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Original scientific paper

COMPARATIVE CHEMOMETRIC ANALYSIS, RANKING AND SELECTION OF LIPOPHILICITY PARAMETERS OF 6-CHLORO-1,3,5-TRIAZINE DERIVATIVES WITH ACYCLIC AND CYCLIC SUBSTITUENTS

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In the present paper, the chemometric analysis, ranking and selection of the most suitable in silico lipophilicity parameters of eight alkyl and cycloalkyl s-triazine derivatives were carried out. The lipophilicity parameters were calculated using various computational approaches and computer programs. The conducted analysis is the basis for further studies aimed to define, compare and examine the influence of alkyl and cycloalkyl substituents, introduced in 6-chloro-1,3,5-triazine-2,4-diamine structure, on molecular lipophilicity and bioactivity. The chemometric methods used in the study are pattern recognition methods, such as hierarchical cluster analysis (HCA) and sum of ranking differences (SRD). The obtained ranking results indicate that the following in silico lipophilicity descriptors can be chosen as the most suitable for interpretation of lipophilicity of the studied series of s-triazine derivatives: AlogP, MlogP, WLOGP, $logP_{KLOP}$ and $logP_{PHYS}$. The lipophilicity descriptor iLOGP was marked as the least suitable lipophilicity descriptor of the studied series of compounds. The ranking results were validated by 7-fold cross-validation approach and by comparison of ranks by random numbers (CRRN).

Keywords: chemometrics, lipophilicity, pesticides, sum of ranking differences, triazines.

INTRODUCTION

Symmetric triazines (*sym*- or *s*-triazines) are a class of chemical compounds with proven effective herbicide (1, 2) and antimicrobial activity (3). Structurally, they are based on 1,3,5-triazine ring on which various substituents are attached (chlorine or other halogen elements, amino, alkylamino, isoalkylamino, cycloalkylamino, methoxyalkylamino groups, etc.). Considering the fact that important chemical products from the group of pesticides, including triazine and chloroacetanilide herbicides, have been withdrawn or cancelled because of significant environmental persistence issues and toxicity in humans, as well as quite high registration costs (4), the work on design of novel compounds or modification of existing compounds is necessary. The compounds that are of interest in the present study are the derivatives of 2-chloro-4,6-bis((cyclo)alkylamino)-*s*-triazine. The synthesis of these derivatives begins from 2,4,6-trichloro-*s*-triazine (cyanuric chloride) (**I**) and (cyclo)alkylamine (R_1-NH_2 and/or R_2-NH_2) under basic conditions, over the 2,4-dichloro-6-(alkylamino)-*s*-triazine (**II**) obtained in the first step, and eventually the desired compound (**III**) synthesized in the second step, according to the following synthetic route (5):

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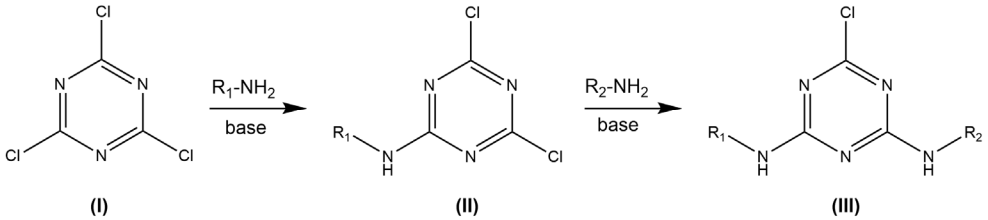

Figure 1. The synthetic route of the synthesis of 2-chloro-4,6-bis(alkylamino)-*s*-triazine derivatives

The importance of lipophilicity of the compounds in the assessment of their biological properties was emphasized in numerous publications. The lipophilicity is one of the most important parameters in estimation and prediction of bioavailability and biological activity of various bioactive compounds, including pesticides, the compounds with antifungal, antibacterial, antioxidant activity, anticancer compounds, etc (6-8). The experimental lipophilicity of various series of *s*-triazines has been studied in terms of their chromatographic behaviour (chromatographic/anisotropic lipophilicity) in thin-layer chromatography (TLC) and high-performance liquid chromatography (HPLC), mostly on reversed phases (RP) (9-13).

