

Research Article

Application of RP-HPTLC and Ościk's Equation for the Evaluation of Lipophilic Properties of Selected Biologically Active Compounds

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Abstract

The aim of this study was to compare different methods including theoretical based on various computer software as well as simple thin-layer chromatography in reversed phase system in the determination of lipophilicity of various classes of biologically active compounds, such as fatty acids, esters of nicotinic acid and also bile acids. The lipophilicity descriptor expressed as partition coefficient (logP) predicted by five computational algorithms (AlogP_s, IlogP, ClogP, logP_{KOWWIN}, xlogP) and also experimental value of logP (determined by shake-flask method) which is available for selected of examined compounds belonging to esters of nicotinic acid and also bile acids can provide useful information about lipophilic character of these active compounds in their preliminary study. Experimentally determined retention parameter (R_M) by means of RP-HPTLC method using binary system methanol-water on silica gel RP-18WF₂₅₄ is applicable to predict other lipophilicity parameters denoted by R_{MWS} and R_{MWO} which have been calculated accordance with Soczewinski-Wachtmeister's and Ościk's equations, respectively. The results obtained in present study demonstrate that R_{MWO} may be a good alternative in describing of the lipophilic character of biologically active compounds with higher lipophilicity (i.e., fatty acids and bile acids). In the case of active substances with lower lipophilicity R_{MWS} proved to be more reliable than R_{MWO} in describing their lipophilic character.

Keywords: Fatty acids; Esters of nicotinic acid; Bile acids; Lipophilicity; LogP; RP-HPTLC; Ościk's equation

Introduction

Lipophilicity, expressed through the Partition coefficient (P) or its decimal logarithm (logP) of neutral compound between two immiscible solvents, usually n-octanol and water is one of the most important descriptors which has a significant impact on the behavior (i.e., absorption, distribution, metabolism, excretion) of organic compounds in biological system (ADME system). Because lipophilicity is associated with biological activity and plays important role in the pharmacodynamics and toxicological profile of drugs, it is very often applied in medicinal chemistry, in preclinical study of potential new drugs in order to predict their ADME properties [1]. The traditional procedure of determining of this parameter is shake-flask method. This method is simple to use but it is time-consuming and requires large amount of sample and solvents. Moreover, the logP values determined by shake-flask method are limited to the range of -3 and +3. For this reason, this method cannot be used to very hydrophilic or very hydrophobic compounds.

In recent days, the classical shake-flask method is successfully replaced by the Reversed-Phase Thin-Layer Chromatography (RP-TLC) and the Reversed-Phase High Performance Liquid Chromatography (RP-HPLC) [2,3]. Currently, the chromatographic determination of lipophilicity is most preferred due to less laborious and a wide range of measurable lipophilicity values, comparing to extraction method. Although, in the case of chromatographic

methods, especially RP-TLC or RP-HPTLC, respectively a very small amount of sample and not very pure is needed. Numerous papers describe the determination of lipophilicity by both TLC techniques for different classes of biologically active compounds, such as mercaptopurine derivatives, phnylthioamides, alkaloids and others [4-10].

Recently, an alternative in prediction of the lipophilicity parameter (logP) is the use of *in silico* study [7,11]. Computationally determined partition coefficient has become crucial in preclinical study of newly synthesized drug candidates. Because of the fact that the computed methods of prediction of logP are in development until today and show different power of calculation of this descriptor, in order to obtain reliable lipophilicity parameter, the computed logP values should be always compared with experimental values.

This work is continuation of our previous researches on lipophilicity determination of various biologically active compounds using the thin-layer chromatography methods (RP-TLC and RP-HPTLC) as well as comparison of these results with computed logP and also with experimental value of logP obtained by means of shake-flask method [12-14]. In continuation of this assay, the aim of this study was the determination applicability of RP-HPTLC technique and both, Soczewinski-Wachtmeister's and Ościk's equations to predict measurable lipophilicity values of selected compounds which belong to three classes: fatty acids, esters of nicotinic acid and also

bile acids. Although, comparison of two chromatographic parameters of lipophilicity which have been determined by Soczewinski-Wachtmeister's and Ościk's equations (denoted as R_{MWS} and R_{MWO}), respectively with that predicted by computer programs, such as $AlogP_s$, $IAllogP$, $ClogP$, $\log P_{KOWWIN}$, $xlogP$ and $\log P_{exp}$ was done.

