DOI: 10.17344/acsi.2023.8602 *Acta Chim. Slov.* **2024,** *71,* 226–235

Scientific paper

QSRR Modeling of Lipophilicity of New Spirohydantoin Derivatives Determined with Various TLC Systems

Kristina A. Tot,[1,*] Anita M. Lazić[2] and Tatjana Lj. Djaković Sekulić[1]

[1] *University of Novi Sad, Faculty of Sciences, Department of Chemistry, Biochemistry and Environmental Protection, Trg Dositeja Obradovića 3, 2100 Novi Sad, Republic of Serbia*

[2] *University of Belgrade, Faculty of Technology and Metallurgy, Karnegijeva 4, 11000 Belgrade, Republic of Serbia*

* *Corresponding author: E-mail: kristina.tot@dh.uns.ac.rs*
Fax: +381 21 454 065, Phone: +381 21 485 2743

Received: 12-28-2023

Abstract

A Quantitative structure-retention relationship *(QSRR) analysis has been* performed on the chromatography parameters of lipophilicity of selected spirohydantoins. Multiple linear regression (MLR) was applied to construct the QSRR models. The chromatographic parameters of lipophilicity were determined by reversed-phase thin-layer chromatography. Chromatographic analyses were performed on C-18 modified silica gel with a two-component mobile phase consisting of water and protic organic solvent (ethanol, n-propanol, i-propanol, or t-butanol) in different ratios. QSRR models were also created for additional four aqueous mobile phases: acetone-water, acetonitrile-water, tetrahydrofuran-water, and 1,4-dioxane-water (results published before). In total, chromatographic lipophilicity parameters obtained for two types of organic solvents were subject of the QSRR. The predictive ability of each model was evaluated using internal and external validation. The best QSRR model for predicting the chromatographic parameter of lipophilicity was obtained for tetrahydrofuran as an organic solvent.

Keywords: QSRR modeling, lipophilicity, RP-TLC, spirohydantoins

1. Introduction

Spirohydantoins represent a pharmacologically important class of heterocyclic compounds.[1] These compounds are mostly small and lipophilic molecules, which easily reach the target cells. Derivatives of hydantoin exhibit various pharmacological activities, such as anticonvulsant,[2] antiarrhythmic,[3] antiviral,[4] anti-inflammatory,[5] and anti-HIV activity.[6] Well known hydantoin-based drug is phenytoin (5,5-diphenylhydantoin, Dilantin), which is widely used in treating epilepsy and cardiac arrhythmias.[7] Derivatives of hydantoin can impact cancer metastasis, and for this reason, these derivatives have been recognized as promising therapeutic agents in cancer treatment.[8–14]

The main factor that determines the activity of the compound is chemical structure.[15–17] Some structural parameters are more important for the activity than others. The selection of appropriate parameters that are important for the activity of compound is facilitated by an *in silico* approach. This approach is based on various models, such as QSARs (quantitative structure–activity relationships) or QSPRs (quantitative structure–property relationships).[18] These models allow quantitative assessment of molecular properties or compound activity based on structural characteristics (expressed by various molecular descriptors). Understanding the relationship between the activity, structure and physicochemical properties of various compounds provides an opportunity to identify features that are important for the compound activities, as well as to identify potential bioactive compounds.[19,20]

In recent years the progress in the QSPR approaches has been increasing due to the fast-developing field of chemometrics.[21] QSRR is a specific type of quantitative structure-property relationship. QSRR model is an important approach for assessing and interpreting retention data in relation to the chemical structure of the analyzed substances which is numerically expressed by molecular descriptors.[22] The QSRR model can be used for identifying unknown compounds and understanding the molecular mechanism of separation operating in a specific chromatographic system.[23–29] The logarithm of the partition coefficient, log *P*,

which represents the ratio of equilibrium concentrations of the compound dissolved in the two phase system consisting of two non-soluble solvents (n-octanol and water),[30] is very often included in models as a molecular descriptor. This is not surprising since log *P* is a quantitative expression of lipophilicity, widely used as a structural descriptor. Lipophilicity is one of the key properties associated with the transport and distribution of drugs in organisms, drug–receptor interactions, metabolism, and toxicity, and also plays a role in the onset and duration of the drug's effect.[31]

Reversed-phase thin-layer chromatography (RP-TLC) is often used to determine the lipophilicity due to its simplicity, possibility of examination of a large number of samples in small quantities, reproducibility, and low-cost price.[32–35] Measured values of chromatographic lipophilicity can be used instead of log *P* values as independent variables in the QSAR/QSRR models. The QSRR models allow retention data prediction of the new, not yet synthesized compounds, using their molecular descriptors.[36–38]

The aim of this study was to establish new QSRR models, which will provide insight into which molecular properties are important for the lipophilicity of new spirohydantoins.

2. Experimental

2. 1. Investigated Compounds and Their Solutions

The analyzed compounds were three series of 3-(4-substituted benzyl)-cycloalkylspiro-5-hidantoins, respectively derivatives of 3-(4-substitutedbenzyl)-cyclopentanespiro-5-hydantoin, 3-(4-substituted benzyl)- cyclohexanespiro-5-hydantoin and 3-(4-substituted benzyl)-cycloheptanespiro-5-hydantoin. Chemical structures, substituents and numbering of the investigated spirohydantoins are presented in Figure 1 and Table 1.

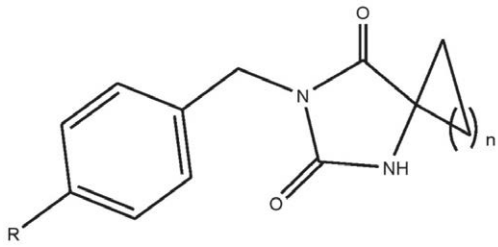

Figure 1: Molecular structure of the investigated 3-(4-substituted benzyl)cycloalkylspiro-5-hydantoins.

The solutions of the investigated compounds were prepared by dissolving 5 mg of each spirohydantoin in 1 ml of ethanol. The 1 ml of each solution was spotted on high-performance thin-layer chromatographic (HPTLC) plates.

2. 2. Reversed-Phase Thin-Layer Chromatography

Thin-layer chromatography was performed on commercially available 10×10 cm high-performance RP-18 modified silica gel (HPTLC plates) with fluorescent indicator F254s (Merck, Darmstadt, Germany). Mobile phases used were mixtures of water and one out of four organic solvents: ethanol (Sigma-Aldrich) (φ(ethanol) = 0.5–0.70 v/v), *n*-propanol (Sigma-Aldrich) (φ(*n*-propanol) = 0.5–0.74 v/v), *i*-propanol (Lachema) (φ(*i*-propanol) = 0.5–0.70 v/v), *t*-butanol (Sigma-Aldrich) (φ(*t*-butanol) = 0.5–0.70 v/v).

