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ORIGINAL ARTICLE

Chemometric characterization of *s*-triazine derivatives in relation to structural parameters and biological activity

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Abstract

Objective: In this study 14 newly synthesized *s*-triazine derivatives were investigated by means of reversed-phase thin-layer chromatography (TLC) on C-18 stationary and five different mobile phases: acetone–water, acetonitrile–water, methanol–water, 2-propanol–water, and tetrahydrofuran–water. *Methods*: Principal component analysis (PCA) was performed to explore and visualize similarities and differences among the compounds and among the mobile phases. Observations from the PCA were supported using hierarchical cluster analysis (HCA). *Results*: Physicochemical parameters that are significant for activity, that is, absorption, distribution, and bonding for different receptors in target tissues were calculated. *Conclusion*: Highly predictive models, describing quantitative relationships between chromatographic retention and parameters that influence activity, were obtained using partial least squares (PLS) method.

Key words: *HCA; PCA; PLS; QSAR; screening activity; s-triazines; structure-based design*

Introduction

1,3,5-Triazines (or *s*-triazines) are a class of compounds well known for a long time and are still being the object of considerable interest, mainly because of their applications in agriculture as the basis for various herbicides[1]. Furthermore, some *s*-triazines display important biological activities, such as cytotoxic[2], anticancer[3], or antibacterial[4], which makes them attractive in various medical applications. The concern over the use of synthetic herbicides in agriculture and medicine makes the need to discover new, potent *s*-triazines with no or low toxicity to plants, mammals, and insects increasingly urgent. Development of new *s*-triazine derivatives as potential drugs or herbicidal agents and determination of their interactions with environment is important for the modern *s*-triazine chemistry. In this sense understanding the chemistry of life processes is essential to unravel the basic chemical reactions at their heart of molecular level.

The pharmacokinetic/pharmacodynamic processes of drug action are considered to have much in common with the processes on which chromatographic separations are based. The same basic molecular properties (hydrophobic, electronic, and steric) affect not only transport processes and drug–biological target interactions, but also compound retention in a chromatographic system under specific experimental conditions. Consequently, chromatography can be used as powerful technique for estimating physicochemical parameters and biological activities. In addition, chromatographic techniques are dynamic systems that permit the strict control of experimental conditions, thus very reproducible retention data can be obtained. That is the reason why reversed-phase liquid chromatography has attracted considerable attention as an in vitro model to predict the pharmacological and pharmacokinetic properties of drugs in the early stages of the drug discovery phase. The application of retention parameters to obtain descriptive

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and predictive models of pharmacological responses gives rise to a new field, quantitative retention–activity relationships, which is the part of broader quantitative structure–activity relationships (QSAR). In that sense use of statistical and mathematical methods to build models, which relate molecular structure to physical, chemical, or biological properties, has recently found growing acceptance and application[5–7]. In this study computational methods are used to recognize the chromatographic system, which is the most similar to biological processes, focusing on virtual screening and introducing selection criteria, such as molecular diversity, drug likeness, Lipinski's criteria for bioavailability, passive transport partition, distributive pathways, and predicted receptor-binding affinity.

Materials and methods

The investigated compounds were 1,3,5-triazines substituted at positions 4 and 6 by smaller and larger groups with various lipophilic characteristics (Table 1). Compounds were synthesized in the laboratory at the Department of Organic Chemistry in Faculty of Technology and Metallurgy, University of Belgrade[8,9].

Chromatographic analyses were performed on 10 × 10 cm high-performance thin-layer chromatography (HPTLC) plates coated with C18 silica F_{254} (Merck, Darmstadt, Germany). The plates were developed in unsaturated chambers by ascending technique with aqueous solutions of different organic modifiers: acetone (50–80%, v/v), acetonitrile (50–90%, v/v), methanol (65–95%, v/v), 2-propanol (40–70%, v/v), and tetrahydrofuran (50–75%, v/v).