Experimental

Chemicals and reference standards: The reference standards of examined compounds included oleic acid, palmitic acid, elaidic acid, stearic acid belonging to fatty acids, esters of nicotinic acid: methyl nicotinate, ethyl nicotinate, butyl nicotinate, benzyl nicotinate, isopropyl nicotinate, hexyl nicotinate, and selected bile acids, such as cholic acid, deoxycholic acid, lithocholic acid, glycolithocholic acid, glycodeoxycholic acid, glycocholic acid and chenodeoxycholic acid were supplied by Sigma-Aldrich (St. Louis, MO, USA). Methanol which has been used as mobile phase component was purchased from POCh (Gliwice, Poland). Distilled water was from Institute of Analytical Chemistry (School of Pharmacy and the Division of Laboratory Medicine, Medical University of Silesia, Sosnowiec, Poland). Standard solutions of examined compounds at concentration of 5 mg/mL each were prepared in methanol or in the case of fatty acids in chloroform (from POCh, Gliwice, Poland). All reagents were of analytical grade of purity.

RP-HPTLC analysis

The TLC experiment was done by thin-layer chromatography on RP-HPTLC plates: RP-18WF₂₅₄ (E. Merck, Darmstadt, Germany, and Art. 13124). The solutions of examined compounds were spotted separately onto chromatographic plates using micropipettes in quantity of 2 μ L. The chromatograms were developed using the mixtures of methanol-water in different volume compositions. The content of organic modifier (methanol) in mobile phase was gradually varied by 5% (v/v) from 40-100 (% v/v). Fifty mL of mobile phase used was placed into a classical chromatographic chamber (Art. 022.5255, Camag, Muttenz, Switzerland). The chamber was saturated with solvent vapor for 30 minutes. The chromatograms were developed to distance 75 mm at temperature of 18 (\pm 1) °C. After developing, the plates were dried at room temperature. Each chromatogram was done in triplicate. The spots were localized in UV at $\lambda=254$ nm with accuracy of ± 1 nm in the case of the esters of nicotinic acid. The chromatograms of bile acids were previously sprayed with 10% ethanolic solution of phosphomolybdic acid and next heated at temperature 120°C for 20 minutes. In order to visualize the spots of fatty acids, exposition to iodine vapor was applied.

For subsequent calculations of lipophilicity parameters of all investigated compounds, mean R_f values obtained for each chromatographic conditions were used.

Calculations

Chromatographic parameter of lipophilicity R_{MWS} : In order to determine the lipophilicity parameter based on Soczewinski-Wachtmeister's procedure the R_f values obtained under applied chromatographic conditions were converted to R_M values according to the expression:

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

Linear relationship between R_M and volume content of methanol in mobile phase (ϕ) permits an extrapolation of calculated R_M values to the zero concentration of methanol accordance with Soczewinski-Wachtmeister's equation (2). The value of intercept (R_{MWS}) represents the lipophilicity parameter of the studied compound [1].

$$R_M = R_{MWS} - S \cdot \phi \quad (2)$$

Where: R_M - is the R_M value of the examined compound, R_{MWS} - is the R_M value extrapolated to zero concentration of methanol (organic modifier) in mobile phase: methanol-water, S - is the slope of the regression plot, ϕ - is the volume fraction of methanol in mobile phase.

Chromatographic parameter of lipophilicity R_{MWO} : Measurable lipophilicity value expressed as R_{MWO} was determined according to Ościk's equation [15-18]:

$$G(x_{org}) = \frac{x_{org}(1-x_{org})}{R_M - x_{org}R_{Morg} - (1-x_{org})R_{MWO}} = ax_{org} + b \quad (3)$$

Where: R_M , R_{Morg} , R_{MWO} are the solute retention factors in: mixed mobile phase, pure organic solvent, and water respectively; x_{org} is the molar fraction of organic solvent in the mobile phase; a , b are constants in the linear correlation between $G(x_{org})$ and x_{org} in mobile phase used.

