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Chemometrical study of the anaesthetical activity of alkoxyphenylcarbamic acid esters

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Several chemometrical techniques were applied to elucidate anaesthetical activity of hydrochlorides of alkoxyphenylcarbamic acid esters. The studied five types of esters contained morpholin-4-ylethyl-, piperidin-1-ylethyl-, piperidin-1-ylpropyl-, azepan-1-ylethyl- and dimethylaminoethyl- groups. The surface anaesthetical activity, designated by *A*, and the infiltration anaesthetical activity, indicated by *B*, were correlated to lipophilicity, expressed in different ways – using (a) the logarithm of 1-octanol-water partition coefficient, $\log P$, (b) the logarithm of the HPLC retention factor, $\log k$, (c) the length of the side alkoxy chain represented by the number of carbon atoms, *n*, (d) molar mass, *M*. Principal component analysis and cluster analysis were used for close characterization of alkoxyphenylcarbamic acid esters as the potential anaesthetics, and techniques of discrimination analysis were used for predicting the extent of both types of anaesthetic activity. Artificial neural networks were successful in predicting surface anaesthetical activity but prediction of infiltration anaesthetical activity was far less favourable.

1. Introduction

Quantitative structure-activity/property relationships (QSAR/QSPR) studies provide information that is useful for molecular design and medicinal chemistry (Schmidli 1997; Hansch et al. 2001; Wold et al. 2001; Hemmateenejad et al. 2002). The basic target of the QSAR is the prediction of compound properties. The basic assumption is that the compounds with similar structure dispose of a similar biological activity (Hansch and Leo 1995). In the QSAR studies, chemical structures are often represented by the calculated topological, geometric, electrostatic, quantum chemical, or thermodynamic descriptors. These chemical descriptors are subsequently used to construct a statistical model between chemical structures and its biological activities or chemical properties (Altamora et al. 2000; Hollosy et al. 2002; Perioli et al. 2004; Remko and von der Lieth 2004; Katritzky et al. 2005; Arakawa et al. 2006; Yang et al. 2008). The application of several chemometrical techniques, mainly methods of multivariate data analysis, enable to extend the palette of descriptors so that e.g. also analytical and physicochemical data are utilized (Wold and Sjöström 1998; Wold et al. 2001; Gonzáles et al. 2002; Hemmateenejad 2005; Fatemi and Gharaghani 2007).

After discovery of a biologically active compound with a new structure, the next phase of the activity optimization is usually characterized by varying the basic structure in order to achieve maximal biological activity. The hydrochlorides of basic ethyl and propyl esters of alkoxy-substituted phenylcarbamic acids have been studied as potential local anaesthetics. The HPLC capacity factor was used for characterization of the lipophilicity of the tested compounds (Hatrík et al. 1995a,b).

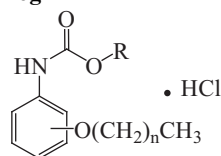
In this study, the anaesthetical activity was correlated to the relevant chemical shifts in the ¹H NMR and ¹³C NMR spectra as well as to the calculated $\log P$ of the investigated compounds. It is worth mentioning that, in addition, the antituberculous activity of these compounds was measured and the relationship between structure and antimycobacterial activity was investigated by Free-Wilson analysis (Waisser et al. 2003, 2004, 2006).

2. Investigations, results and discussion

The subjects of the study were two data sets consisting of 62 and 68 compounds, for which the anaesthetic activities $\log A$ and $\log B$ were acquired, respectively (Table 1). The list of investigated species is given in the Experimental part; 18 variables describing the molecule properties were used: $\log P$ – octanol-water partition coefficient, $\log k$ – HPLC retention factor, *n* – number of carbon atoms in the side alkoxy chain, *M* – molar mass of the investigated compound, the ¹³C NMR chemical shifts designated as C1, C2, C3, C4, C5, C6, C8, C10, C12 in Fig. 1, as well as the ¹H NMR chemical shifts of the terminal methyl proton, the ring protons, and the quaternary nitrogen proton located in the ester part, denoted by HCH3, H1, H2, H12, and qH, respectively, and also shown in Fig. 1.