After development the compounds were detected in UV light at $\lambda = 254$. The R_F values were averages from at least three measurements for each solute–mobile phase combination. For subsequent calculations mean R_M values were calculated using Equation (1):

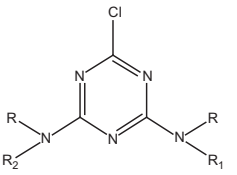
$$R_M = \log\left(\frac{1}{R_F} - 1\right), \tag{1}$$

and then the R_M values for different mobile phases were used to check the linearity of their relationship with the volume fraction of organic solvent (modifier) (Equation 2):

$$R_M = R_M^0 + m\varphi, \tag{2}$$

where φ is the volume fraction of organic modifier in the mobile phase, R_M^0 (intercept) is the extrapolated value obtained at $\varphi = 100\%$ water, and m is the slope (Table 2). Extrapolation to pure water leads to the estimation of lipophilicity parameter R_M^0, which has been commonly used as a quantitative TLC retention descriptor[10–12]. The Equations (1) and (2) are considered to be the basis for deriving data for QSAR studies.

Table 1. The structures of the compounds investigated.



Series I

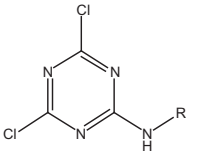
No.	Compound	R	R_1	R_2
1	I.1	$-CH_3(CH_3)-C_6H_5$	H	H
2	I.2	$-CH_3(CH_3)-C_6H_4-4-CH_3$	H	H
3	I.3	$-CH_3(CH_3)-C_6H_4-4-Cl$	H	H
4	I.4	$-CH_3(CH_3)-C_6H_4-4-Br$	H	H

Series II

No.	Compound	R	R_1	R_2
5	II.1	1,1-Methylcyclopentyl	H	H
6	II.2	1,1-Methylcyclohexyl	H	H
7	II.3	1,1-Methylcycloheptyl	H	H

Series III

No.	Compound	R	R_1	R_2
8	III.1	C_6H_{11}	H	H
9	III.2	C_6H_{11}	CH_3	CH_3
10	III.3	C_6H_{11}	C_6H_5	H
11	III.4	C_6H_{11}	C_6H_5	C_6H_5



Series IV

No.	Compound	R
12	IV.1	1,1-Methylcyclopentyl
13	IV.2	1,1-Methylcyclohexyl
14	IV.3	1,1-Methylcycloheptyl

Physicochemical properties and application, distribution within the body, metabolism, and elimination properties were calculated using Molinspiration (Molinspiration Cheminformatics, Bratislava, Slovak Republic) and ShemSilico software (Chem Silico, LLC, Tewksbury, MA, USA). Chemometric analyses were carried out using Matlab software version 6.0 (MathWorks: Natick, MA, USA). For the principal component analysis (PCA) and hierarchical cluster analysis (HCA) data were organized in the matrix $\mathbf{X}(5 \times 14)$, whose rows represent five different chromatographic systems, whereas columns correspond to 14 compounds, specified in Table 1. A comparison of 14 tested compounds studied in five chromatographic systems was performed for the centered data.

Table 2. Data for linear correlation R_M^0 and m (see Equation 2) between R_M values and the volume fraction of organic solvent in the mobile phase for investigated compounds, correlation coefficient (r), and number of data points (N).