The availability of numerous computer programs for molecular design and prediction of molecular properties enables fast and easy calculation of lipophilicity parameters of many ionizable and non-ionizable compounds. However, different calculation approaches result in different values of lipophilicity of the same compounds. This refers to the experimental approaches as well. Therefore, the selection of the most representative lipophilicity measure of homologous series of compounds is desirable so it can be further used for prediction of various molecular features, particularly of bioactivity and bioavailability. The lipophilicity is particularly of interest in Quantitative Structure-Activity Relationship (QSAR) studies and molecular docking analysis (14).

The present study is focused on the comparison, selection and ranking of the *in silico* lipophilicity parameters of alkyl and cycloalkyl *s*-triazine derivatives since this parameter could be crucial for further investigation of their experimental lipophilicity and prediction of bioactivity, bioavailability and environmental persistence.

MATERIAL AND METHODS

THE SERIES OF THE STUDIED TRIAZINE DERIVATIVES

The analysed set included eight *s*-triazine derivatives whose IUPAC names are listed in Table 1. 2D structures of the compounds are presented in Figure 2. Based on the type of substituents, the analysed set can be divided into two separate groups:

- the group 1 contains derivatives with alkyl substituents in positions 1 and 2 of the triazine ring (compounds **1**-**4**);
- the group 2 contains derivatives with cycloalkyl substituents in positions 1 and 2 of the triazine ring (compounds **5**-**8**).

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The analysed compounds have been synthesized at the Faculty of Technology and Metallurgy, University of Belgrade, according to the procedure described in literature (15, 16).

Table 1. The IUPAC names of the studied triazine derivatives

No.	the IUPAC name
1	6-chloro-N^2,N^4-dipropyl-1,3,5-triazine-2,4-diamine
2	6-chloro-N^2,N^4-bis(propan-2-yl)-1,3,5-triazine-2,4-diamine (propazine)
3	N^2,N^4-bis(butan-2-yl)-6-chloro-1,3,5-triazine-2,4-diamine
4	6-chloro-N^2,N^4-bis(2-methylpropyl)-1,3,5-triazine-2,4-diamine
5	6-chloro-N^2,N^4-dicyclopentyl-1,3,5-triazine-2,4-diamine
6	6-chloro-N^2,N^4-dicyclohexyl-1,3,5-triazine-2,4-diamine
7	6-chloro-N^2,N^4-dicycloheptyl-1,3,5-triazine-2,4-diamine
8	6-chloro-N^2,N^4-dicyclooctyl-1,3,5-triazine-2,4-diamine