2.1. Correlation analysis

The correlation analysis shows the measure of correlation expressed by the pair (Pearson) correlation coefficients, *r*, between all pairs of the studied variables. In this study, several

Table 1: Chemical structures of esters of alkoxyphenylcarbamic acids and observed values of their anaesthetical activity log *A* and log *B*

No	R	X	<i>n</i>	log <i>A</i>	log <i>B</i>	No	R	X	<i>n</i>	log <i>A</i>	log <i>B</i>	No	R	X	<i>n</i>	log <i>A</i>	log <i>B</i>
1	M	o	4	0.30	0.30	29	P	m	2	0.20	1.46	57	PP	o	7	2.08	2.41
2	M	o	6	1.45	0.90	30	P	m	3	1.04	1.55	58	PP	o	8	2.42	1.27
3	M	o	7	1.84	1.00	31	P	m	5	1.90	2.13	59	PP	o	9	2.21	1.22
4	M	o	8	1.58	0.78	32	P	m	6	1.92	1.89	60	PP	m	2	0.59	0.59
5	M	o	9	1.82	1.20	33	P	m	7	1.83	1.78	61	PP	m	3	1.34	0.52
6	M	o	10	1.26	0.30	34	P	p	4	0.67	n.d.	62	PP	m	4	1.46	1.73
7	M	m	3	0.85	n.d.	35	P	p	5	1.13	n.d.	63	PP	m	5	1.98	0.94
8	M	m	4	1.20	0.60	36	P	p	6	1.40	n.d.	64	PP	m	6	1.77	0.90
9	M	m	5	1.64	0.60	37	P	p	7	1.28	n.d.	65	PP	m	7	2.10	1.00
10	M	m	6	1.86	0.85	38	A	o	3	0.55	1.27	66	PP	m	8	1.74	0.96
11	M	m	7	1.94	0.70	39	A	o	4	1.02	1.18	67	D	o	1	n.d.	0.64
12	M	m	8	1.61	0.95	40	A	o	5	1.77	1.88	68	D	o	2	n.d.	1.11
13	M	m	10	0.48	n.d.	41	A	o	6	1.80	1.42	69	D	o	3	n.d.	1.19
14	M	p	5	0.78	n.d.	42	A	o	7	2.06	2.28	70	D	o	4	n.d.	1.88
15	M	p	6	1.34	n.d.	43	A	m	3	1.43	1.97	71	D	o	5	n.d.	1.52
16	M	p	7	1.58	n.d.	44	A	m	4	1.76	1.60	72	D	o	6	n.d.	2.37
17	M	p	8	0.78	n.d.	45	A	m	5	1.81	1.78	73	D	o	7	n.d.	2.43
18	P	o	1	n.d.	1.25	46	A	m	6	1.78	1.44	74	D	o	8	n.d.	2.14
19	P	o	2	n.d.	1.32	47	A	m	8	1.18	0.83	75	D	o	9	n.d.	1.87
20	P	o	3	n.d.	1.52	48	A	p	3	0.70	n.d.	76	D	m	2	n.d.	1.54
21	P	o	4	1.10	1.34	49	A	p	5	0.68	n.d.	77	D	m	3	n.d.	1.63
22	P	o	5	1.46	2.00	50	A	p	6	0.92	n.d.	78	D	m	4	n.d.	1.70
23	P	o	6	1.96	2.02	51	A	p	7	1.32	n.d.	79	D	m	5	n.d.	1.81
24	P	o	7	2.00	2.23	52	PP	o	2	0.49	0.56	80	D	m	6	n.d.	1.59
25	P	o	8	1.98	2.17	53	PP	o	3	0.68	0.78	81	D	m	7	n.d.	1.72
26	P	o	9	1.97	1.43	54	PP	o	4	1.07	1.16	82	D	m	9	n.d.	1.42
27	P	o	10	1.43	0.85	55	PP	o	5	1.70	1.83						
28	P	m	1	n.d.	1.20	56	PP	o	6	1.87	2.24						