Chromatograms were developed by the ascending technique at room temperature (22±2˚C) without previous saturation of the chromatographic chamber (CAMAG, Muttenz, Switzerland) with mobile phase vapor. The developing distance was approximately 45 mm. After development of chromatograms, the plates were dried at room temperature, and individual chromatographic zones were detected under UV light at 254 nm wavelength (CAMAG, Muttenz, Switzerland).

For subsequent calculations, the R_M values were calculated for each investigated compound according to Bate-Smith and Westall's equation:[39]

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

In Eq. (1) R_F is the retardation factor, which was calculated as the ratio of the distance of a solute's target zone and the distance of the solvent front.

Table 1: Overview of substituents of the investigated 3-(4-substituted benzyl)cycloalkylspiro-5-hydantoins.

Cyclopentanespiro-5-hydantoins			Cyclohexanespiro-5-hydantoins			Cycloheptanespiro-5-hydantoins		
No.	**n**	**R**	**No.**	**n**	**R**	**No.**	**n**	**R**
CI.1	3	H	**II.1**	4	H	**III.1**	5	H
I.2	3	CH_3	**II.2**	4	CH_3	**III.2**	5	CH_3
I.3	3	OCH_3	**II.3**	4	OCH_3	**III.3**	5	OCH_3
I.4	3	Cl	**II.4**	4	Cl	**III.4**	5	Cl
I.5	3	Br	**II.5**	4	Br	**III.5**	5	Br
I.6	3	CN	**II.6**	4	CN	**III.6**	5	CN
I.7	3	NO_2	**II.7**	4	NO_2	**III.7**	5	NO_2

The R_M values of each compound are determined in the presence of different organic solvent content in the mobile phase. The linear relationship between the R_M values and different mobile phase proportions is established, and the partition coefficient is calculated by extrapolating to a pure water mobile phase:[40]

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

In Eq. (2), φ is the volume fraction of organic solvent in the mobile phase, R_M^0 is the intercept and S is the slope of Eq. (2). Intercept, R_M^0, correspond to retention extrapolated to 0 % (v/v) of organic solvent and represents the chromatographic lipophilicity parameter.[41]

2. 3. Molecular Descriptors Calculation

Molecular descriptors were calculated by Dragon[42] (40 molecular descriptors in total: MW (molecular weight), Sv (sum of atomic van der Waals volumes), Se (sum of atomic Sanderson electronegativities), Sp (sum of atomic polarizabilities), Si (sum of first ionization potentials), nAT (number of atoms), nBT (number of bonds), RBN (number of rotatable bonds), nH (number of Hydrogen atoms), nC (number of Carbon atoms), nN (number of Nitrogen atoms), nO (number of Oxygen atoms), nCl (number of Chlorine atoms), nHet (number of heteroatoms), nX (number of halogen atoms), ARR (aromatic ratio), nHAcc (number of acceptor atoms for H-bonds), nHDon (number of donor atoms for H-bonds), Hy (hydrophilic factor), AMR (Ghose-Crippen molar refractivity), TPSA(NO) (topological polar surface area using N,O polar contributions), TPSA(Tot) (topological polar surface area using N, O, S, P polar contributions), MLOGP (Moriguchi octanol-water partition coeff. (logP)), MLOGP2 (squared Moriguchi octanol-water partition coeff. (logP^2)), ALOGP (Ghose-Crippen octanol-water partition coeff. (logP)), ALOGP2 (squared Ghose-Crippen octanol-water partition coeff. (logP^2)), Vx (McGowan volume), VvdwMG, (van der Waals volume from McGowan volume), VvdwZaz (van der Waals volume from Zhao-Abraham-Zissimos equation), PDI (packing density index), RBF (rotatable bond fraction), ECC (eccentricity), DBI (Dragon branching index), SAtot (total surface area from P_VSA-like descriptors), SAacc (surface area of acceptor atoms from P_VSA-like descriptors), Uc (unsaturation count), Ui (unsaturation index), Pol (polarity number), IAC (total information index on atomic composition) and ISIZ (information index on molecular size)), ChemDraw Ultra 7.0[43] (for calculation values of ClogP, $\log P_{Crippen}$, $\log P_{Viswanadhan}$ and $\log P_{Brotto}$), Molinspiration[44] (for miLogP), and ADMETlab[45] (for calculation values of log P, log D (distribution coefficient), and log S (water solubility)). The calculated descriptors for each investigated compound are listed in Table S1 (Supplementary Materials).

2. 4. QSRR Modeling

QSRR models were created using chromatographic lipophilicity parameters as dependent variables and calculated molecular descriptors as independent variables. The methodology used for QSRR modeling was multiple linear regressions. All of the calculations were made using data analysis software Statistica v.14.0 (StatSoft (Europe), GmbH, Hamburg).

Before implementing MLR, the number of molecular descriptors was reduced. First, molecular descriptors with the same numerical value for all investigated compounds were excluded. Then, molecular descriptors whose values are not available for all investigated compounds were eliminated. The next step in the elimination of molecular descriptors from the analysis was to exclude descriptors with a high mutual correlation (r>0.800), respectively only one of them was used.[46] The final regression equations were obtained using two methods: the forward stepwise method and the backward stepwise method.

The developed models were validated by cross-validation methodology. The predictivity of each model was measured by the cross-validated regression coefficient (Q^2) defined as (Eq, 3):

$$Q^2 = 1 - \Sigma(Y_{pred} - Y_{exp})^2 / \Sigma(Y_{exp} - Y_{mean})^2 \quad (3)$$

where Y_{pred}, Y_{exp} and Y_{mean} are predicted, experimental, and mean values of the target properties (retention), respectively. For a model to have a high predictive power, it is essential that Q^2 has the high value. The accepted cross-validation of the Q^2 value is considered to be $Q^2 > 0.7$.[47]

3. Results and Discussion

3. 1. Chromatographic Lipophilicity Parameters

The lipophilicity was assessed using reversed-phase thin-layer chromatography (RP-TLC).

The chromatographic lipophilicity parameters of cycloalkylspiro-5-hydantoins were determined using four different mixtures of mobile phase, which differ in organic component, i.e., ethanol, n-propanol, i-propanol, and t-butanol. Calculated chromatographic lipophilicity parameters, intercepts (R_M^0), slopes (S) as well as coefficient of correlations (r), are listed in Table 2.