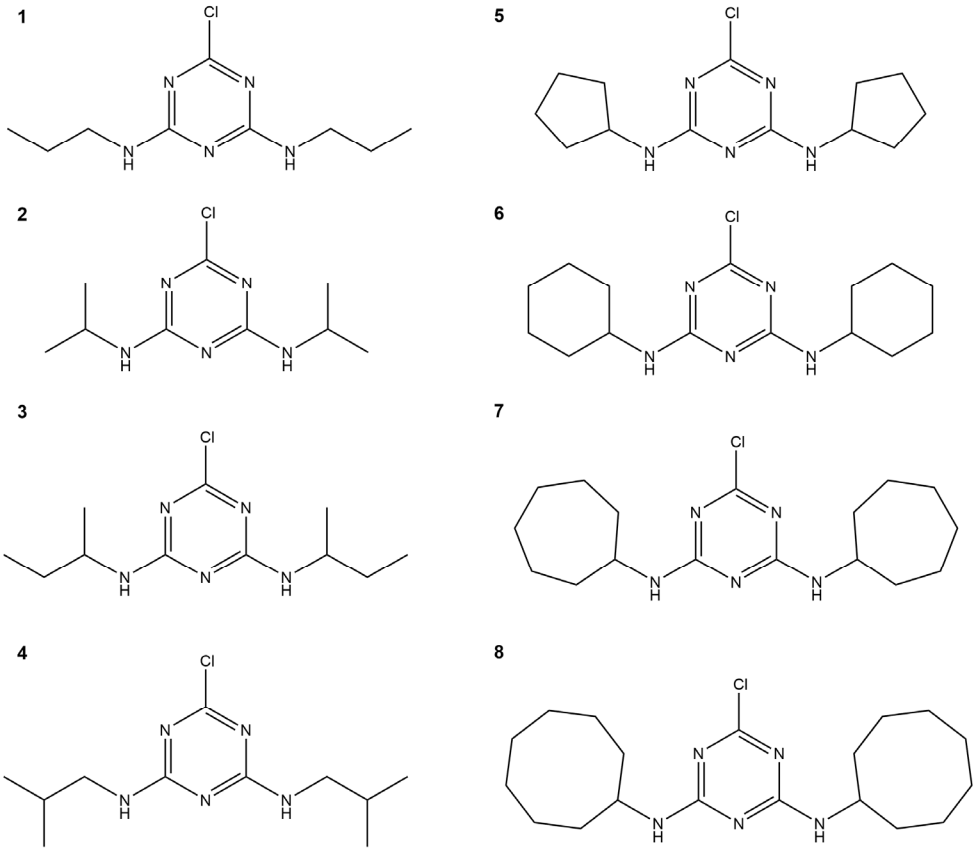

Figure 2. The molecular structures of the studied triazine derivatives with alkyl (**1**-**4**) and cycloalkyl substituents (**5**-**8**)

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Original scientific paper

The analysed set of compounds was selected for analysis so the influence of the constitutional isomerism on lipophilicity can be chemometrically estimated: the compounds **1** and **2**, as well as the compounds **3** and **4** from the series 1 are structural isomers; also, the compounds from the series 2 contain the substituents from homologous series of cycloalkanes: cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl group, which is in this case interesting to compare the influence of the ring size on the lipophilicity and compare it to the lipophilicity of the compounds from the series 1 by using chemometric methods. The compound **2** (propazine) is well-known herbicide and environmental contaminant (17).

COMPUTATIONAL ESTIMATION OF LIPOPHILICITY PARAMETERS

The lipophilicity parameters of the analysed compounds were calculated using the following programs:

- ALOGPS 2.1 (18, 19) was used for calculation of descriptors ALOGPs, AClogP, AlogP, MlogP, XlogP2 and XlogP3;
- $SWISS_{ADME}$ (20) was applied for calculation of descriptors iLOGP and WLOGP;
- MarvinSketch 14.09.15.0 (21) was used for calculation of descriptors $logP_{VG}$, $logP_{KLOP}$ and $logP_{PHYS}$;
- ChemBioDraw 13 (22) was used for calculation of descriptors $LogP_{ChDr}$ and ClogP.

Based on the calculated logP descriptors, the consensus logP values as the row average were calculated (ConsensusLogP). Some of the calculated logP descriptors are based on electrotopological state (E-state) of atoms (ALOGPs descriptor). Generally, the descriptors ALOGPs, AClogP, ALOGP, MLOGP, ClogP, XLOGP2 and XLOGP3 are obtained by fragmentation/group contribution-based methods (23). AlogP descriptor is calculated by using the atomic contribution method of Ghose, Crippen, and Viswanadhan. The logP calculated based on Ghose–Crippen method is labelled as AlogP descriptor (atom-cantered fragment descriptor) (24). MlogP descriptor was calculated using the Moriguchi model based on structural parameters (25). The WLOGP descriptor was calculated using atomistic method based on the fragmental system of Wildman and Crippen, while iLOGP descriptor is calculated using a physics-based method that relies on free energies of solvation in *n*-octanol/water system (20). It is calculated by the Generalized-Born and solvent accessible surface area (GB/SA) model (20). The descriptors $logP_{VG}$ is estimated by Viswanadhan and Ghose method (26), while the $logP_{KLOP}$ is calculated applying Klopman's method (27). The $logP_{PHYS}$ descriptor is calculated by using PHYSPROP© database. In order to estimate the influence of pH on lipophilicity, the dependences of distribution coefficient (logD) of the studied compounds on pH values were predicted by MarvinSketch program. The calculated VGlogD descriptor was estimated by Viswanadhan and Ghose method (26).

CHEMOMETRIC METHODS

Hierarchical cluster analysis (HAC), as a pattern recognition method, was applied on the calculated logP data of the studied compounds in order to gain an overview of similarities and dissimilarities among the compounds. The results of the HCA are presented graphically as a dendrogram. The Ward's method was used as an amalgamation (linkage) rule and Euclidean distances were used as a distance measure.