In Ościk's procedure various R_{MWO} values are fitted numerically to Equation 3 in order to obtain linearity between $G(x_{org})$ and x_{org} . Other parameters, such as R_M and R_{Morg} are measured experimentally at 0.1 increments of x_{org} (in respective range of methanol) for appropriate compound. The linear relationship between $G(x_{org})$ vs. x_{org} allows an estimation of R_{MWO} of examined compound.

Determining the theoretical partition coefficients (logP): The computationally calculated logP values expressed as $AlogP_s$, $ClogP$, $IAllogP$, $\log P_{KOWWIN}$, $xlogP$ and also experimental $\log P_{exp}$ for selected of examined compounds were determined by online software (available at VCCLAB.org website) [19].

Regression and simple cluster analysis (CA): Regression and simple cluster analysis of obtained results were performed with the use of computer program STATISTICA v. 10.0 (Statsoft Poland, Kraków, Poland).

Results and Discussion

The main aim of this study was to estimate the applicability of simple thin-layer chromatography method (RP-HPTLC) and also both, Soczewinski-Wachtmeister's and Ościk's equations to evaluate lipophilicity of selected biologically active compounds belonging to the three groups of organic compounds: fatty acids, esters of nicotinic acid and also bile acids. In order to predict the measurable values of lipophilicity parameters expressed as R_{MWS} (accordance with Soczewinski-Wachtmeister's equation) for the members of the three examined classes of organic compounds, the experimental data of R_M values which have been obtained on silica gel RP-18WF₂₅₄ using methanol-water in different volume compositions as mobile phase were extrapolated to an methanol content of zero by Equation 2. In all cases the equations were linear with correlation coefficient

Table 1: Summary of lipophilicity study of examined compounds.

Substance	Lipophilicity parametrs							
	logP _{exp}	AlogP _S	IlogP	ClogP	logP _{KOWWIN}	xlogP	R _{MWO}	R _{MWS}
Fatty acids								
Oleic acid	-	7.51	7.48	7.79	7.73	6.50	7.15	4.07
Elaidic acid	-	7.51	7.48	7.79	7.73	6.50	8.88	5.06
Palmitic acid	-	6.90	7.00	7.21	6.96	6.09	7.26	4.20
Stearic acid	-	7.91	7.91	8.27	7.94	7.02	7.06	4.94
Esters of nicotinic acid								
Methyl nicotinate	0.83	0.61	0.82	0.77	0.64	0.71	1.42	1.25
Ethyl nicotinate	1.32	1.27	1.33	1.30	1.33	1.13	2.05	1.56
Isopropyl nicotinate	-	1.65	1.64	1.61	1.55	1.59	2.20	1.69
Butyl nicotinate	2.27	2.16	2.29	2.35	2.11	2.06	3.06	1.96
Hexyl nicotinate	3.51	3.12	3.27	3.41	3.10	3.19	3.14	2.87
Benzyl nicotinate	2.40	2.25	2.00	2.60	2.35	2.42	2.50	2.18
Bile acids								
Lithocholic acid	-	4.38	5.31	6.60	6.19	6.57	4.57	5.29
Deoxycholic acid	3.50	3.30	3.26	4.51	5.06	5.76	3.76	3.96
Chenodeoxycholic acid	4.15	3.01	3.68	4.51	5.06	4.91	3.57	3.72
Glycolithocholic acid	-	3.71	4.11	5.89	5.08	5.75	3.22	3.62
Cholic acid	2.02	2.26	2.12	2.43	3.52	4.09	2.91	4.42
Glycodeoxycholic acid	2.25	2.69	2.40	3.80	3.95	4.93	2.68	3.76
Glycocholic acid	1.65	1.70	1.09	1.71	2.41	3.27	1.92	2.43

above 0.9. As was presented in experimental part, the intercepts in these equations can be considered as a measure of lipophilicity. All calculated intercepts have been accepted as lipophilicity descriptors (R_{MWS}). Obtained lipophilicity parameters with the use of Soczewinski-Wachtmeister's equation are listed in Table 1. As shown the lipophilicity of tested compounds is in agreement with their structure (non-polar character). R_{MWS} results in Table 1 indicate that in the group of investigated fatty acids this parameter is the highest of all and is placed in the range of 4.07 to 5.06. In the case of bile acids the lipophilicity descriptor R_{MWS} exists in the range from 2.43 to 5.29. For esters of nicotinic acid the R_{MWS} is lower (from 1.25 to 2.87).