Legend: M – morpholin-4-ylethyl-, P – piperidin-1-ylethyl-, A – azepan-1-ylethyl-, PP – piperidin-1-ylethyl-, D – dimethylaminoethyl-; X – position of the alkoxy chain: o – ortho-, m – meta-, p – para-; *n* – number of carbon atoms in side alkoxy chain; n.d. – not determined

significant dependences of log *A* and/or log *B* on the used descriptors were observed. The significance of the correlations was discovered by comparing the calculated correlation coefficient with the critical value r_{crit} obtained for the significance level 0.05 and the corresponding number of degrees of freedom (the number of compounds minus two). With regard to log *A* the most important descriptors are: HCH3 (negative correlation), *M*, *n*, log *k*, log *P* and C3 (negative correlation). With regard to log *B* the most important descriptors are: qH (negative correlation), C10 (negative correlation), H12 and log *k*. All details are summarized in Table 2. It is interesting that lipophilicity, expressed directly by log *k* and log *P*, and indirectly by *M* and *n*, is the factor most influencing the log *A* type of anaesthetic

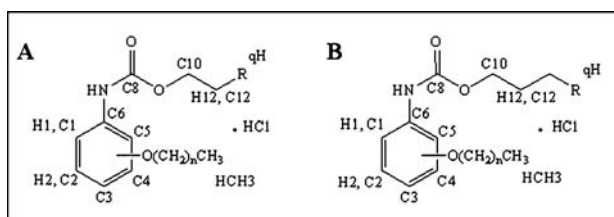


Fig. 1: Structure of the studied derivatives of alkoxyphenylcarbamic acid with *n* = 0 – 9 where R = morpholin-4-yl-, piperidin-1-yl-, azepan-1-yl- or dimethylamino- (for log *B* only) in part A, and piperidin-1-yl- in part B with the labelled chemical shifts of the corresponding carbons and protons

activity; among the NMR shifts significant correlations to log *A* were found for HCH3 and C3 protons. The correlations to log *B* are in general less pronounced and the descriptors most influencing log *B* are the protons qH and H12 (in a smaller extent) and the carbon C10 of the ester part of the molecule.

Table 2: The pair correlation coefficients of the selected molecule properties with anaesthetical activity log *A* and log *B*, respectively

Property	log <i>A</i>	log <i>B</i>	Property	log <i>A</i>	log <i>B</i>
log <i>P</i>	0.412	−0.090	C6	−0.006	−0.123
log <i>k</i>	0.458	0.206	C8	−0.230	0.020
<i>n</i>	0.504	0.120	C10	0.156	−0.297
<i>M</i>	0.555	0.056	C12	−0.159	0.193
C1	−0.131	−0.059	HCH3	−0.606	−0.198
C2	0.197	−0.122	H1	0.118	0.130
C3	−0.291	0.127	H2	0.117	−0.128
C4	0.042	−0.130	H12	−0.152	0.212
C5	0.116	0.123	qH	−0.016	−0.333

Note: bold typeface – significant correlations with respect to the critical values of correlation coefficient, which are:

$r_{crit} = 0.211$ ($n = 62$, $\alpha = 0.05$) for the data set with the measured log *A* and $r_{crit} = 0.201$ ($n = 68$, $\alpha = 0.05$) for the data set with log *B*

