.762\,(PC - 1) - 1.9932 \quad \text{Eq.7}$$

$$ALog\,P = 0.9686R_{Mw} + 0.8307 \quad \text{Eq.8}$$

Furthermore, separation by reversed-phase chromatography is assumed to be similar to the extraction of compounds from water into an organic solvent such as *n*-octanol, where the more hydrophobic compounds are more strongly retained on the non-polar C_{18} stationary phase. The hydrophobic index, φ_0, for the studied compounds is shown in Table II. These values can be taken into account in the case of separation of these compounds by RP-HPLC. The retention time is a function of the chromatographic hydrophobic index values, and it increases with the increase of the hydrophobic index.

The loading plots represent the original variable in the two-dimensional space of the principal components. The loading of a single variable indicates the extent to which this variable participates in defining the PC. The square of the loadings indicates their percentage in the PC as can be seen in Figure 2B. The variable, which contributes the most, are plotted around the borders of the plot. On the other hand, the variables, having a small contribution to the PCs, have small loading values and are plotted around the center of the plot. In this case, as shown in Figure 2B, the R_{Mw} experimental value and ACD-Log *D*, at a calculated pH of 4–7, has the highest contribution to the percentage in the PCs.

Conclusion

RP-HPTLC is a suitable method for the determination of the chromatographic hydrophobicity index, φ_0, which may be used as a hydrophobic parameter for several compounds. Linear correlations between the chromatographic parameter, R_M, and the concentration of methanol in the mobile phase with a high $R^2 > 0.98$ were obtained. A good linear correlation between R_{Mw} vs. the slope was obtained for all compounds studied. By applying PCA to the matrices containing the chromatographic parameter R_{Mw}, in combination with computed log *P*, it was demonstrated that the compounds can be divided into two groups. The first group is formed of eight compounds, 1–8,

and the second of four compounds, 9–12. Each of these two groups showed similarities in the repartition coefficient *n*-octanol–water. In conclusion, RP-HPTLC is a simple method that allows for the determination of the chromatographic hydrophobic index rapidly and in ecological conditions.