	Acetone–water				Acetonitrile–water				Methanol–water				2-Propanol–water				Tetrahydrofuran–water			
Compound	R_M^0	m	r	N	R_M^0	m	r	N	R_M^0	M	r	N	R_M^0	m	r	N	R_M^0	m	r	N
I.1	3.185	−4.721	0.999	7	2.110	−3.501	0.998	8	2.457	−3.087	0.996	6	1.900	−3.34	0.999	7	3.439	−5.218	0.998	6
I.2	3.580	−5.078	0.997	7	2.786	−4.194	0.995	9	3.188	−3.738	0.997	6	2.525	−4.196	0.993	7	3.567	−5.289	0.993	6
I.3	3.839	−5.370	0.997	7	2.887	−4.215	0.996	9	3.976	−4.570	0.992	7	2.617	−4.153	0.991	7	3.538	−5.214	0.996	6
I.4	4.303	−5.984	0.998	7	2.896	−4.098	0.995	9	4.407	−4.984	0.989	7	2.764	−4.332	0.993	7	3.351	−4.912	0.996	6
II.1	3.743	−5.197	0.993	7	2.388	−3.347	0.997	9	3.181	−3.829	0.995	7	2.183	−3.826	0.997	7	3.289	−4.748	0.995	6
II.2	3.935	−5.262	0.997	7	2.753	−3.699	0.997	9	3.320	−3.868	0.994	7	2.384	−4.024	0.998	7	3.401	−4.816	0.996	6
II.3	4.218	−5.446	0.998	7	3.000	−3.788	0.995	9	4.530	−5.070	0.998	7	3.013	−4.811	0.997	7	4.071	−5.730	0.994	6
III.1	4.118	−5.741	0.993	7	2.356	−3.304	0.995	9	3.440	−4.086	0.991	7	2.251	−3.962	0.996	7	3.426	−5.06	0.991	6
III.2	4.626	−6.004	0.998	7	3.284	−4.197	0.998	9	3.998	−4.452	0.994	7	2.769	−4.437	0.996	7	3.611	−5.140	0.994	6
III.3	4.019	−5.306	0.998	7	3.101	−4.076	0.998	9	3.980	−4.471	0.995	7	2.691	−4.383	0.998	7	3.387	−4.912	0.996	6
III.4	4.693	−5.951	0.996	7	3.556	−4.394	0.997	9	5.295	−5.764	0.995	7	2.747	−4.117	0.998	7	3.902	−5.503	0.998	6
IV.1	1.672	−2.707	0.994	6	1.497	−2.592	0.997	9	1.526	−2.206	0.999	7	1.118	−2.422	0.992	7	1.733	−2.897	0.996	6
IV.2	2.034	−3.184	0.995	7	1.590	−2.629	0.995	9	1.626	−2.242	0.988	7	1.400	−2.910	0.991	7	1.795	−2.900	0.996	6
IV.3	2.257	−3.286	0.995	6	1.956	−2.821	0.996	9	1.756	−2.090	0.993	7	1.779	−3.164	0.984	7	2.222	−3.340	0.995	6

Results and discussion

Generally, the entire pharmacokinetic profile is influenced by the physicochemical properties of a compound, such as molecular weight, lipophilicity, hydrogen bond donors, and acceptors. These molecular properties are independent from pharmacological or therapeutic targets[13,14]. On the basis of Lipinski's 'rule of five'[15], it is possible to identify compounds with a high risk of poor bioavailability. The starting points of the rule are four parameters, which define the 'drug-likeness': (1) log P (where P is the octanol–water partition coefficient); (2) H-bond donors, HBD; (3) H-bond acceptors, HBA; and (4) molecular weight, MW. The numerical values of these four parameters should be close to five or a multiple of five. For the investigated compounds the values of Lipinski's four parameters as well as their cutoff values are listed in Table 3.

The last column of Table 3 lists the score for Lipinski's four parameters. Score = 4 for compounds 1, 2, 5, 6, 8, 9, 12–14 confirms that they are predicted to have good absorption or permeability properties. At the same time lipophilicity of these compounds is not too high. Score = 3 for compounds 3, 7, 10, and 11, with the largest log P indicates that the prediction for the same properties is indeterminate. The lowest score (=2) and hence less possibility to be a bioactive compound has only one compound (no. 4).

Analysis of R_M^0 values obtained with different mobile phase modifiers

Besides a very good fit of Equation (2) the statistics from Table 2 illustrate different calculated R_M^0 values for various modifiers used. Higher R_M^0 values were obtained for acetone (average value 3.561) than for methanol (average value 3.315), tetrahydrofuran (average value 3.195), acetonitrile (average value 2.582), and 2-propanol (average value 2.274). Even though R_M^0 depends on the organic modifier it is most often the thin-layer chromatography (TLC) parameter that is used in QSAR correlations. Variation between R_M^0 values calculated for different modifiers may be simply expressed by correlation coefficients, which range from 0.9465 (for modifiers acetonitrile–methanol) to 0.8648 (for acetonitrile–tetrahydrofuran). To investigate whether there is any substantial difference between R_M^0 values PCA and HCA were used.

Table 3. Values of the Lipinski's numbers for the investigated compounds 1–14.

No.	Compound	Log P	No. of HBA	No. of HBD	MW	Lipinski's number
1	I.1	3.87	6	2	353.85	4
2	I.2	4.79	6	2	381.91	4
3	I.3	5.06	8	2	422.74	3
4	I.4	5.42	6	2	511.65	2
5	II.1	3.70	6	2	309.84	4
6	II.2	4.82	6	2	337.90	4
7	II.3	5.95	6	2	365.95	3
8	III.1	3.74	6	2	309.84	4
9	III.2	4.82	6	0	337.90	4
10	III.3	5.36	5	1	385.94	3
11	III.4	7.07	4	0	462.04	3
12	IV.1	2.85	6	1	247.13	4
13	IV.2	3.41	6	1	261.15	4
14	IV.3	3.98	6	1	275.18	4
Cutoff values[a]		≤5	≤10	≤5	≤500	

[a]Values recommended for good absorption or permeability prediction.