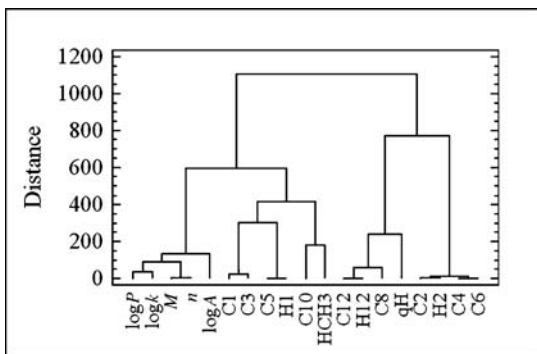


Fig. 2: Cluster analysis of 18 variables (molecule properties) for 62 investigated compounds and surface anaesthetical activity expressed by log *A*. Ward's clustering method and the Squared Euclidean distance was used. Software Statgraphics Plus 5.1

2.2. Cluster analysis

Cluster analysis seeks to divide a set of objects into a number of homogeneous groups or clusters if any *a priori* information about the group structure of the data does not exist (Bratchell 1987; Vandeginste et al. 1998); the performed classification is often used in many areas of science (Vandeginste et al. 1998). The results of cluster analysis are represented by a dendrogram where the distance serves as a measure of similarity between the investigated objects or variables. The dendrogram depicted in Fig. 2 demonstrates that the shortest distance with respect to the anaesthetic activity $\log A$ (and therefore the largest similarity) was found for M , n and also for $\log k$ and $\log P$. A similar dendrogram was obtained when the City-Block distance was used instead of squared Euclidean distance.

Figure 3 shows the dendrogram with the anaesthetic activity $\log B$, to which the closest (most similar) descriptors are n , M , then $\log k$ and C1 and C10 and $\log P$ – if the squared Euclidean distance is used. When using the City-Block distances, the closest distance to $\log B$ exhibit $\log k$ and n and then $\log P$ and C10. The results of cluster analysis, both for $\log A$ as well as $\log B$, are in quite good accordance with the results of the correlation analysis and confirm the previous findings.

2.3. Principal component analysis

The principal component analysis, PCA, is the multivariate technique most commonly used for extracting chemical information from the investigated data (Gendrin et al. 2008). In PCA, the principal components are calculated by a linear combination of

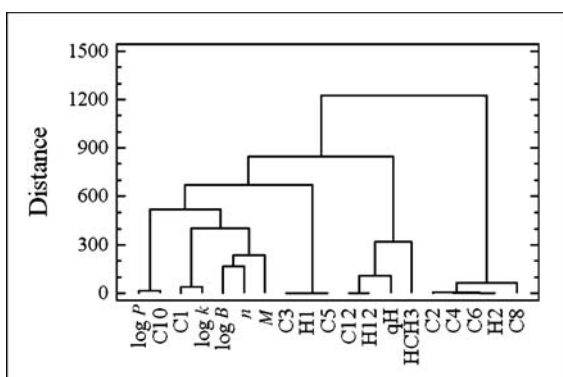


Fig. 3: Cluster analysis of 18 variables for 68 investigated compounds and infiltration anaesthetical activity expressed by log *B*. Ward's clustering method and the Squared-Euclidean distance was used. Software Statgraphics Plus 5.1

the original variables using weights reflecting their importance. Obtained PCs describe the structure or pattern in the data better than the original measurements (Massart et al. 1998; Wold et al. 1998).

The principal component analysis was performed in the biplot form. The biplot represents the studied problem by means of variables (descriptors, molecule properties) – depicted by the rays, as well as the studied objects (the investigated compounds) – depicted by the symbols or numbers denoting the selected groups of objects (differentiated by anaesthetic activity in the studied case).

The PCA results were achieved separately for the data set with the activity measured as $\log A$ and $\log B$, respectively. Neither $\log A$ nor $\log B$ was important with respect to the first two principal components (PC1 and PC2) but they were important for the PC3 as demonstrated by a long ray of $\log A$ on the PC3-PC1 biplot shown as an example in Fig. 4 (for the data set with $\log A$). A strong correlation of $\log A$ to n , M , $\log P$ and partly to $\log k$ is here observed. In addition, a very strong inverse dependence of $\log A$ on the terminal CH_3 ^1H NMR chemical shift is observed. It was also found that the variables most correlated to $\log B$ are n and M , and in a smaller extent also to $\log k$ and the carbon C1 ^{13}C NMR chemical shift. Similarly to $\log A$, a strong inverse correlation of $\log B$ with the terminal CH_3 ^1H NMR chemical shift was observed as well.