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Original scientific paper

The sum of ranking differences (SRD) analysis is a ranking method developed by Héberger and Kollár-Hunek (28, 29). The ranking of the objects (compounds) is performed in regard to the reference ranking. In this study the reference ranking was consensus logP values as row average. The validation of the SRD procedure was done by comparison of ranks by random numbers (CRRN) and 7-fold cross-validation approaches (30). The SRD analysis was carried out on the normalized logP data. The logP data were scaled on the range 0.01-0.99 by using *min-max* normalization method.

The detailed explanation about basics of HCA and SRD approaches can be found elsewhere (28-31).

RESULTS AND DISCUSSION

IN SILICO LIPOPHILICITY MEASURES OF TRIAZINE DERIVATIVES

The results of calculation of logP descriptors are presented in Table 2. All of the analysed compounds can be considered lipophilic since all the logP values are greater than 0. The obtained data indicate that the compounds **1**-**4** possess lower lipophilicity than the compounds **5**-**8**. One of the reasons for this can be the fact that the compounds **5**-**8** have highly lipophilic substituents – cyclic hydrocarbons (cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl groups). Considering the majority of the logP descriptors, similar lipophilicity can be noticed between structural isomers **1** (possesses propyl group) and **2** (possesses isopropyl group). The compound **2** has slightly lower lipophilicity than the compound **1**. Also, similar lipophilicity can be noticed between the compounds **3** and **4**. The compound **4** (possesses methylpropyl group) has slightly lower lipophilicity than the compound **3** (possesses isobutyl group).

Table 2. *In silico* logP values of the analyzed series of triazine derivatives

Compound	ALOGPS 2.1						$SWISS_{ADME}$		MarvinSketch			ChemBioDraw		ConsensusLogP
	ALOGPs	AClogP	AlogP	MlogP	XlogP2	XlogP3	iLOGP	WLOGP	$logP_{VG}$	$logP_{KLOP}$	$logP_{PHYS}$	$LogP_{ChDr}$	CLogP	
1	3.12	3.00	3.21	2.89	1.92	3.23	3.05	1.79	2.58	3.08	2.81	2.60	3.45	2.83
2	2.94	2.88	2.91	2.89	2.12	2.93	2.98	1.78	2.47	2.47	2.54	2.26	3.01	2.63
3	4.11	3.81	3.96	3.47	2.84	3.98	3.44	2.56	3.41	3.94	3.62	3.24	4.07	3.57
4	3.79	3.68	3.84	3.47	2.51	4.11	3.43	2.28	3.39	3.79	3.49	3.40	4.25	3.49
5	4.08	3.74	4.26	4.00	2.88	4.03	3.42	2.85	3.34	4.09	3.90	3.21	4.28	3.70
6	4.91	4.38	5.18	4.51	4.01	5.07	3.75	3.63	4.13	5.03	4.84	4.05	5.40	4.53
7	5.71	5.01	6.09	4.99	5.15	6.16	4.04	4.41	4.92	5.97	5.77	4.88	6.52	5.36
8	6.46	7.62	7.00	5.45	6.29	7.24	3.69	5.19	5.72	6.90	6.71	5.72	7.63	6.28

Since the ion formation has significant influence on lipophilicity of compounds, the pH-VGlogD profile of each triazine derivative was calculated and presented in Figure 3. Unlike logP, VGlogD descriptor takes into account overall ratio of ionized and unionized compound. This is particularly important since the ionization has significant influence on absorption of the compound.

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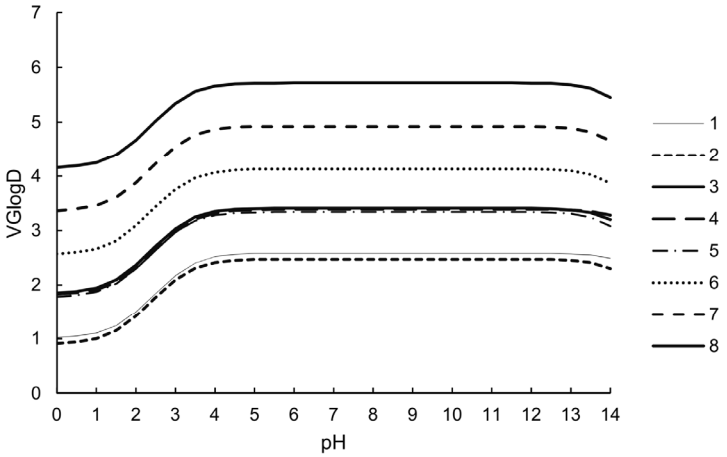