Principal component analysis

PCA is the most common chemometric technique of exploratory analysis of multivariate data set. It allows reducing the experimental data dimensionality, their visualization, and interpretation[16–18]. In PCA data matrix **X** is decomposed into two matrices, **S** and **D**, called score matrix and loading matrix, respectively. Scores and loadings matrices are orthogonal, i.e., **S´S** = **D´D** = **I**. Each column of matrix **S** is called a principal component (PC). PC is constructed as a linear combination of original variables with weights maximizing description of the variance of the data. The portion of the variance that is modeled by the corresponding PC is defined as the sum of the squared elements of each PC. The obtained PCA model with two significant PCs describes 96.19% of the total data variance (Figure 1).

The differences between five chromatographic systems are visualized in the score plot, whereas the loading plot shows similarities between 14 analyzed compounds. Score plot and loading plot are given in Figure 2.

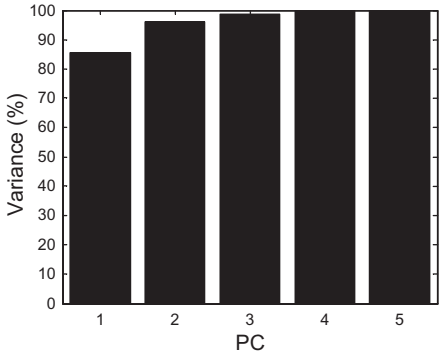


Figure 1. Percentage of the data variance described by the consecutive principal components.

Along PC1 (describing 85.38% of the total variance) it is possible to distinguish the differences between chromatographic systems based on the mobile phase used. Namely, the mobile phase modifiers acetone, methanol, and tetrahydrofuran (objects 1, 3, and 5 in Figure 2a) are characterized by negative values of PC1, whereas acetonitrile and propanol (objects 2 and 4) have positive values of PC1. Moreover the PC2, which describes 10.80% of the total variance, was constructed mainly because of the differences between objects 3 and 5, which correspond to methanol and tetrahydrofuran mobile phase modifiers, respectively.

Loading plot PC1–PC2 (in Figure 2b) allows investigating the behavior of the compounds in chromatographic systems with different mobile phases. Along PC1 the greatest dissimilarity in retention behavior is observed for compound 11 (diphenyl-substituted compound) and compounds 12, 13, and 14 (monosubstituted compounds, series IV). Moreover, PC2 allows revealing the differences between compounds 1, 2, 5, 6, 8, 12, 13, 14, and all the remaining ones. The most significant difference is observed between compounds 1 and 11; both disubstituted compounds but the first one with the lowest and the latest one with the greatest log *P* value.

Based on biplot (given in Figure 3), which presents a simultaneous projection of score and loading for the first two components, it is possible to conclude that similar retention properties are expected for compounds 2 and 5 and for compounds 12 and 13, and entirely different for compounds 1 and 11.

Hierarchical clustering

It is generally a good practice to test the conclusions drawn on the basis of one method of chemometric analysis by submitting the data to analysis by another