Relatively high correlation coefficients (r > 0.99) and low standard deviation indicate that calculated equations are statistically significant. Figure 2 shows the impact of the size of cycloalkyl group and the substituent R on R_M^0 values in mobile phase ethanol-water. Graphs showing the size impact of the cycloalkyl group and the substituent R on the values of R_M^0 for other applied solvents are provided in Supplementary material (Figure S1-S3).

Table 2: Intercepts, R_M^0, slopes, S, and correlation coefficients, r, of the equation (2) applied for the various mobile phase.

Investigated compounds	ethanol R_M^0	ethanol −S	ethanol r	n-propanol R_M^0	n-propanol −S	n-propanol r
I.1	1.926(±0.053)	3.312(±0.090)	0.999(±0.016)	1.189(±0.060)	2.732(±0.092)	0.998(±0.017)
I.2	2.528(±0.065)	3.975(±0.110)	0.998(±0.019)	1.441(±0.036)	2.880(±0.056)	0.999(±0.011)
I.3	1.985(±0.126)	3.490(±0.213)	0.993(±0.037)	1.145(±0.044)	2.679(±0.069)	0.999(±0.013)
I.4	2.665(±0.057)	4.056(±0.096)	0.999(±0.017)	1.302(±0.056)	2.740(±0.087)	0.998(±0.016)
I.5	2.783(±0.147)	4.116(±0.248)	0.993(±0.043)	1.329(±0.051)	2.757(±0.079)	0.999(±0.015)
I.6	1.776(±0.094)	3.665(±0.159)	0.996(±0.028)	0.884(±0.047)	2.611(±0.072)	0.999(±0.014)
I.7	2.033(±0.053)	3.449(±0.089)	0.999(±0.015)	1.090(±0.010)	2.609(±0.016)	1.000(±0.003)
II.1	2.523(±0.091)	4.008(±0.154)	0.997(±0.027)	1.416(±0.029)	2.860(±0.045)	1.000(±0.009)
II.2	3.057(±0.057)	4.537(±0.097)	0.999(±0.017)	1.354(±0.034)	2.771(±0.052)	0.999(±0.010)
II.3	2.169(±0.087)	3.551(±0.147)	0.997(±0.026)	1.219(±0.038)	2.757(±0.059)	0.999(±0.011)
II.4	3.046(±0.070)	4.468(±0.118)	0.999(±0.021)	1.408(±0.043)	2.799(±0.067)	0.999(±0.013)
II.5	2.925(±0.070)	4.162(±0.118)	0.998(±0.021)	1.532(±0.022)	2.900(±0.034)	1.000(±0.006)
II.6	2.129(±0.072)	3.934(±0.121)	0.998(±0.021)	1.362(±0.106)	3.285(±0.164)	0.996(±0.031)
II.7	2.513(±0.054)	4.034(±0.092)	0.999(±0.016)	1.095(±0.038)	2.645(±0.060)	0.999(±0.011)
III.1	2.988(±0.045)	4.489(±0.076)	0.999(±0.013)	1.366(±0.065)	2.806(±0.101)	0.998(±0.019)
III.2	3.159(±0.118)	4.526(±0.200)	0.996(±0.035)	1.464(±0.025)	2.843(±0.038)	1.000(±0.007)
III.3	2.729(±0.081)	4.215(±0.136)	0.998(±0.024)	1.267(±0.086)	2.796(±0.134)	0.996(±0.025)
III.4	3.196(±0.115)	4.495(±0.194)	0.996(±0.034)	1.518(±0.039)	2.867(±0.061)	0.999(±0.011)
III.5	3.390(±0.110)	4.715(±0.186)	0.997(±0.032)	1.621(±0.041)	3.000(±0.064)	0.999(±0.012)
III.6	2.466(±0.092)	4.268(±0.155)	0.997(±0.027)	1.189(±0.092)	2.998(±0.142)	0.996(±0.027)
III.7	2.692(±0.103)	4.085(±0.174)	0.996(±0.030)	1.259(±0.045)	2.749(±0.069)	0.999(±0.013)

TABLE 2 Continuation

Investigated compounds	i-propanol R_M^0	i-propanol −S	i-propanol r	t-butanol R_M^0	t-butanol −S	t-butanol r
I.1	1.146(±0.037)	2.420(±0.062)	0.999(±0.010)	1.248(±0.075)	2.697(±0.125)	0.997(±0.021)
I.2	1.334(±0.051)	2.482(±0.084)	0.998(±0.014)	1.574(±0.092)	3.055(±0.152)	0.996(±0.025)
I.3	1.140(±0.047)	2.488(±0.078)	0.999(±0.013)	1.222(±0.049)	2.667(±0.082)	0.999(±0.013)
I.4	1.365(±0.025)	2.517(±0.042)	1.000(±0.007)	1.464(±0.035)	2.843(±0.059)	0.999(±0.010)
I.5	1.510(±0.060)	2.679(±0.100)	0.998(±0.016)	1.626(±0.051)	3.061(±0.084)	0.999(±0.014)
I.6	0.948(±0.043)	2.386(±0.071)	0.999(±0.012)	1.513(±0.084)	3.203(±0.138)	0.997(±0.023)
I.7	1.161(±0.056)	2.518(±0.093)	0.998(±0.015)	1.393(±0.015)	2.952(±0.025)	1.000(±0.004)
II.1	1.430(±0.029)	2.742(±0.049)	1.000(±0.008)	1.423(±0.067)	2.808(±0.112)	0.998(±0.018)
II.2	1.376(±0.093)	2.531(±0.154)	0.995(±0.025)	1.623(±0.066)	3.067(±0.110)	0.998(±0.018)
II.3	1.266(±0.064)	2.573(±0.105)	0.998(±0.017)	1.494(±0.081)	2.976(±0.134)	0.997(±0.022)
II.4	1.664(±0.060)	2.846(±0.100)	0.998(±0.016)	1.603(±0.026)	3.036(±0.043)	1.000(±0.007)
II.5	1.678(±0.080)	2.806(±0.133)	0.997(±0.022)	1.646(±0.045)	3.088(±0.075)	0.999(±0.012)
II.6	1.265(±0.091)	2.799(±0.151)	0.996(±0.025)	1.521(±0.077)	3.264(±0.127)	0.998(±0.021)
II.7	1.399(±0.046)	2.735(±0.076)	0.999(±0.013)	1.404(±0.036)	2.877(±0.060)	0.999(±0.010)
III.1	1.760(±0.087)	3.083(±0.145)	0.997(±0.024)	1.597(±0.043)	3.027(±0.071)	0.999(±0.012)
III.2	2.053(±0.063)	3.309(±0.104)	0.998(±0.017)	1.674(±0.071)	3.098(±0.117)	0.998(±0.019)
III.3	1.646(±0.067)	2.933(±0.110)	0.998(±0.018)	1.663(±0.056)	3.168(±0.093)	0.999(±0.015)
III.4	1.857(±0.094)	3.007(±0.156)	0.996(±0.026)	1.802(±0.075)	3.222(±0.124)	0.998(±0.020)
III.5	1.913(±0.075)	3.033(±0.124)	0.997(±0.020)	1.830(±0.057)	3.281(±0.095)	0.999(±0.016)
III.6	1.582(±0.122)	3.196(±0.201)	0.994(±0.033)	1.578(±0.050)	3.377(±0.082)	0.999(±0.014)
III.7	1.528(±0.027)	2.820(±0.045)	1.000(±0.007)	1.603(±0.037)	3.118(±0.061)	0.999(±0.010)