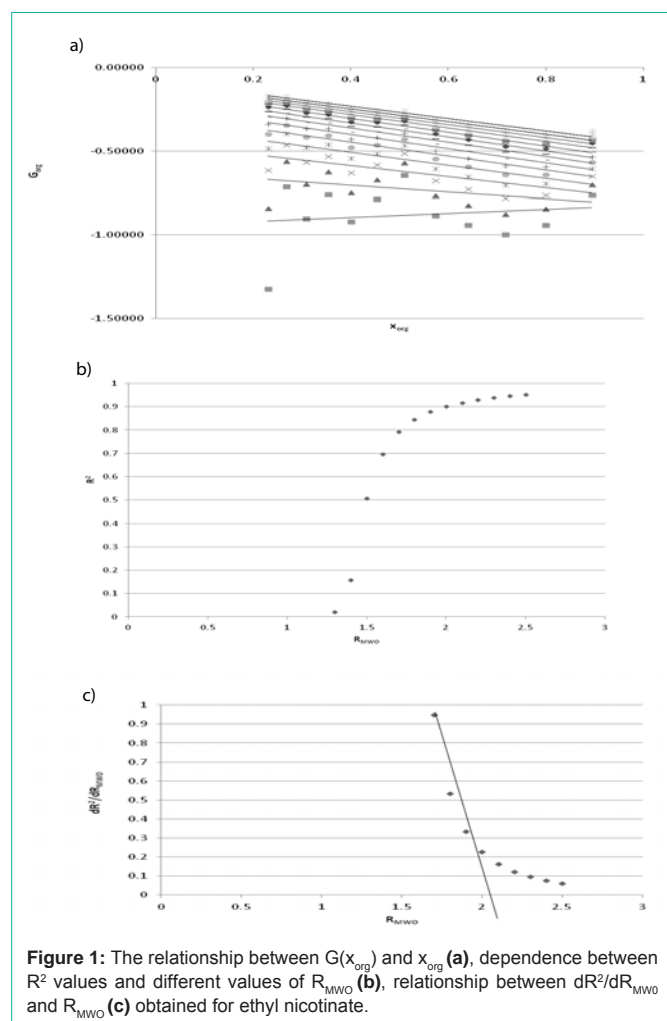
The second of discussed lipophilicity parameters (R_{MWO}) was determined according to the methodology presented by Janicka et al. [16,17] on the basis of previously obtained R_M values on silica gel RP-18WF₂₅₄ using methanol-water. The R_{MWO} values have been predicted for examined compounds in the three steps which are accurately illustrated in Figure 1, for example for ethyl nicotinate. In the first step (Figure 1(a)) various R_{MW} values were fitted to Equation 3 with respective step in order to check if a linear relationship exists between the two variables G_{org} and x_{org} . The second step examines the determination coefficient R^2 (from Figure 1(b)) depending on R_{MWO} . As can be seen, the values of R^2 grow exponentially, next moderately, and finally they could be changed insignificantly in order to achieve unity. During the last step the relation R^2 vs R_{MWO} is derived. Lipophilicity parameter R_{MWO} is calculated by extrapolation of linear part of obtained graph (Figure 1(c)) in direction of zero changes of R^2 .

Similar plots and procedures were done for other examined compounds. The values of R_{MWO} estimated for all compounds studied are presented in Table 1.

The results of obtained R_{MWO} values similarly like above mentioned R_{MWS} confirm that the most lipophilic properties of all studied compounds show fatty acids and bile acids, which R_{MWO} is placed in the range of 7.06 to 8.88 and from 1.92 to 4.57, respectively. The lipophilicity parameter R_{MWO} determined for the esters of nicotinic acid ranged from 1.42 to 3.14.