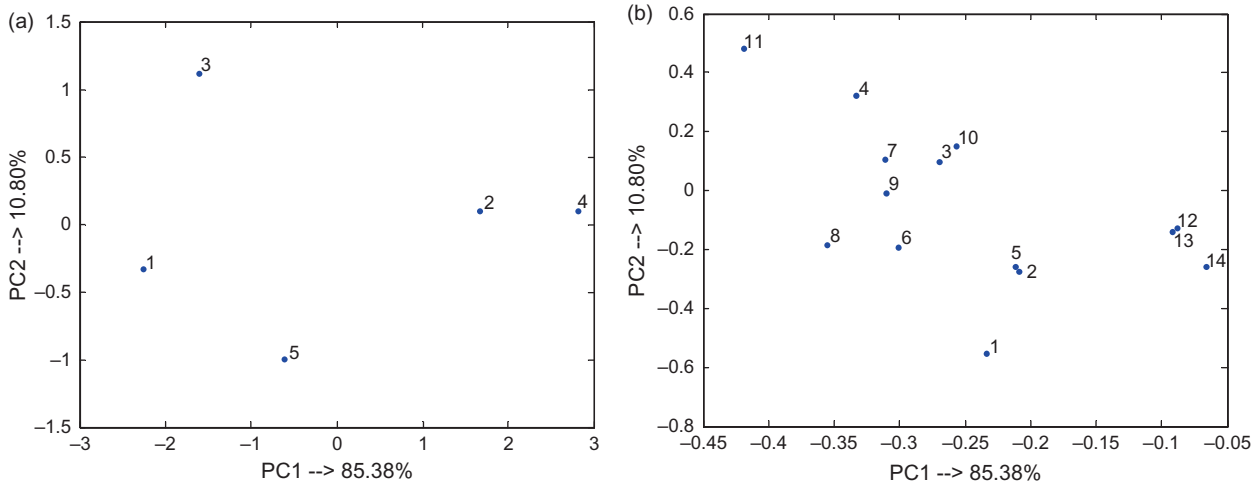


Figure 2. (a) Score plot and (b) loading plot as a result of PCA for chromatographic data **X**(5×14).

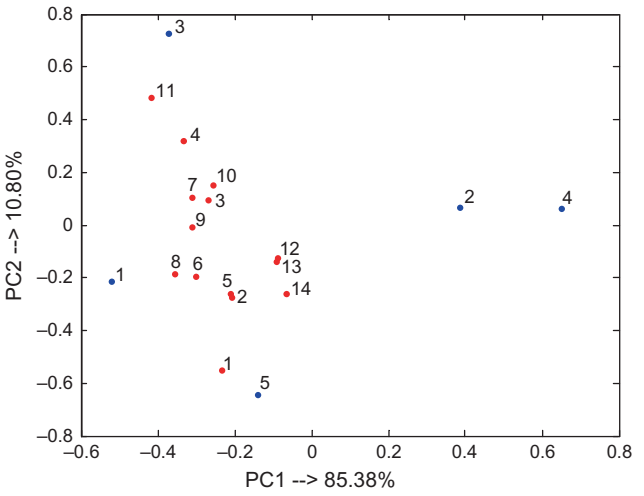


Figure 3. Biplot presenting a simultaneous projection of scores and loadings on PC1–PC2.

method. Hierarchical clustering reveals similarities/dissimilarities between objects in the variable space, or similarities/dissimilarities between variables in the objects space. Hierarchical clustering methods are characterized by the similarity measure used and the way the resulting subclusters are linked. Usually different linkage methods are applied to the same data set and their performance is determined mostly by interpretability of the results. Sometimes, interpretability of clustering is not an easy task, especially when clustering is performed in high dimensional space of parameters.

The results presented in Figure 4 are based on the Euclidean distance and the Ward linkage algorithm. The dendrogram (Figure 4a) reveals two distinct clusters of chromatographic systems: cluster A containing chromatographic systems with modifiers acetonitrile and propanol (objects 2 and 4) and cluster B with mobile phase modifiers acetone, methanol, and tetrahydrofuran (objects 1, 3, and 5).

The dendrogram constructed for 14 compounds in the space of five chromatographic systems (Figure 4a) reveals three main classes (A, B, and C). Class A contains compounds 2, 5, 1, 6, 8, and 9. Class B is constituted by compounds 12, 13, and 14, whereas class C belongs to compounds 3, 10, 7, 4, and 11. Moreover, these main clusters have additional substructures. In cluster A two following subgroups can be distinguished: subgroup A1 (compounds 2, 5, and 1) and subgroup A2 (compounds 6, 8, and 9). One subgroup (with compounds 13 and 14) is observed in cluster B (monosubstituted) and in cluster C (compounds 3, 10, and 7).