Compared to the nonsubstituted derivate, the retention of spirohydantoins with nonpolar methyl substituent R in most cases is higher. Higher retention was also observed in the presence of halogens; the highest retention was observed for bromide as a substituent.The type of organic solvent used additionally influence the R_M^0 value. Generally, properties of solvent are described by Hansen's solubility parameters,[48] i.e. dipole interactions (δ_p), dispersion interactions (δ_d), and the ability of the solvent to form hydrogen bonds (δ_h), as well as the dielectric constant (ε).[49]

Based on the values in Table 2 can be noticed that the higher the polarity of the organic solvent (δp and ε) is, the

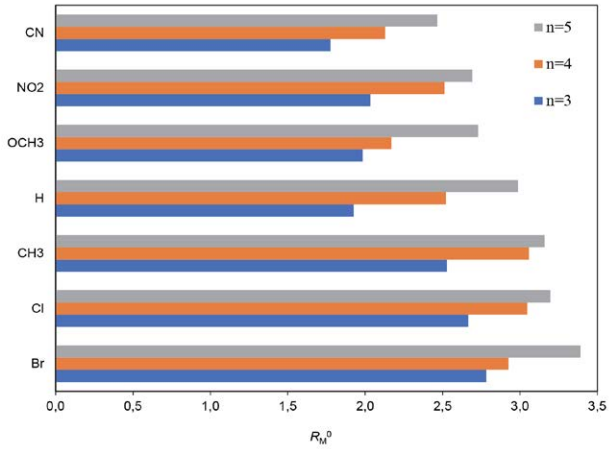

Figure 2: The impact of the size of cycloalkyl group and the substituent R on R_M^0 values in mobile phase ethanol-water.

higher are R_M^0 values. Generally, solvents increase the R_M^0 in the following order:

n-propanol < *t*-butanol < *i*-propanol < ethanol.

The highest R_M^0 values are observed with ethanol and the lowest with *n*-propanol. This can be explained by the fact that ethanol is the most polar of all used solvents, and has the greatest tendency toward polar interactions of all used organic solvents. Compared to other solvents, ethanol has the highest dipole interactions, the ability to form hydrogen bond, as well as the dielectric constant.

3. 2. QSRR

In order to describe the quantitative relationship between chromatographic lipophilicity parameters and molecular descriptors QSRR modeling was performed. QSRR models were also created for additional four aqueous mobile phases: acetone-water, acetonitrile-water, tetrahydrofuran-water, and 1,4-dioxane-water - aprotic organic solvents (results published before).[50] In total, chromatographic lipophilicity parameters obtained for two types of organic solvents: four protic and four aprotic organic solvents were analyzed using QSRR. The obtained models are listed in Tables 3 and 4. The statistical quality of the models was assessed by the coefficient of adjusted determination R^2_{adj}, the standard error of estimate (s), the probability value (p), the Fisher test for significance of the equation (F-value), and the predictive ability of the models (Q^2). The acceptance level for the individual independent variables was set at the 95% significance level.

Table 3: QSRR equations obtained for protic solvents.

Regression equations	Q^2	No. models
$R_M{}^0{}_{ethanol}$ = 0.747(±0.121) + 0.649 (±0.041)ClogP p(intercept) = 0.000; p(ClogP) = 0.000 R^2_{adj} = 0.925; F = 247.928; p = 0.000	0.929	1
$R_M{}^0{}_{ethanol}$ = 0.437(±0.164) + 0.776 (±0.058)miLogP p(intercept) = 0.015; p(miLogP) = 0.000 R^2_{adj} = 0.900; F = 181.297; p = 0.000	0.905	2
$R_M{}^0{}_{n\text{-}propanol}$ = 1.330(±0.274) + 0.244 (±0.030)ClogP – 0.012(±0.005)IAC p(intercept) = 0.000; p(ClogP) = 0.000; p(IAC) = 0.026 R^2_{adj} = 0.760; F = 32.628; p = 0.000	0.784	3
$R_M{}^0{}_{n\text{-}propanol}$ = 0.906 (±0.423) – 0.345 (±0.074)Sv + 0.343(±0.067)Sp p(intercept) = 0.046; p(Sv) = 0.000; p(Sp) = 0.000 R^2_{adj} = 0.565; F = 13.990; p = 0.000	0.609	4
$R_M{}^0{}_{i\text{-}propanol}$ = 0.166(±0.111) + 0.469 (±0.039)miLogP p(intercept) = 0.150; p(miLogP) = 0.000 R^2_{adj} = 0.878; F = 145.597; p = 0.000	0.885	5
$R_M{}^0{}_{i\text{-}propanol}$ = 0.380(±0.101) + 0.384 (±0.035)ClogP p(intercept) = 0.001; p(ClogP) = 0.000 R^2_{adj} = 0.860; F = 123.471; p = 0.000	0.867	6
$R_M{}^0{}_{t\text{-}butanol}$ = 0.832(±0.092) + 0.256 (±0.032)ALOGP p(intercept) = 0.000; p(ALOGP) = 0.000 R^2_{adj} = 0.755; F = 62.655; p = 0.000	0.767	7
$R_M{}^0{}_{t\text{-}butanol}$ = −0.374 (±0.292) – 0.087 (±0.019)Se + 0.209(±0.033)Sp p(intercept) = 0.217; p(Se) = 0.000; p(Sp) = 0.000 R^2_{adj} = 0.721; F = 26.835; p = 0.000	0.749	8

Table 4: QSRR equations obtained for aprotic solvents.

