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Short communication

SMILES-based quantitative structure–property relationships for half-wave potential of *N*-benzylsalicylthioamides

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ABSTRACT

Optimal descriptors calculated with Simplified Molecular Input Line Entry System (SMILES) notation have been used in quantitative structure–property relationships (QSPR) of half-wave potential of *N*-benzylsalicylthioamides. The QSPR developed is one-variable model based on the optimal descriptors calculated with the Monte Carlo method. The approach has been checked up with three random splits into the training and test sets. Mechanistic interpretations (structural alerts related to the half-wave potential) of the model are discussed.

1. Introduction

Quantitative structure–activity/property relationship (QSAR/QSPR) studies are important areas in chemometrics, as they are able to answer: which factors are operating during a physical, chemical, and/or biochemical phenomenon? Nowadays, the molecular descriptors characterizing the whole structure of a compound are more frequently used in QSPR, instead of classical partial descriptors embodying only the substituent (e.g., Hammett or Hansch constants). These molecular descriptors, as a rule, are presented as atoms (vertices) and their bonds (edges) in molecular graphs [1]. The Simplified Molecular Input Line Entry System (SMILES) can be used as an alternative to the molecular graphs [2,3]. The SMILES-based optimal descriptors have transparent interpretation: each molecular fragment shows a defined influence upon a phenomenon. There are several reasons to search for SMILES-based QSPR models. The first, comparison of models based on the substituent descriptors those based on SMILES can be useful from a heuristic point of view. The second, the number of SMILES-based databases available on the Internet gradually increases. The third, SMILES notation can be built for substances which cannot be represented by molecular graphs, e.g. for mixtures or for inorganic substances. The SMILES-based QSPR models have been successfully applied on the prediction of diverse physicochemical properties, such as reaction rate constants [4], charge transfer rates [5], flash points [6], solubility [7], partition coefficient [8], enthalpies of formation [9].

We have used SMILES for the modeling of electrochemical half-wave potential by one-variable correlation [10,11]. The electrochemical properties (e.g., half-wave potential) are supposed to be important in the interactions of substance with biological systems. They can be correlated with biological properties, as there is a set of similarities between electrochemical and biological reactions concerning electron transfer pathways, which are not duplicated in other chemical systems. Consequently, data on this endpoint may be useful for biological and medicinal investigations [12].

Within the frame of systematic research of new antituberculous agents, the attention is also focused on the antimycobacterial properties of thioamide derivatives [13]. Given the similarity in structure, we synthesized a set of *N*-benzylsalicythioamides, and having found that they belong to the group of very active compounds against tuberculosis [14]. Moreover, the derivatives also possess antimycotic [15] and antibacterial [16] activity. The aim of

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the present study is to estimate the CORAL software [17] as a tool for QSPR analysis of the half-wave potentials of *N*-benzylsalicylthioamides. CORAL software has recently been suggested as an efficient tool for the QSPR analysis. The CORAL models represent one-variable correlations between an endpoint and optimal descriptors. The optimal descriptors are calculated with special coefficients related to presence of various molecular features (molecular fragments and physicochemical characteristics of molecules). These coefficients (correlation weights) are obtained by the Monte Carlo method. One can use as the representation of the molecular structure for the optimal descriptors hydrogen-suppressed molecular graph (HSG) [18], SMILES [19], or a hybrid representation, which includes both the HSG and SMILES.

2. Method

2.1. Determination of electrochemical data

The synthesis and the analytical data of studied *N*-benzylsalicylthioamides are in full detail described in Ref. [20]. Acetonitrile Chromasolv (Sigma Aldrich) with water content below 2×10^{-3} vol.% (determined by gas chromatography) was used for the measurements. Sodium perchlorate purity for HPLC (Fluka) served as a basic electrolyte. All other chemicals were of analytical grade.

The half-wave potentials were measured using an Eko-Tribo Polarograph (Polaro-Sensors, Prague) on a platinum rotating disk electrode (active surface area 14 mm^2) with constant rotation speed of 1226 rpm. A scan rate of 10 mV s^{-1} was maintained. The reference electrode was a silver plate immersed in a solution of 0.01 M $AgNO_3$ in 1 M $NaClO_4$ in acetonitrile and separated from measured solution by a salt bridge filled with 0.5 M $NaClO_4$ in acetonitrile. The platinum rod served as a counter electrode. All measurements were made in at least triplicate; the average reproducibility of each determination was better than 1.0%.