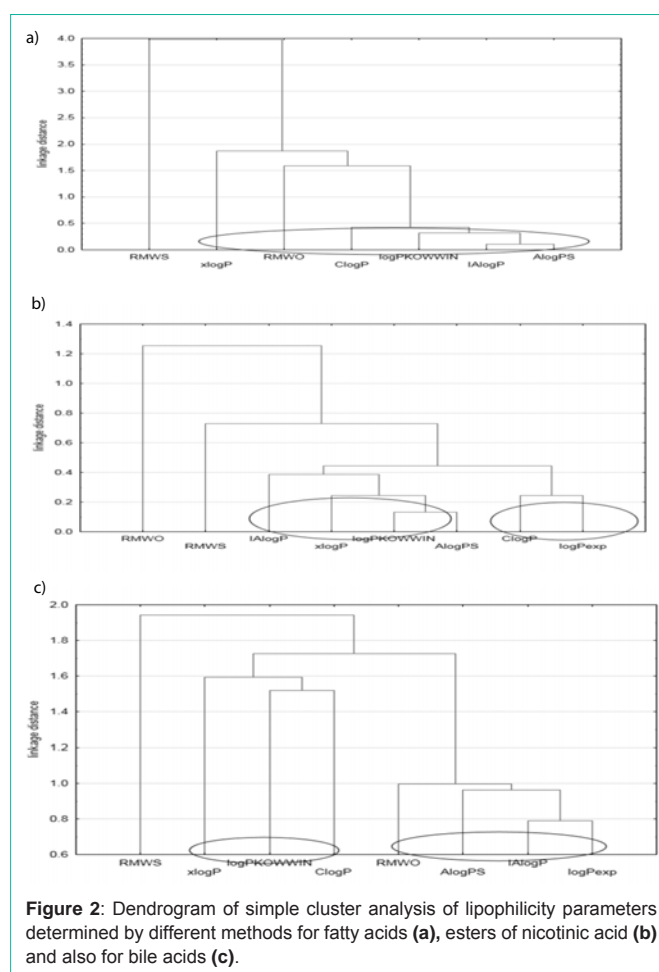
In order to evaluate the possibility of the applying of both lipophilicity descriptors: R_{MWS} and R_{MWO} which have been calculated using Soczewinski-Wachtmeister's and Oscik's equations for the determination of the lipophilicity of all examined compounds, the results of obtained R_{MWS} and R_{MWO} values were compared with partition coefficient (logP) predicted by means of computer software: AlogP_S, ClogP, IlogP, logP_{KOWWIN}, xlogP available at VCCLAB.org website (as Interactive analysis logP prediction). Moreover, in the case of the selected esters of nicotinic acids and also some bile acids this program enabled determine the experimental value of partition coefficient (logP_{exp}) which was found by shake-flask method. The computationally calculated lipophilicity values expressed as logP and also experimental logP_{exp} for appropriate compounds are summarized in Table 1.

To compare different calculation methods (AlogP_S, ClogP, IlogP, logP_{KOWWIN}, xlogP) and also chromatographically determined



R_{MWS} and R_{MWO} parameters (using Soczewinski-Wachtmeister's and Ošcik's equations), simple cluster analysis of all obtained lipophilicity parameters for three groups of analyzed compounds was done.

Dendrogram in Figure 2(a) represents the results of cluster analysis (*Euclidean distance*) of lipophilicity parameters which have been determined for four examined fatty acids: oleic, elaidic, palmitic and also stearic. Figure 2(a) suggests that generally all theoretical lipophilicity parameters ($\log P$) and also R_{MWO} calculated using Ošcik's equation form one subgroup which confirms their similarity. The second, single subgroup in this dendrogram forms R_{MWS} . Among partition coefficients predicted using different calculation methods the biggest similarity show IALogP and AlogP_s. Observed big similarity between both theoretical parameters of lipophilicity of studied fatty acids confirms that IALogP could be successfully replaced by AlogP_s in lipophilicity study of these substances. Of two chromatographically determined lipophilicity descriptors, the lipophilicity parameter R_{MWO} indicates better agreement with theoretical partition coefficients than R_{MWS} calculated using Soczewinski-Wachtmeister's equation. Thus, it could be concluded that simple thin-layer chromatography in reversed phase system (RP-HPTLC) and experimentally determined (using Ošcik's equation), lipophilicity parameter R_{MWO} is a good alternative to the theoretical values of lipophilicity parameters and also to other experimental partition coefficients whose determination



by extraction method, especially in the case of very lipophilic compounds, like for example fatty acids is too difficult or impossible.