From the biplots calculated for both data sets it was also observable that two groups of the studied compounds were clearly separated. By a detailed inspection of Fig. 4 it was found that one group is created by ortho and para derivatives (the right group) and another group is formed mainly by the meta derivatives (the left group). The dataset with log *B* consists only from the ortho and meta derivatives, which form two observed distinct groups. The PC3 axis can be assigned to anaesthetical activity – the higher PC3 the larger log *A* or log *B*. Since no one of the above mentioned two groups of compounds are located at higher or lower PC3 values it can be concluded that the position of the alkoxy chain is not influencing significantly any of the anaesthetical activities. Much more important is the length of the alkoxy chain, which is consistent with higher values of molar mass *M* and the HPLC retention factor *k* so that a larger anaesthetical activity is predicted for a larger lipophilicity. The ¹H NMR chemical shift of the terminal CH₃ is inversely dependent on the length of the alkoxy chain, which is in accordance with the conclusions mentioned above.

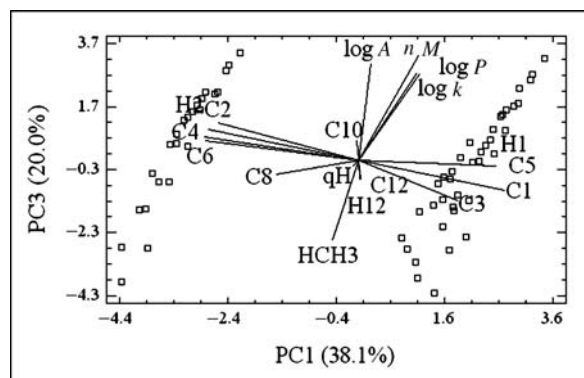


Fig. 4: Biplot of principal component analysis using 19 variables and 62 compounds. The rays represent the selected variables (molecule properties). The symbols on the left side (low PC1 values) correspond to the compounds with meta position of the alkoxy chain in the aromatic ring and those on the right side (high PC1 values) correspond to ortho and para positions of the alkoxy chain. The compounds with highest log A are located at high PC3 values. Software Statgraphics Plus 5.1

Table 3: The results expressed by per cents of true classifications for three discriminant techniques and software packages SPSS, JMP and Trajan

Classification method		SPSS 15						JMP 6.0			
		Training set		Leave-1-out		Validation set		Training set		Validation set	
		log A	log B	log A	log B	log A	log B	log A	log B	log A	log B
LDA	% true:	85.1	82.4	63.8	56.9	80.0	64.7	87.2	82.4	80.0	64.7
QDA	% true:	85.1	84.3	n.c.	n.c.	73.3	64.7	n.c.	n.c.	n.c.	n.c.
LR	% true:	100.0	100.0	n.c.	n.c.	66.7	52.9	97.9	100.0	60.0	47.1

		Trajan					
		Training set		Select set		Validation set	
		log A	log B	log A	log B	log A	log B
ANN	% true:	76.1	73.0	62.5	90.0	100.0	50.0

Note: n.c. – not calculated. The best results are indicated by bold typefaces

2.4. Classification by discriminant techniques

Three categories of alkoxyphenylcarbamic acid esters, organized by increasing anaesthetic activity log A and log B, respectively, were used for categorization of the samples by discriminant analysis. The calculated PC components were used as the variables instead of original descriptors. The advantage of this approach is elimination of correlations and noise in data since the principal components, unlike the original descriptors, are uncorrelated and hierarchically ordered. Classification results were obtained by linear discriminant analysis, LDA, quadratic discriminant analysis, QDA, and logistic regression, LR, which belong to the group of discriminant classification techniques (Khattree and Naik 2000). They are summarized in Table 3 distinctively for the data sets with log A and log B, respectively. The results express how many compounds out of the total amount were correctly classified into the appropriate group.