Regression equations	Q^2	No. model
$R_M{}^0{}_{acetonitrile}$ = 1.926(±0,098) + 0.187(±0.019)MLOGP2 p(intercept) = 0.000; p(MLOGP2) = 0.000 R^2_{adj} = 0.825; F = 95.135; p = 0.000	0.834	9
$R_M{}^0{}_{acetonitrile}$ = −1.084 (±0.992) + 0.527 (±0.109)Sp – 0.244 (±0.060)nAT p(intercept) = 0.255; p(Sp) = 0.000; p(nAT) = 0.000 R^2_{adj} = 0.543; F = 12.904; p = 0.000	0.589	10
$R_M{}^0{}_{acetone}$ = 0.301(±0.154) + 0.891(±0.057)logP p(intercept) = 0.066; p(logP) = 0.000 R^2_{adj} = 0.924; F = 242.976; p = 0.000	0.927	11
$R_M{}^0{}_{acetone}$ = −2.842 (±1.005) + 0.615 (±0.119)Sp – 0.261 (±0.065)nAT p(intercept) = 0.011; p(Sp) = 0.000; p(nAT) = 0.000 R^2_{adj} = 0.624; F = 17.609; p = 0.000	0.662	12
$R_M{}^0{}_{THF}$ = −4.185(±0.494) + 0.791(±0.034) miLogP + 1.516(±0.171)Uc – 0.029(±0.006)Pol p(intercept) = 0.000; p(miLogP) = 0.000; p(Uc) = 0.000; p(Pol) = 0.000 R^2_{adj} = 0.980; F = 322.182; p = 0.000	0.985	13
$R_M{}^0{}_{THF}$ = −1.993(±0.422)+0.005(±0.002)V_x−0.555(±0.117)logS+0.072(±0.625)logD p(intercept) = 0.000; p(V_x) = 0.012; p(logS) = 0.000; p(logD) = 0.264 R^2_{adj} = 0.898; F = 59.766; p = 0.000	0.926	14
$R_M{}^0{}_{1,4\text{-dioxane}}$ = −2.477(±0.800) + 0.999(±0.052)logP + 0.748(±0.227)Uc p(intercept) = 0.006; p(logP) = 0.000; p(Uc) = 0.000 R^2_{adj} = 0.952; F = 198.896; p = 0.000	0.957	15
$R_M{}^0{}_{1,4\text{-dioxane}}$ = 1.442(±0.101) + 0.241(±0.020)MLOGP2 p(intercept) = 0.000; p(MLOGP2) = 0.000 R^2_{adj} = 0.879; F = 146.809; p = 0.000	0.885	16

From Tables 3 and 4 can be seen that the calculated logarithm of the partition coefficient, log *P* (ClogP, miLogP, ALOGP, MLOGP2, logP) is the dominant descriptor in the most of the QSRR models. Moreover, half of the models are monoparametric (namely models nos. (1), (2), (5), (6), (7), (9), (11), and (16)) with partition coefficient as a descriptor; the most of them calculated for protic solvents.

The regression coefficients of the descriptor log *P* in monoparamertic as well as multiparametric QSRR models were always positive. As expected the higher the chromatographic lipophilicity, calculated log *P* increases. Besides log *P* in some of the models was present Sp (sum of atomic polarizability) (nos. (4), (8), (10), and (12)). Furthermore, two more descriptors are present in the models namely nAT (number of atoms) (models nos. (10) and (12)) and Uc (number of unsaturated bonds) (models nos. (13) and (15)). In five out of eight QSRR models the partition coefficient (log *P*) was no present. These are models nos. (4), (8), (10), (12), and (14). These five models are obtained for the following organic solvents: n-propanol, t-butanol, acetonitrile, acetone, and THF.

The value of the adjusted coefficient of determination (R^2_{adj}) ranging from 0.755 to 0.980 indicates that in QSRR models (1-3), (5-7), (9), (11), (13), (15) and (16) exist strong dependence between the variables. High F-parameter values indicate good data compatibility. The predictive ability of the QSRR models is described in the validation coefficient Q^2. The calculated models are valid if the value of Q^2 is greater than 0.7, while low values for Q^2 indicate a low predictive ability of the model. The values of the validation coefficient Q^2 (Tables 3 and 4) for these QSRR models range from 0.767 to 0.985. A high value of R^2_{adj}, F, and p indicates that all proposed QSRR models are statistically significant. High values of the validation coefficient Q^2 indicated that the models are reliable for predicting the chromatographic lipophilicity of similar compounds and their chromatographic behavior.

Based on the value of the statistical parameter Q^2 can be concluded that models nos. (4), (10), and (12) are evaluated as models with poor predictive characteristics. The values of the Q^2 parameter indicate that models nos. (8) and (14) have good predictive capabilities. However, in the model no. (8) it is observed that the regression coefficient describing the intercept is not statistically significant ($p > 0.05$), while in the model no. (14), it is noticed that the regression coefficient describing the molecular descriptor logD is not statistically significant ($p>0.05$). Therefore, QSRR models nos. (4), (8), (10), (12), and (14) are less suitable for the prediction of the chromatographic lipophilicity parameter. Accordingly, the mentioned models will be omitted from further consideration.

The multiparametric QSRR model no. (3) for the chromatographic system with n-propanol as an organic solvent include molecular descriptors ClogP (partition coefficient) and IAC (total information index on atomic composition). The negative value of the coefficient for IAC indicates that the dependent variable and molecular descriptor of IAC are negatively correlated. The coefficient value of the molecular descriptor of IAC is very small. However, based on the values of molecular descriptors in Table S1, it can be concluded that the contribution to lipophilicity of a molecular descriptor of IAC is almost identical as it is the contribution of the molecular descriptor of ClogP.

Based on the values of the statistical parameters R^2_{adj} and F, it can be noticed that the QSRR model no. (13) is the best-rated of all the presented models (Tables 3 and 4). The QSRR model no. (13) calculated for tetrahydrofuran as an organic solvent is multiparametric. This model is described with three molecular descriptors (miLogP, Uc, and Pol). The regression coefficient next to the molecular descriptor of Pol is negative and this indicates a negative correlation with dependent variable. The molecular descriptor Uc and miLogP display much higher contribution to lipophilicity than the molecular descriptor of Pol. Besides, Q^2 indicates that this model has the best predictive characteristics suggesting that solvents such as THF, which is seldomly used as a modifier, should be considered more often.

The multiparametric QSRR model no. (15) calculated for the 1,4-dioxane contains molecular descriptors logP (partition coefficient) and Uc (unsaturation count). The regression coefficients of both molecular descriptors are positive. The values of the regression coefficients indicate that both molecular descriptors significantly contribute to lipophilicity.

The experimental and predicted R_M^0 values using QSRR models are compared and presented in Figure 3.

Figure 3 shows linear dependence of the best QSRR model for predicting the chromatographic parameter of lipophilicity.