Interpretation of the second dendrogram (Figure 2(b)) which performs the results of simple cluster analysis of the lipophilicity parameters (theoretical and chromatographic) obtained for the next group of investigated organic compounds belonging to esters of nicotinic acid indicates that in this case, the R_{MWS} demonstrates bigger similarity with other parameters of lipophilicity including experimental partition coefficient ($\log P_{exp}$) which is determined by shake-flask method than R_{MWO} . Among computed $\log P$ values, great similarity (the smallest *Euclidean distance*) indicates AlogP_s and $\log P_{KOWWIN}$ but the most similar to known in literature experimental partition coefficient values ($\log P_{exp}$) for all examined esters (except of isopropyl nicotinate) is ClogP which forms with this theoretical partition coefficient exactly one subgroup.

The last dendrogram in Figure 2(c) refers to cluster analysis of the lipophilicity parameters of the third of examined groups, namely bile acids. Comparison of theoretical $\log P$ with chromatographically determined lipophilicity descriptors, such as R_{MWO} and R_{MWS} and also with $\log P_{exp}$ (except of lithocholic and glycolithocholic acids) shows that all lipophilicity parameters could be divided into two main subgroups. The first subgroup form $xlogP$, $\log P_{KOWWIN}$ and ClogP. The second one includes AlogP_s, IALogP, $\log P_{exp}$ and R_{MWO} . The biggest similarity indicates IALogP and $\log P_{exp}$. Thus, it suggests that $\log P_{exp}$

may be successfully replaced by IALogP. Moreover, analogously like in the case of fatty acids better correlation with computed logP demonstrates R_{MWO} comparing with R_{MWS} .

Taking into account the observed agreement between the R_{MWO} or R_{MWS} values, respectively and also computational lipophilicity descriptors (logP) obtained for the three examined groups of biologically active compounds, such as fatty acids, esters of nicotinic acid and bile acids, it may be concluded that R_{MWO} appears to be the most suited lipophilicity descriptor for the class of organic compounds which show very high lipophilicity like for example fatty acids and bile acids(examined in the present study). In the case of active compounds indicating intermediary lipophilicity or very low lipophilicity, such as the esters of nicotinic acid, the second of two proposed lipophilicity parameters denoted as R_{MWS} seems to be most useful. The results of presented study confirm that the R_{MWS} and R_{MWO} may be selected and considered as reliable lipophilicity measures of different classes of biologically active compounds including that which show strong lipophilic properties, like for instance the two examined groups: fatty acids and bile acids.

Conclusion

The results obtained in the present study show that:

- Partition coefficient (logP) predicted by means of different computational algorithms (ALogP_s, IALogP, ClogP, logP_{KOWWIN}, xlogP) can provide useful information about lipophilic character of various classes of biologically active compounds i.e., fatty acids, esters of nicotinic acid and bile acids but in their preliminary study only,
- RP-HPTLC method and lipophilicity parameters denoted by R_{MWS} and R_{MWO} which have been calculated based on retention parameters (R_M) accordance with Soczewinski-Wachtmeister's and Oscik's equations, respectively may be the alternates to others like for example to logP determined by shake-flask method in describing of lipophilic character of active compounds belonging to the following classes: fatty acids, esters of nicotinic acid and also bile acids,
- The R_{MWO} values could be suitable for the determination of lipophilic character of biologically active compounds with high lipophilicity (i.e., fatty acids and bile acids),
- In the case of active substances with lower lipophilicity, R_{MWS} proved to be more reliable in describing of their lipophilic character than R_{MWO} .

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