The shown classification results were evaluated for three groups of the investigated compounds: (a) those included into the training set and utilized for calculation of the classification model; (b) the compounds left out from the training set in a step by step mode and evaluated by the leave-one-out validation method (Massart et al. 1997); (c) the compounds pre-categorized into a special validation data set, not contained in the training set. As generally accepted, the reliability of prediction expressed in the modes (b) and (c) is much higher than that for (a) since in these two cases the data are independent of those used for calculating the classification model. Considering this fact it can be concluded that the best results (80 %) are provided by the LDA technique.

2.5. Artificial neural network

The artificial neural network is a nonlinear modeling method used to construct a nonlinear model between explanatory and dependent variables (Vandeginste et al. 1997), which is often applied for modeling and prediction of biological activity of the investigated compounds using molecular descriptors as independent variables (González et al. 2002; Hemmateenejad 2005; Arakawa et al. 2006; Fatemi and Gharaghani 2007).

The module Intelligent Problem Solver of Trajan 6.0 Professional software (Trajan Software 2005) was used to identify the best type of neural network. Eight anaesthetics out of 62 investigated compounds were chosen randomly into the validation set and for calculation of the best neural network all remaining anaesthetics were used. Finally the surface anaesthetical activity

log A of eight compounds of the validation set was predicted using the developed ANN model. Using Intelligent Problem Solver of Trajan software the five best networks were retained out of hundred examined networks; the correlation coefficients of the selected five networks were between 0.950–0.957, with the mean value of 0.954.

A considerable advantage of artificial neural networks is a possibility to employ the ANN output in two forms using (1) classification of the investigated objects (here the studied compounds) into the pre-selected categories, (2) direct prediction of the chosen target variable (here the log A or log B anaesthetic activity) by regression. In this work both possibilities were used: the classification output is summarized in Table 3, the predicted anaesthetical activity values, log A, from the best neural network are listed in Table 4 together with the mean values of the best five networks.

Ordinary linear least squares regression method was used to construct a statistical model describing the dependence between the predicted log A and the measured log A for the best network (Fig. 5). The *t*-test confirmed statistical significance of both regression parameters. Compared to the log A case, the agreement between the predicted and the measured log B anaesthetical activity was not as good; for the best neural network

Table 4: Comparison of the logarithm of surface anaesthetical activity predicted by the best network or the mean of 5 best performing neural networks with regard to the corresponding values experimentally determined for 8 compounds of the validation set

No	log A		
	experimental	predicted by MLP 17-4-1	predicted mean of 5 MLPs
2	1.40	1.36	1.58
29	1.80	1.86	1.80
30	0.67	0.96	0.80
42	1.80	1.90	1.82
43	1.20	1.26	1.17
47	1.30	1.20	0.94
48	0.49	0.26	0.37
55	2.20	2.21	2.10

Notes: No = number of the investigated compound randomly selected to the test set; the mean value was acquired by averaging the results of 5 best performing neural networks. The best classification results were obtained with the three-layer perceptron neural network (MLP 17-4-1) with 17 input, 4 hidden and 1 output neurons

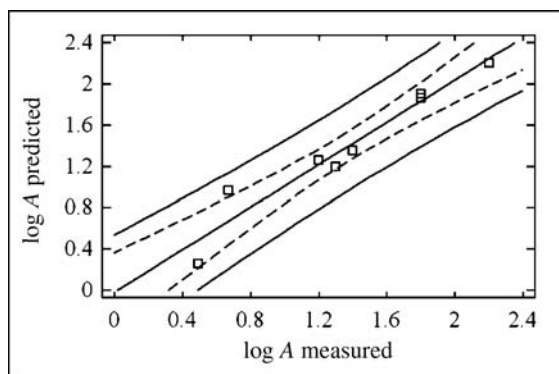


Fig. 5: Plot of the fitted model $\log A$ predicted vs. $\log A$ measured; dashed line – confidence band (determining the true position of the regression straight-line), full line – prediction band (determining the position of one future observation); both bands were calculated for 95 % probability. The calculated regression equation is: $\log A_{\text{predicted}} = -0.0197 + 1.028 \log A_{\text{measured}}$