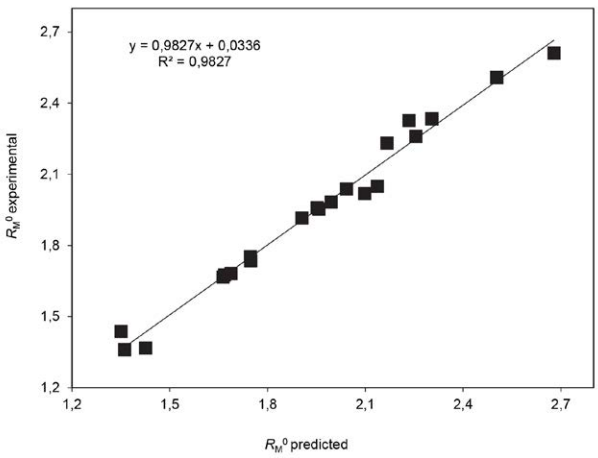

Figure 3: Comparison of experimental and predicted R_M^0 values calculated from the QSRR model no. (13) for the THF-water mobile phase.

3. 3. External Validation of QSRR Models

In order to evaluate the validity of the obtained QSRR models additional external validation was done. The investigated set of 21 compounds was split into the training (76%) and test (24%) sets. The training set is consisted of 16 compounds namely I.2, I.4, I.5, I.6, I.7, II.1, II.2, II.3, II.4, II.7, III.1, III.2, III.3, III.5, III.6, and III.7; the test set includes 5 compounds (I.1, I.3, II.5, II.6, and III.4).

The calculated QSRR equations, using the training set, are listed in Table 5. The statistical quality of the models was assessed by the coefficient of adjusted determination R^2adj, the standard error of estimate (s), the probability value (p), and the Fisher test for significance of the equation (F-value). The acceptance level for the individual independent variables was set at the 95% significance level. Further, the statistical quality of the models was judged using different validation parameters like Q^2 and R^2_{pred}, and also some novel metrics like r_m^2(test). The calculated models are valid if the value of Q^2 is greater than 0.7. The values of R^2_{pred} and r_m^2(test) for an acceptable model should be more than 0.5.[51] The values of validation parameters Q^2, R^2_{pred}, and r_m^2(test) are provided in Table 5.

The Q^2 value (Table 5) range from 0.728 (for acetonitrile) to 0.980 (for THF). Also, the accuracy of models 19-24 was checked using validation parameters R^2_{pred} and r_m^2(test) (Table 5). The R^2_{pred} value for all QSRR models is equal and greater than 0.727, which shows good predictive ability of the model. Values of r_m^2 metrics (r_m^2(test)) more than 0.5 imply the goodness of predictions of these models. In general, high values of the statistical parameters (Q^2, R^2_{pred}, r_m^2(test), R^2_{adj}, F, and p) indicate that the models are statistically significant and convenient for predicting chromatographic lipophilicity.

The QSRR models listed in Tables 5 and 3 are very similar. Both methods (without and with splitting the data) give the models with almost identical molecular descriptors. Also, the calculated QSRR equations do not have significant variations of the statistical parameters. Slightly better statistical data of QSRR equations were obtained using internal validation, compared to external validation. This is due to the larger dataset (21 compounds), which is used for calculating equations in internal validation unlike to 16 compounds in the external validation

4. Conclusion

QSRR modeling is an important tool for processing and evaluation of the experimental chromatographic data in biomedical and chemical research.

Most calculated QSRR models include partition coefficient log *P* as molecular descriptor with the most significant influence on the chromatographic behavior of investigated compounds. Internal validation confirmed that most of the calculated QSRR models have good pre-

Table 5: QSRR equations obtained for all applied solvents.

Regression equations	Q^2	R^2_{pred}	r_m^2(test)	No. models	
$R_M{}^0{}_{ethanol}$ = 0.672(±0.123) + 0.591 (±0.041)ClogP + 0.133(±0.045)logD p(intercept) = 0.000; p(ClogP) = 0.000; p(ClogP) =0.012 R^2_{adj} = 0.949; F = 139.232; p = 0.000	0.955	0.898	0.922	17
$R_M{}^0{}_{n\text{-}propanol}$ = 1.043(±0.161) + 0.238 (±0.028)ClogP – 0.002(±0.001)ECC p(intercept) = 0.000; p(ClogP) = 0.000; p(ECC) = 0.006 R^2_{adj} = 0.849; F = 43.189; p = 0.000	0.969	0.937	0.537	18
$R_M{}^0{}_{i\text{-}propanol}$ = 0.097(±0.160) + 0.496 (±0.056)miLogP p(intercept) = 0.553; p(miLogP) = 0.000 R^2_{adj} = 0.838; F = 78.80; p = 0.000	0.849	0.963	0.843	19
$R_M{}^0{}_{t\text{-}butanol}$ = 1.267(±0.049) + 0.037 (±0.006)ALOGP2 p(intercept) = 0.000; p(ALOGP2) = 0.000 R^2_{adj} = 0.724; F = 40.45; p = 0.000	0.743	0.727	0.623	20
$R_M{}^0{}_{acetonitrile}$ = 2.031 (±0.139) + 0.168 (±0.027) MLOGP2 p(intercept) = 0.000; p(MLOGP2) = 0.000 R^2_{adj} = 0.709; F = 37.55; p = 0.000	0.728	0.931	0.770	21
$R_M{}^0{}_{acetone}$ = 0.508 (±0.158) + 0.826 (±0.058) logP p(intercept) = 0.006; p(logP) = 0.000 R^2_{adj} = 0.929; F = 199.09; p = 0.000	0.934	0.900	0.787	22
$R_M{}^0{}_{THF}$ = −1.419(±0.212)+0.025(±0.003)AMR−0.682(±0.036)MLOGP p(intercept) = 0.000; p(AMR) = 0.000; p(MLOGP) = 0.000 R^2_{adj} = 0.977; F = 325.23; p = 0.000	0.980	0.986	0.959	23
$R_M{}^0{}_{1,4\text{-}dioxane}$ = −2.348(±0.896) + 0.965(±0.068) logP + 0.731(±0.243)Uc p(intercept) = 0.021; p(logP) = 0.000; p(Uc) = 0.010 R^2_{adj} = 0.937; F = 112.739; p = 0.000	0.945	0.964	0.920	24

dictive capabilities and that they potentially provide useful information about lipophilicity. This was additionally confirmed by external validation. The exceptions are models nos. (4), (8), (10), (12), and (14), whose values of statistical parameters indicate their poor predictive properties.

The best QSRR model for prediction of the chromatographic lipophilicity parameter is model where the lipophilicity was determined using THF as an organic solvent. Therefore, solvents such as THF, which are rarely used as a modifier, should be considered more often in these kinds of studies. Since the models have good statistical parameters and high predictive accuracy the possibility of their application to predict the lipophilicity of new structurally similar compounds was confirmed.