Figure 3. The dependence of VGlogD of the analyzed triazine derivatives on pH

In Figure 3 it can be noticed that all eight triazine derivatives have stable logD values in the range of pH between 4 and 13. In a highly acidic environment (pH < 4), all the analysed compounds have protonated N^3-atom of the triazine ring. However, under the highly basic conditions (pH > 13), N-atom of the amine group is ionized realizing the H-atom. The major microspecies of the compound **6** under acidic and basic conditions are presented in Figure 4. Besides, Figure 3 indicates that compounds **1** and **2** have almost overlapping pH-VGlogD profile, so it can be concluded that isomerism in substituents of these compounds does not have significant influence on their distribution coefficient. It is interesting to notice that the same phenomenon can be observed in the case of compounds **3** and **4**. However, what is not quite expected is the fact that the compound **5**, that has cyclopentyl substituents, possesses almost the same pH-VGlogD profile as the compounds **3** and **4**. This can be explained by the fact that C-atom from methylene group has lower lipophilicity increment than a C-atom from methyl group. Also, despite the fact that cyclopentyl group has one more C-atom than butyl and isobutyl groups, the C-atom from cyclopentyl substituent that is directly bonded to N-atom from amine group possesses negative lipophilicity increment. The conclusions are based on the calculations performed in MarvinSketch software based on $logP_{VG}$ descriptor.

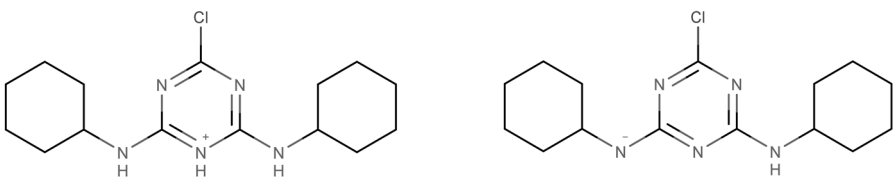

Figure 4. Major microspecies of the compound **6** (a) under pH < 3 and (b) under pH > 13 predicted by MarvinSketch program

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Original scientific paper

HIERARCHICAL CLUSTER ANALYSIS OF LIPOPHILICITY PARAMETERS OF TRIAZINE DERIVATIVES

Hierarchical clustering of the compounds was carried out by HCA based on Ward's algorithm and Euclidean distances. The obtained result is presented in Figure 5 in the form of a dendrogram. The clustering was achieved based on lipophilicity parameters. The dendrogram consists of two main clusters: the cluster I than contains the compounds **6**, **7**, and **8**; the cluster II with the compounds **1**, **2**, **3**, **4** and **5**. The cluster II contains two subclusters. The compounds **1** and **2** are placed together in the same subcluster, while the compounds **3**, **4** and **5** belong to the other subclusters. The most similar lipophilicity can be observed between the compounds **3** and **4**. This pair of compounds has the smallest linkage distance on the dendrogram. Compounds **1** and **2** are also very similar in terms of lipophilicity (but a little less than the compounds **3** and **4** since they have a bit higher linkage distance on the dendrogram). Those similarities are expected due to structural isomerism. The compound **5** is attached to them in the same subcluster despite the fact that unlike the compounds **3** and **4** it contains cyclic substituents, which is discussed in the previous section. The compounds **6**, **7** and **8**, that also contain cyclic substituents, are placed in the separate cluster due to the significant increase in lipophilicity measures. These compounds have large cyclic substituents with quite lipophilic characteristics. The linkage distance between those compounds is higher than in the case of compounds from the cluster II.