References

1. Boyce, C.B.C.; Milborrow, B.V.A. A simple assessment of partition data for correlating structure and biological activity using thin-layer chromatography. *Nature* **1965**, *208*, 537–539.
2. Fujita, T.; Iavasa, J.; Hansch, C.J. A new substituent constant, π, derived from partition coefficient. *J. Am. Chem. Soc.* **1964**, *86*, 5175–5180.
3. Bate-Smith, E.C.; Westfall, R.G. Chromatographic behavior and chemical structure. 1. Some naturally occurring phenolic substances. *Biochim. Biophys. Acta* **1950**, *4*, 427–440.
4. Cserhati, T.; Forgacs, E.; Kiss, G.C.; Augustin, J. Effect of salts on the hydrophobicity parameters of sulfosuccinic esters studied by reversed-phase thin-layer chromatography. *J. Planar Chromatogr.* **1997**, *10*, 441–446.
5. Forgacs, E.; Cserhati, T.; Kaliszan, R.; Haber, P.; Nasal, A. Reversed-phase thin-layer chromatographic determination of the hydrophobicity parameters of non steroidal anti-inflammatory drugs. *J. Planar Chromatogr.* **1998**, *11*, 383–387.
6. Darwish, Y.; Cserhati, T.; Forgacs, E. Relationship between lipophilicity and specific hydrophobic surface area of a non-homologous series of pesticides. *J. Planar Chromatogr.* **1993**, *6*, 458–462.
7. Darwish, Y.; Cserhati, T.; Forgacs, E. Reversed-phase characteristics of some bioactive heterocyclic compounds. *J. Chromatogr. A* **1994**, *668*, 485–494.
8. Wallerstein, S.; Cserhati, T.; Fischer, J. Determination of the lipophilicity of some anti-hypoxia drugs: comparation of TLC and HPLC methods. *Chromatographia* **1993**, *35*, 275–280.
9. Cserhati, T.; Forgacs, E.; Hajos, G. Determination of the lipophilicity of fused-ring nitrogen heterocycles by reversed-phase thin-layer chromatography. *J. Planar Chromatogr.* **1998**, *11*, 64–69.
10. Gocan, S.; Irimie, F.; Cimpan, G. Prediction of the lipophilicity of some plant growth-stimulating amido esters of ethanolamine using reversed-phase thin-layer chromatography. *J. Chromatogr. A* **1994**, *675*, 282–285.
11. Cimpan, G.; Irimie, F.; Gocan, S. Prediction of the lipophilicity of some n-hydroxyethylamides of aryloxyalkylene and pyridine carboxylic acides by reversed-phase thin-layer chromatography. *J. Planar Chromatogr.* **1998**, *11*, 342–345.
12. Cimpan, G.; Gocan, S.; Olah, N.; Grosu, I.; Mager, S. Lipophilicity characterization of a large number of dioxanes and spirans by reversed-phase thin-layer chromatography. *Studia Univ. Babes-Bolyai, Chemia: XLIII* **1998**, *1–2*, 257–266.
13. Harnisch, M.; Mockel, H.J.; Schulze, G. Relationship between log POW, shake-flask values and capacity factors derived from reversed-phase high-performance liquid chromatography for n-alkylbenzenes and some oecd reference substance. *J. Chromatogr. A* **1983**, *282*, 315–332.
14. Dorsey, J.G.; Khaledi, M.G. Hydrophobicity estimations by reversed-phase liquid chromatogpaphy: Implication for biological partitioning processes. *J. Chromatogr. A* **1993**, *656*, 485–499.
15. Perisic-Janjic, N.U.; Tatjana, Li.; Popov-Pergal, K. Effect of stationary phase and mobile phase modifier on retention of some thiazoles. Correlation with the lipophilicity of the compounds. *J. Planar Chromatogr* **2003**, *16*, 363–368.
16. Perisic-Janjic, N.U.; Lucic, B.; Janjic, N.J.; Agbaba, D. Study of the lipophilicity and retention behaviour of some β-adrenoceptor antagonists. *J. Planar Chromatogr.* **2003**, *16*, 347–350.
17. Natic, M.; Markovic, R.; Andelcovik, K.; Milojkovic-Opsenic, D. Reversed-phase thin-layer chromatography of stereodefined 2-alkylidene-4-oxothiazolidines and 1,2-dithioles. *J. Planar Chromatogr.* **2004**, *17*, 323–327.
18. Valko, K.; Slegel, P. New chromatographic hydrophobicity index (φ_0) based on the slope and the intercept of the log k' versus organic phase concentration plot. *J. Chromatogr. A* **1993**, *631*, 49–61.
19. Valko, K.; Bevan, C.; Reynolds, D. Chromatographic Hydrophobicity Index by fast-gradient RP-HPLC: A high-throughput alternative to log P/ log D. *Anal. Chem.* **1997**, *69*, 2022–2029.
20. Valko, K.; Plass, M.; Bevan, C.; Reynolds, D.; Abraham, M.H. Relationships between the chromatographic hydrophobicity indices and solute descriptors obtained by using several reversed-phase, diol, nitrile, cyclodextrin and immobilized artificial membrane-bonded high-performance liquid chromatography columns. *J. Chromatogr. A* **1998**, *797*, 41–55.
21. Cserhati, T.; Forgacs, E. Relationship between the hydrophobicity and specific surface area of pesticides determined by high-performance liquid chromatography compared with reversed-phase thin-layer chromatography. *J. Chromatogr. A* **1997**, *771*, 105–109.
22. Gocan, S.; Cobzac, S.; Grinberg, N. Prediction of lipophylicity of some plant growth stimulators by RP-TLC and relationship between slope and intercept of TLC equation. *J. Liq. Chromatogr & Relat. Technol.* **2007**, *30*, 1669–1676.
23. Mannhold, R.; Cruciani, G.; Dross, K.; Rekker, R. *J. Computer-Aided Mol. Design.* **1998**, *12*, 573–581.
24. Oros, Gy.; Cserhati, T. Reversed-phase thin layer chromatographic behavior of some acylamide fungicides. *J. Liq. Chromatogr & Relat. Technol.* **2009**, *32*, 1317–1330.
25. Laufer, R.; Bathori, M.; Csermely, T.; Petroianu, G.; Kuca, K.; Toth, N.; Kalasz, H. TLC Determination of hydrophilicity parameter of some pyridinium aldoximes. *TLC J. Liq. Chromatogr & Relat. Technol.* **2007**, *30*, 2337–2344.
26. Cserhati, T.; Forgacs, E. Effect of TLC support characteristics and coating on the lypophilicity determination of phenols and aniline derivatives. *J. Chromatogr. Sci.* **2002**, *40*, 568–578.
27. Ignat, A. Ph.D Thesis, Univ. Babes-Bolyai, Cluj-Napoca, Ro, Nov. (2010).
28. Ertl, P.; Rohde, B.; Selzer, P. Fast calculation of molecular polar surface area as sum of fragment based contributions and its application to the prediction of drug transport properties. *J. Med. Chem.* **2000**, *43*, 3714–3717.
29. Ertl, P. "Polar surface area", in *Molecular Drug Properties*, Mannhold, R. (Ed), Wiley-VCH, Darmstadt, Germany, pp. 111–126, 2007.
30. Ghose, A.K.; Viswanadhan, V.N.; Wendoloski, J.J. Prediction of hydrophobic (lipophilic) properties of small organic molecules using fragmental methods: An analysis of Alog P and Clog P methods. *J. Phys, Chem. A* **1998**, *102*, 3762–3772. http://www.daylight.com/daycgi/clogp
31. Collander, R. The partition of organic compounds between higher alcohols and water. *Acta Chem. Scand.* **1951**, *5*, 774–780.