Acknowledgments

The authors gratefully acknowledge the financial support of the Ministry of Science, Technological Development and Innovation of the Republic of Serbia (Grants No. 451-03-66/2024-03/200125 & 451-03-65/2024-03/200125.)

Supplementary Materials

The calculated descriptors of investigated compounds are listed in Table S1.

Graphs of the size impact of the cycloalkyl group and the substituent R on the values of $R_M{}^0$ for organic solvents *n*-propanol, *i*-propanol, and *t*-butanol are shown in the Figures S1-S3.

5. References

1. L. Konnert, F. Lamaty, J. Martinez, E. Colacino, *Chem. Rev.* **2017**, *117*, 13757−13809. **DOI:**10.1021/acs.chemrev.7b00067
2. J. H. Block and J. J. M. Beale, (12th ed.): Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry, Lippincott Williams and Wilkins, Philadelphia, **2004**.
3. A. Czopek, H. Byrtus, A. Zagorska, A. Siwek, G. Kazek, M. Bednarski, J. Sapa, M. Pawłowski, *Pharmacol. Rep.* **2016**, *68*, 886–893. **DOI:**10.1016/j.pharep.2016.04.018
4. A. Tijsma, H. J. Thibaut, D. Franco, K. Dallmeier, J. Neyts, *Antivir. Res.* **2016**, *133*, 106–109. **DOI:**10.1016/j.antiviral.2016.07.023
5. H. Lu, D. Kong, B. Wu, Y. Wang, *Lett. Drug Des. Discov.* **2012**, *9*, 638–642. **DOI:**10.2174/157018012800673092
6. R. N. Comber, R. C. Reynolds, J. D. Friedrich, R. A. Manguikian, R. W. Buckheit Jr., J. W. Truss, W. M. Shannon, J. A. Secrist III, *J. Med. Chem.* **1992**, *35*, 3567−3572.

DOI:10.1021/jm00097a014
7. T. L. Lemke and D. A. Williams, (6th ed): Foye's Principles of Medicinal Chemistry, Lippincott Williams and Wilkins, Philadelphia, **2008**.
8. G. A. Dijkman, R. A. Janknegt, T. M.de Reijke, F. M. J. Debruyne, *J. Urol.* **1997**, *158*, 160–163. **DOI:**10.1097/00005392-199707000-00051
9. C. Carmi, A. Cavazzoni, V. Zuliani, A. Lodola, F. Bordi, P. V. Plazzi, R. R. Alfieri, P. G., Petronini, M. Mor, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4021–4025. **DOI:**10.1016/j.bmcl.2006.05.010
10. L. Jiang, B. Zeng, *Adv. Mater. Res.* **2014**, *89*, 512–515. **DOI:**10.1016/j.contraception.2013.12.017
11. C. S. A. Kumar, S. B. B. Prasad, K. Vinaya, S. Chandrappa, N. R. Thimmegowda, K. S. Rangappa, S. Swarup, *Invest. N. Drugs.* **2009**, *27*, 131–139. **DOI:**10.1007/s10637-008-9150-3
12. C. V. Kavitha, M. Nambiar, P. B. Narayanaswamy, E. Thomas, U. Rathore, C. S. A. Kumar, B. Choudhary, K. S. Rangappa, S. C. Raghavan, *PloS One.* **2013**, *8*, 1–10.
13. I. Gomez-Monterrey, G. Santelli, P. Campiglia, D. Califano, F. Falasconi, C. Pisano, L. Vesci, T. Lama, P. Grieco, E. Novellino, *J. Med. Chem.* **2005**, *48*, 1152–1157. **DOI:**10.1021/jm0408565
14. L. H. Ramadani, O. Talhi, N. Taibi, L. Delort, C. Decombat, A. Silva, K. Bachari, M. P. Vasson, F. Caldefie-Chezet, *Anticancer Res.* **2016**, *36*, 6399–6408. **DOI:**10.21873/anticanres.11237
15. A. Atrrog, M. Natić, T. Tosti, D. Milojković-Opsenica, I. Đorđević, V. Tešević, Z. Tešić, *Biomed. Chromatogr.* **2009**, *23*, 250–256. **DOI:**10.1002/bmc.1091
16. A. Czopek, M. Kołaczkowski, A. Bucki, H. Byrtus, M. Pawłowski, G. Kazek, A. Wesołowska, *Bioorg. Med. Chem.* **2015**, *23*, 3436–3447. **DOI:**10.1016/j.bmc.2015.04.026
17. E. H. Rabtti, M. Natić, D. Milojković-Opsenica, J. Trifković, I. Vucković, V. Vajs, Ž. Tešić, *J. Braz. Chem. Soc.* **2012**, *23*, 522–530.
18. A. R. Katritzky, M. Kuanar, S. Slavov, C. D. Hall, M. Karelson, I. Kahn, D. A. Dobchev, *Chem. Rev*. **2010**, *110*, 5714–5789. **DOI:**10.1021/cr900238d
19. R. Kaliszan, *Chem. Rev.* **2007**, *107*, 3212–3246. **DOI:**10.1021/cr068412z
20. K. Heberger, J. Chromatogr. A. **2007**, *1158*, 273–305. **DOI:**10.1016/j.chroma.2007.03.108
21. B. J. Neely, S. V. Madihally, R. L. Robinson, K. A. M. Gasem, *J. Pharm. Sci.* **2009**, *98*, 4069–4084. **DOI:**10.1002/jps.21678
22. R. Kaliszan, T. Baczek, A. Bucinski, B. Buszewski, M. Sztupecka, *J. Sep. Sci.* **2003**, *26*, 271–282. **DOI:**10.1002/jssc.200390033
23. M. Golubović, J. Protić, A. Otašević, B. Zečević, *Talanta* **2016**, *150*, 190–197. **DOI:**10.1016/j.talanta.2015.12.035
24. P. R. Talebi, M. Schuster, G. Shellie, R. A. Szucs, R. Haddad, *J. Chromatogr. A* **2015**, *1424*, 69–76. **DOI:**10.1016/j.chroma.2015.10.099
25. L. T. Qin, S. S. Liu, F. Chen, Q. S. Wu, *J. Sep. Sci.* **2013**, 36, 1553–1560. **DOI:**10.1002/jssc.201300069
26. Y. Bodzioch, K. Durand, A. Kaliszan, R. Baczek, T. Vander Heyden, *Talanta* **2010**, *81*, 1711–1718. **DOI:**10.1016/j.talanta.2010.03.028
27. P. Riahi, S. Pourbasheer, E. Ganjali, M. R. Norouzi, *J. Hazard. Mater.* **2009**, *166*, 853–859. **DOI:**10.1016/j.jhazmat.2008.11.097
28. S. Riahi, M. R. Ganjali, E. Pourbasheer, P. Norouzi, *Chromatographia* **2008**, *67*, 917–922. **DOI:**10.1365/s10337-008-0608-4
29. R. Kaliszan, and T. Baczek, Recent Adv. *QSAR Stud.* **2010**, *8*, 223–259. **DOI:**10.1007/978-1-4020-9783-6_8
30. E. Rutkowska, K. Paja.k, K. Jóźwiak, *Acta Pol. Pharm.* **2013**, *70*, 3–18.
31. J. A. Platts, S. P. Oldfield, M. M. Reif, A. Palmucci, E. Gabano, D. Osella, J. Inorg. Biochem. **2006**, *100*, 1199–1207. **DOI:**10.1016/j.jinorgbio.2006.01.035
32. S. S. P. Wahajuddin, K. S. R. Raju, A. Nafis, G. K. Jain, *J. Pharm. Biomed. Anal.* **2012**, *67–68*, 71–76. **DOI:**10.1016/j.jpba.2012.03.048
33. R. Mannhold, G. I. Poda, C. Ostermann, I. V. Tetko, *J. Pharm. Sci.* **2009**, *98*, 861–893. **DOI:**10.1002/jps.21494
34. L. R. Jevrić, M. Ž. Karadžić, A. I. Mandić, S. O. Podunavac-Kuzmanović, S. Z. Kovačević, A. R. Nikolić, A. M. Oklješa, M. N. Sakač, K. M. Penov Gaši, S. Z. Stojanović, *J. Pharm. Biomed. Anal.* **2017**, *134*, 27–35. **DOI:**10.1016/j.jpba.2016.11.015
35. M. Ž. Karadžić, D. M. Lončar, G. Benedeković, I. Kovačević, V. Popsavin, S. Z. Kovačević, L. R. Jevrić, S. O. Podunavac-Kuzmanović, *Eur. J. Pharm. Sci.* **2017**, *105*, 99–107. **DOI:**10.1016/j.ejps.2017.05.006
36. M. Zapadka, M. Kaczmarek, B. Kupcewicz, P. Dekowski, A. Walkowiak, A. Kokotkiewicz, M. Łuczkiewicz, A. Buciński, *J. Pharm. Biomed. Anal.* **2019**, *164*, 681–689. **DOI:**10.1016/j.jpba.2018.11.024
37. M. A. Fouad, E. H. Tolba, M. A. El-Shal, A. M. El Kerdawy, *J. Chromatogr. A* **2018**, *1549*, 51–62. **DOI:**10.1016/j.chroma.2018.03.042
38. J. Trifunović Ristovski, N. Janković, V. Borčić, S. Jain, Z. Bugarčić, M. Mikov, *J. Pharm. Biomed. Anal.* **2018**, *155*, 42–49. **DOI:**10.1016/j.jpba.2018.03.038
39. E. C. Bate-Smith, R. G. Westall, Biochim. *Biophys. Acta.* **1950**, *4*, 427–440. **DOI:**10.1016/0006-3002(50)90049-7
40. E. Soczewinski, G. Matysik, *J. Chromatogr. A* **1968**, *32*, 458–471. **DOI:**10.1016/S0021-9673(01)80519-7
41. J. Dorsey, M. Khaledi, *J. Chromatogr. A* **1993**, *656*, 485–499. **DOI:**10.1016/0021-9673(93)80815-P
42. DRAGON for windows (Software for molecular descriptor calculation), Version 5.5–Talete srl, http://www.talete.mi.it 2007
43. Chemdraw Ultra 7.0 and Chem3D Ultra, Cambridge Soft Corporation, Cambridge, USA, http://cambridgesoft.com
44. http://www.molinspiration.com (accessed April 3, 2019)
45. J. Dong, N. N. Wang, Z. J. Yao, *J. Cheminform.* **2018**, *10*, 1–11. **DOI:**10.1186/s13321-018-0283-x
46. L.-T. Qin, Y.-H. Chen, X. Zhang, L.-Y. Mo, H.-H. Zeng, Y.-P. Liang, *Chemosphere* **2018**, *198*, 122-129. **DOI:**10.1016/j.chemosphere.2018.01.142