Partial least squares

Activity of a compound, as very complex process, cannot be considered to result only from the specific interactions

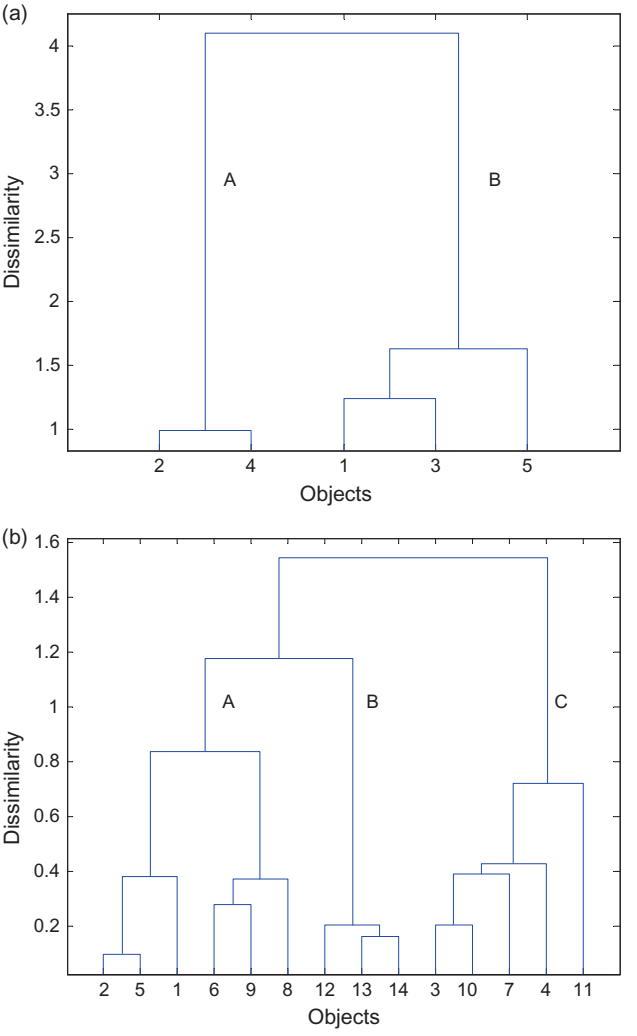


Figure 4. Dendrograms of (a) chromatographic system objects in the space of 14 compounds (listed in Table 1) and (b) compounds in the space of five different chromatographic systems (see Table 2) by the Ward linkage method using Euclidean distance as the similarity measure.

between active compound and appropriate receptor. Besides interaction with the receptors, the ability of active compound to reach the intended site of action is equally important. This occurs through absorption on the site of the application, distribution within the body, metabolism, and elimination processes. To get into the correlation between chromatographic and biological behavior the molecular properties important for activity were considered. These properties influence the processes of absorption of a potentially active compound on the site of the application, which usually occurs by passive transport, the ability of a potentially active compound to reach the intended site of action, and affect the affinity of investigated compounds for different receptors in the target tissue at the site of action. Summarized calculated properties that are of interest to the activity are presented in Table 4.

Table 4. Categories of different types of calculated activity data.

I. Absorption	
1	A log *P*
2	pK_a
3	log *W*
4	MR
5	Etotal
6	GibbsE
7	Volume
II. Distributive pathways	
8	Human intestinal absorption
9	Blood–brain barrier
10	Protein binding
III. Affinity for receptors	
11	GPCR ligand
12	Ion channel modulator
13	Kinase inhibitor
14	Nuclear receptor ligand

In Table 4 data are classified into three categories. First group, labeled as I, corresponds to molecular properties that affect the passive transport, such as partition coefficient (log *P*), dissociation constant (pK_a), water solubility (log *W*), molar refractivity (MR), total energy (Etotal), Gibbs energy (GibbsE), and volume of the molecule (Volume). Group II includes distribution pathways such as human intestinal absorption, blood–brain barrier, and protein binding. Group III includes bonding affinities to different receptors (GPCR, ion channel modulator, kinase inhibitor, and nuclear receptor).

To describe the quantitative relationship between retention data of the tested compounds (in five different chromatographic systems) and calculated activity for the tested compounds the partial least squares (PLS) method[19–21] was used. In PLS a dependent variable **y** (m, 1), here retention data, is presented as a linear combination of the remaining parameters represented as matrix **X** (m, n):