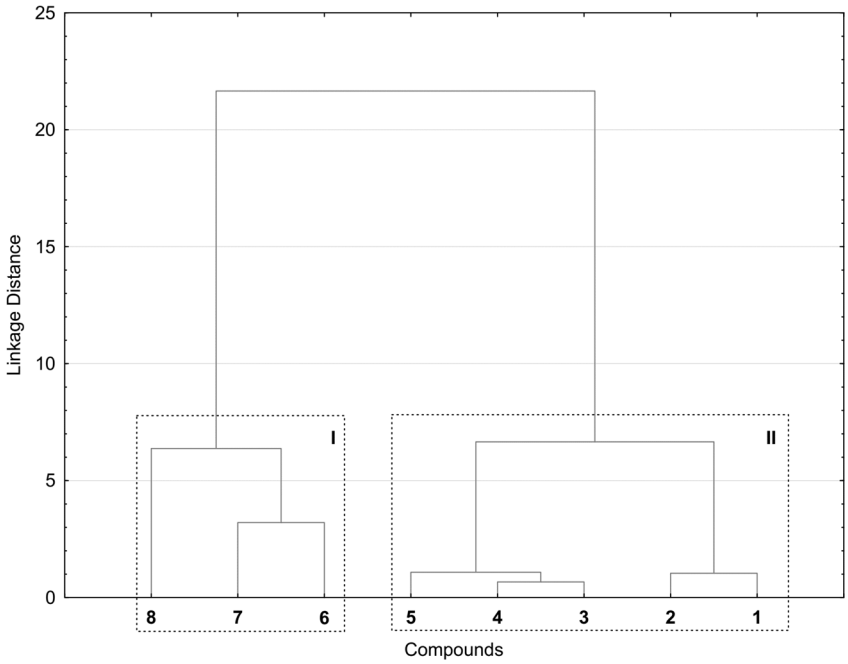

Figure 5. Hierarchical clustering of the triazine derivatives in the space of *in silico* lipophilicity parameters

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Original scientific paper

RANKING APPROACH IN SELECTION OF LIPOPHILICITY MEASURES OF TRIAZINE DERIVATIVES

The SRD method, as a non-parametric and robust approach, was applied in order to rank, group and compare the *in silico* lipophilicity parameters of studied triazine derivatives. The results of the SRD analysis are presented in Figure 6. The obtained results indicate the grouping of the *in silico* logP descriptors into three main groups.

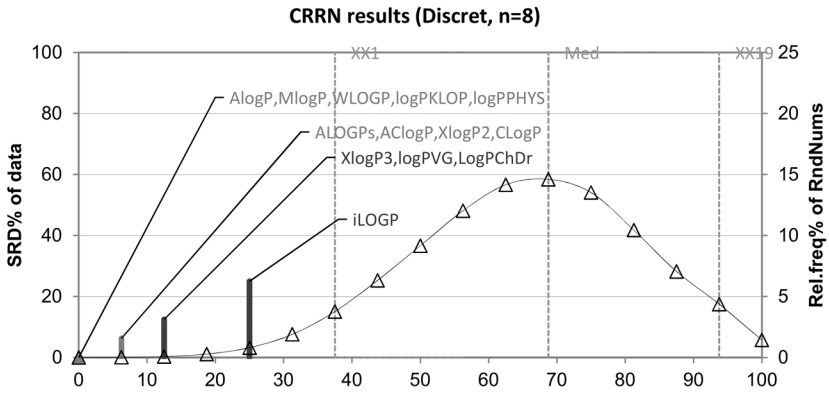

Figure 6. The ranking of normalized lipophilicity descriptors of triazine derivatives by SRD and CRRN approach. The row average (consensus logP) was set as a reference ranking.

The first group of descriptors is placed at the same rank as the reference ranking (SRD = 0) and can be considered the most suitable for lipophilicity estimation. This group includes AlogP, MlogP, WLOGP, $logP_{KLOP}$ and $logP_{PHYS}$ descriptors. The second group of the descriptors is slightly distanced from the reference (SRD = 2) and it contains ALOGPs, AClogP, XlogP2 and ClogP descriptors. In the third group there are XlogP3, logPVG and logPChDr descriptors (SRD = 4). Also, there is one logP descriptor that can be considered an outlier (iLOGP) with SRD = 8 and it is placed furthest form the reference ranking which suggests that this descriptor would not be the most suitable for lipophilicity estimation of the studied series of triazine derivatives. The application of the descriptors in lipophilicity estimation of the analysed triazines from first, second and third group is not questionable since they are depicted with quite low SRD numbers and low p% intervals, as it is presented in Table 3. However, the p% interval for iLOGP descriptor is the highest (0.39-1.20) so this descriptor should be avoided due to the highest probability of random character.