the regression equation $\log B_{\text{predicted}} = 0.073 + 0.890 \log B_{\text{measured}}$ was found, with deviation of 11.0 % rel. from the theoretical slope (equal to 1), compared to the found deviation of only 2.8 % rel. achieved in the $\log A$ prediction (Fig. 5). This observation is in full accordance with much stronger correlations observed between $\log A$ and the most informative NMR chemical shifts compared to analogical correlations determined for $\log B$.

2.6. Concluding remarks

The compound properties, most influencing the targeted $\log A$, are M , n , $\log k$ and $\log P$, as it was found by correlation analysis, cluster analysis as well as the PC3 – PC1 dependence. In these cases there exists a positive correlation of any of these variables to $\log A$. A further factor strongly influencing $\log A$ but with negative correlation is the chemical ^1H shift of CH_3 group. Further chemical shifts with a less significant impact upon $\log A$ are carbons C3 and C8 exhibiting also a negative correlation. Considering the impact of the investigated variables on $\log B$, the above mentioned methods were not in a very good mutual agreement. The most significant influence on $\log B$ in all cases exhibit $\log k$ (positive correlation) and carbon C10 (negative correlation). Variables n , M , $\log k$ and $\log P$ are also influencing but their impact on $\log B$ is different for a different method. Among the chemical shifts, beside C10 also ^1H shifts of qH and H13 are important.

In total, it is evident that higher lipophilicity results in increase of both $\log A$ and $\log B$. Proton chemical shift of HCH3 exhibits a specific negative effect on $\log A$ while the chemical shifts of qH and C10 induce a specific negative effect on $\log B$.

Among three discriminant techniques the best classification and prediction of the compound with the highest $\log A$ value demonstrates linear discriminant analysis, where 80.0 % correct classifications were found for the compounds contained in the validation set. Even a better prediction is possible by ANN, by which 100 % of correct results were achieved. Classification and prediction of the compounds with a high $\log B$ value was not as much successful since 64.7 % correct classifications were obtained by LDA and only 50.0 % by ANN. Despite of this, it is worth to note that even in this case the correct results is significantly higher than 33.3 % expected for a random classification of the investigated compounds into 3 classes.

3. Experimental

Selected nine ^{13}C and five ^1H NMR chemical shifts were simulated using the software package ACD Labs, ver. 7.0, which provides truthful chem-

ical shift values as we have found in our another QSAR study (Nemecek et al. 2009). The position numbering in Fig. 1 was taken from ACD Labs as well. An important advantage of utilization of the simulated chemical shifts is a possibility to omit laborious chemical syntheses of a series of compounds, especially in the first phase of the QSAR study where the structure elucidation of the most active species is the main goal of investigation. The 1-octanol/water partition coefficient was calculated using software ALOGPS 2.1; a sufficient accuracy of these calculations was confirmed by individual measurements.

MS Excel spreadsheets were used for preparation of the data in an appropriate form and their subsequent processing. The investigated compounds were divided into three categories using the following critical values of the surface anaesthetic activity: class 1 for $A \geq 90$, class 2 for $50 \leq A < 90$, class 3 for $10 \leq A < 50$. The same principle was used for organizing three compound categories by the $\log B$ activity. The correlation analysis, cluster analysis, principal component analysis and the employed types of discriminant analysis were performed using software packages JMP 6.0, STATGRAPHICS Plus 5.1 and SPSS 15.0. The QSAR predictions by artificial neural network were performed by means of Trajan 6.0 Professional software.

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