$$\mathbf{y} = \mathbf{X} \cdot \boldsymbol{b} + \boldsymbol{e}, \tag{3}$$

where $\boldsymbol{b}$, $\boldsymbol{e}$ denote the vectors of n PLS regression coefficient and residuals, whereas m and n denote the number of objects and parameters, respectively. The major advantage of PLS stems from the possibility of building models with a use of a set of correlated variables. In PLS it is achieved by the construction of several new orthogonal variables, maximizing a description of a covariance between **X** and **y**. Properly constructed PLS model is characterized by a good fit and a good predictive abilities. The fit ability is expressed as the root mean square error (RMS) obtained for all objects from the model set, whereas the predictive ability is characterized by the RMS of cross-validation (RMSCV). Cross-validation (CV)[22] is used to determine the complexity of the PLS model. The idea of CV procedure is based on the exclusion of a consecutive row or rows (namely leave-one-out or leave-more-out cross-validation) of the data matrix **X** and from the corresponding elements in the variable **y**. The remaining data set are used for construction of PLS models with an increasing number of factors. Based on the constructed models the excluded elements of the dependent variable are predicted and the RMSCV[20] is calculated for different number of factors:

$$\mathrm{RMSCV(fn)} = \sqrt{\frac{\sum_i (y(\mathrm{fn})_{i,\mathrm{pred}} - y_{i,\mathrm{obs}})^2}{m}} \quad \text{for } i = 1,2,\ldots,m, \tag{4}$$

where y_{obs} is the observed value and y_{pred}(fn) is the predicted value of y based on a model with fn factors. Then the number of factors for which RMSCV is minimal is selected to construct the final model.

In Figure 5, the constructed PLS models are presented. They describe retention data for tested compounds in different chromatographic systems in which C-18 plates were used with following mobile phases: acetone ($\mathbf{Y_1}$), acetonitrile ($\mathbf{Y_2}$), methanol ($\mathbf{Y_3}$), propanol ($\mathbf{Y_4}$), and tetrahydrofuran ($\mathbf{Y_5}$).

The RMS and RMSCV values, describing the fit and predictive abilities of these models, are presented in Table 5.

Data given in Table 5 confirm that highly predictive models were obtained. As demonstrated in Figure 5, the PLS models are characterized by good fit and predictive abilities, which are reflected by low %RMS and %RMSCV, respectively. For the presented data the %RMSCV error varies between 11.6% and 17.75%. The worst predictive ability is observed for the model describing retention time for the tested compounds in the chromatographic system developed on C-18 plate with tetrahydrofuran as a mobile phase.

Conclusions

The combination of the chemometric approach and QSAR models allows not only an evaluation of general structural similarities among molecules, but also, in particular, highlighting of the molecular features relevant to their activity. Lipinski's criteria for bioavailability show that most of the compounds are predicted to have good absorption or permeability properties. Visualization of the difference between the chromatographic systems was successfully done by PCA and HCA. Both PCA and hierarchical clustering methods