In order to validate the SRD results, the 7-fold cross-validation procedure was carried out. The results are presented in the form of box and whisker plot in Figure 7. Box and whisker plot contain three separate groups of descriptors. The separation in those groups is not only based on the SRD graph presented in Figure 6, but also based on the results of sign test and Wilcoxon's matched pairs test. These tests confirmed the statistical difference between the groups in terms of SRD values obtained by 7-fold cross-validation and also confirmed the conclusions drown based on the results presented in Figure 7.

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Table 3. The ranking of lipophilicity measures of triazine derivatives p% intervals

Descriptor	SRD	x < p% ≤ y	
AlogP	0	0	2.48E-03
MlogP	0	0	2.48E-03
WLOGP	0	0	2.48E-03
$logP_{KLOP}$	0	0	2.48E-03
$logP_{PHYS}$	0	0	2.48E-03
ALOGPs	2	2.48E-03	1.98E-02
AClogP	2	2.48E-03	1.98E-02
XlogP2	2	2.48E-03	1.98E-02
CLogP	2	2.48E-03	1.98E-02
XlogP3	4	1.98E-02	0.10
$logP_{VG}$	4	1.98E-02	0.10
$LogP_{ChDr}$	4	1.98E-02	0.10
iLOGP	8	0.39	1.20
XX1	12	3.10	6.87
Q1	18	22.37	34.40
Med	22	48.56	63.17
Q3	24	63.17	76.70
XX19	30	94.20	98.57

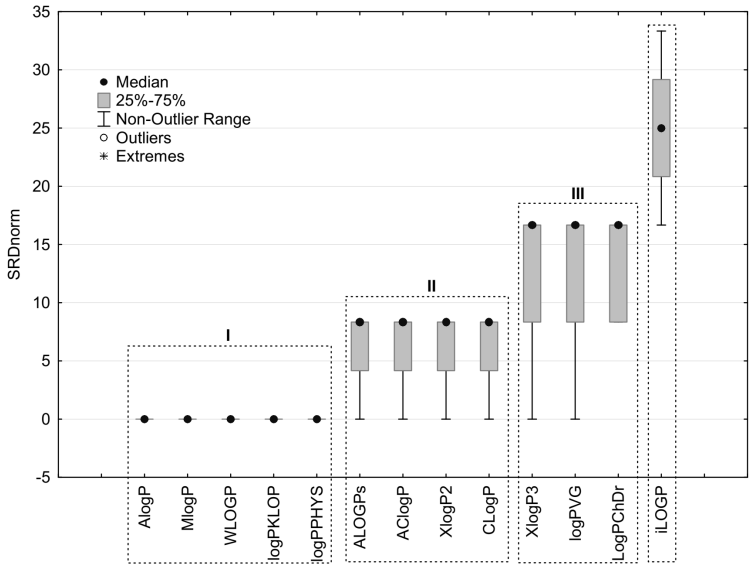

Figure 7. The box and whisker plot of the normalized SRD values obtained by 7-fold cross-validation procedure

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Original scientific paper

CONCLUSION

In the present study, the series of eight 6-chloro-1,3,5-triazine derivatives with cyclic and acyclic substituents was analysed in terms of selection of the most suitable lipophilicity descriptors obtained by *in silico* methods. The obtained results of the SRD approach indicate that the most suitable lipophilicity descriptors for the studied triazine derivatives are AlogP, MlogP, WLOGP, $logP_{KLOP}$ and $logP_{PHYS}$ descriptors, and the descriptor iLOGP can be considered the most unsuitable. Results of the HCA indicated that in the space of the analysed variables the triazines with the acyclic and cyclic substituents overlap so the compound with cyclopentyl group is placed together in the same cluster with the compounds with acyclic substituents (isobutyl and methylpropyl groups). Also, it was determined that all eight triazine derivatives possess stable logD values in the range of pH between 4 and 13.

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