47. A. Golbraikh, J. Tropsha, *J. Mol. Graph. Model.* **2002**, *20,* 269–276. **DOI:**10.1016/S1093-3263(01)00123-1
48. C. M. Hansen, (2nd ed.): Hansen Solubility Parameters, Taylor & Francis Group, New York, **2007**. **DOI:**10.1201/9781420006834
49. C. Reichardt and T. Welton, (4th ed.): Solvents and Solvent Effect in Organic Chemistry, Wiley VCH Verlag GmbH & Co. KGaA, Weinheim, **2011**.
50. K. Tot, A. Lazić, T. Djaković Sekulić, *J. Liq. Chromatogr. Relat. Technol.* **2020**, *43*, 925–933. **DOI:**10.1080/10826076.2020.1856137
51. P. K. Ojha, K. Roy, *Chemom. Intell. Lab. Sys.* **2011**, *109*, 146–161. **DOI:**10.1016/j.chemolab.2011.08.007

Povzetek

Izvedli smo analizo kvantitativnih razmerij med strukturo in retencijo (QSRR) na kromatografskih parametrih lipofilnosti izbranih spirohidantoinov. Uporabili smo tehnike multiple linearne regresije (MLR) za izgradnjo modelov QSRR. Kromatografski parametri lipofilnosti so bili določeni z obratno-fazno tankoslojno kromatografijo. Kromatografske analize smo izvedli na C-18 modificiranem silikagelu z dvokomponentno mobilno fazo, sestavljeno iz vode in protičnega organskega topila (etanol, n-propanol, i-propanol ali t-butanol) v različnih razmerjih. Izdelali smo tudi QSRR modele za dodatne štiri vodne mobilne faze: aceton-voda, acetonitril-voda, tetrahidrofuran-voda in 1,4-dioksan-voda (rezultati so bili objavljeni prej). Skupno smo v tej QSRR študiji proučevali kromatografske parametre lipofilnosti, pridobljene za dve vrsti organskih topil. Napovedno sposobnost vsakega modela smo ocenili z notranjo in zunanjo validacijo. Izmed pridobljenih modelov QSRR za napoved kromatografskega parametra lipofilnosti se je za najboljšega izkazal za tetrahidrofuran kot organsko topilo.