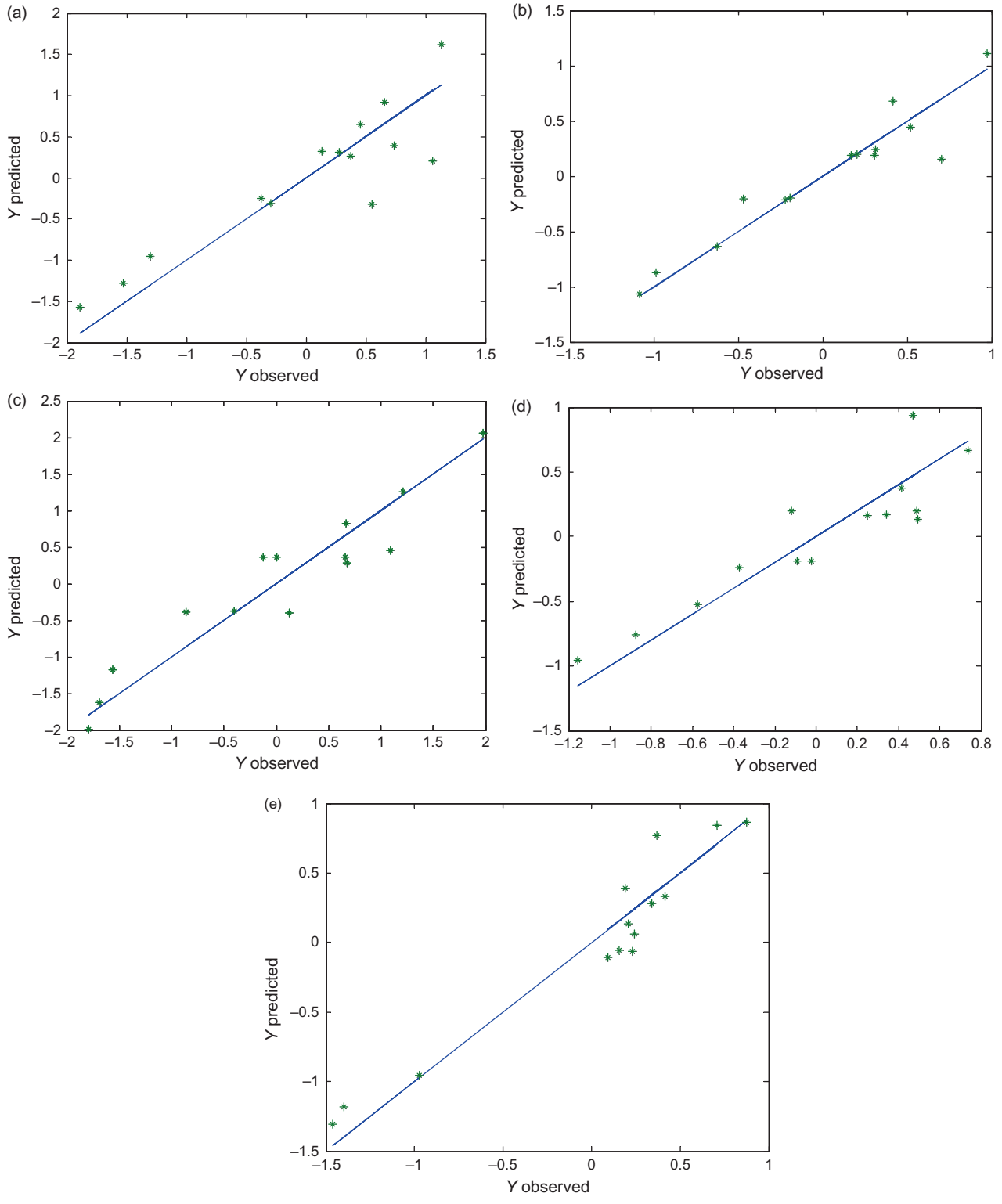


Figure 5. PLS models describing retention times for tested 14 compounds in five chromatographic systems using C-18 plates with the following mobile phases: (a) acetone ($\mathbf{Y_1}$), (b) acetonitrile ($\mathbf{Y_2}$), (c) methanol ($\mathbf{Y_3}$), (d) propanol ($\mathbf{Y_4}$), and (e) tetrahydrofuran ($\mathbf{Y_5}$).

reveal two distinct clusters of chromatographic systems with acetonitrile and propanol as mobile phase modifiers in the first one and acetone, methanol, and tetrahydrofuran in the second one. The differences between 14 investigated compounds result mainly from their lipophilicity properties. Satisfactory PLS method was developed for

Table 5. RMS and RMSCV errors of the PLS models describing retention data for tested compounds in chromatographic systems in which C-18 plates were used with the following mobile phases: acetone ($\mathbf{Y_1}$), acetonitrile ($\mathbf{Y_2}$), methanol ($\mathbf{Y_3}$), propanol ($\mathbf{Y_4}$), and tetrahydrofuran ($\mathbf{Y_5}$).

Parameter	Range	Factor	RMS	RMSCV	RMS%	RMSCV%
$\mathbf{Y_1}$	[1.6720, 4.6920]	2	0.4077	0.5094	13.50	16.87
$\mathbf{Y_2}$	[1.4970, 3.5550]	2	0.1881	0.2567	9.14	12.47
$\mathbf{Y_3}$	[1.5250, 5.2950]	2	0.3542	0.4372	9.40	11.60
$\mathbf{Y_4}$	[1.180, 3.0130]	2	0.2220	0.3015	11.72	15.91
$\mathbf{Y_5}$	[1.7330, 4.0710]	6	0.1908	0.4151	8.16	17.75

s-triazines for different modifiers to describe the quantitative relationships between retention data of the tested compounds in five different chromatographic systems and calculated data, closely correlated to the activity (passive transport, distribution pathways, and receptor-bonding affinity) of the tested compounds. The described approach could be a promising tool for studying the relationships between molecular structure and properties important in terms of the activity.

Declaration of interest

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