2.2. Calculations

SMILES were used for representation of the molecular structure, and they were generated with ACD/ChemSketch software [21]. The CORAL software [17] was used for the calculations. The SMILES-based optimal descriptors checked up in the QSPR/QSAR analyses [22–24] were calculated:

$$\mathrm{DCW}(\mathrm{Threshold},\ N_{\mathrm{epoch}}) = \sum \mathrm{CW}(S_{\mathrm{k}}) \quad (1)$$

where S_{k} are SMILES attributes (the component of SMILES represents one symbol, e.g. C, c, N, n, =, F or two symbols which cannot be separated, e.g. Cl, Br, @@), which are representations of molecular features. $\mathrm{CW}(S_{\mathrm{k}})$ are correlation weights of the SMILES fragments. Threshold and N_{epoch} are parameters of the Monte Carlo optimization, used for calculation of the correlation weights. Threshold is criterion for classification of components of the representation of the molecular structure into two classes: rare (noise) and active (not rare). The correlation weight of a rare component is fixed as zero; hence rare component is not involved in the building up of the model. N_{epoch} is the number of epochs of the Monte Carlo optimization. The optimal values give maximum of correlation coefficient between an endpoint and $\mathrm{DCW}(\mathrm{Threshold}, N_{\mathrm{epoch}})$ for the training set. The threshold and N_{epoch} were calculated according scheme suggested in Refs. [24,25], the range of threshold was 1–3; the range of N_{epoch} was 1–100.

Having numerical data on these $\mathrm{CW}(S_{\mathrm{k}})$ one can calculate $\mathrm{DCW}(\mathrm{Threshold}, N_{\mathrm{epoch}})$ for compounds of training and test sets. Using data on training set one can calculate by Least Squares method model of view

$$E_{1/2}(\mathrm{V}) = C_0 + C_1 \times \mathrm{DCW}(\mathrm{Threshold},\ N_{\mathrm{epoch}}) \quad (2)$$

The predictability of the model calculated with Eq. (2) should be checked with the external validation set. It is to be noted that statistical quality of the model for test and validation sets is a mathematical function of the threshold and the number of epochs of the Monte Carlo optimization. Apparently, that statistical quality of the model for external validation set is most important indicator predictability of an approach. The split of available data into the training set (i.e. "visible" compounds) and test set ("invisible" compounds) has influence for the statistical quality of a QSPR model. Under such circumstances, examination of some group of splits becomes attractive alternative for examination of solely one such split. We have prepared three splits (Table 2) according to the following principles: (i) these splits are random; (ii) they are different; and (iii) the ranges of half-wave potentials for training set and the test set are comparable. It is to be noted that the training set for the CORAL model has three components: sub-training set ("producer of model"); calibration set ("critic of model"); and test set ("preliminary estimator of model"). The role of the validation set is final estimation of predictability of the model [25].

3. Results and discussion

All studied *N*-benzylsalicylthioamides yield a single, drawn-out anodic wave in 0.1 M $NaClO_4$ in acetonitrile; the determined half-wave potentials are represented in Table 1. The half-wave potential of derivative is induced both by substituents on salicyl moiety as well as benzyl (Fig. 1).

Using CORAL the following QSER equations for half-wave potentials of *N*-benzylsalicyl-thioamides were obtained

a) Split 1

$$E_{1/2}(\mathrm{V}) = -0.1051(\pm 0.0913) + 0.0276(\pm 0.0019) \times \mathrm{DCW}(2, 38) \quad (3)$$

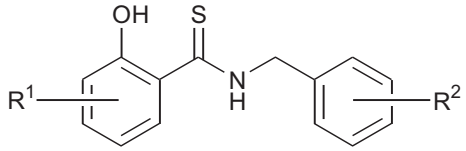
$n = 9$, $r^2 = 0.7333$, $q^2 = 0.6049$, $s = 0.021$, $F = 19$ (sub-training set)
$n = 5$, $r^2 = 0.8312$, $s = 0.031$ (calibration set)
$n = 5$, $r^2 = 0.9250$, $s = 0.036$
$(r^2 - r_0^2)/r^2 = 0.0233 < 0.1$ [26]
$(r^2 - r'^2_0)/r^2 = 0.0039 < 0.1$ [26]
$k = 0.9749$; $0.85 < k < 1.15$ [26]
$k' = 1.0256$; $0.85 < k' < 1.15$ [26]
Average $R^2_{\mathrm{m}} = 0.8294 > 0.5$ [27,28]
$\Delta R^2_{\mathrm{m}} = 0.0806 < 0.2$ [27,28]
Y-randomization $R^2 \approx 0.41$ [29] (test set)
$n = 5$, $r^2 = 0.7295$, $s = 0.028$ (validation set)

b) Split 2

$$E_{1/2}(\mathrm{V}) = 0.1217(\pm 0.1631) + 0.0135(\pm 0.0021) \times \mathrm{DCW}(2, 42) \quad (4)$$

$n = 9$, $r^2 = 0.4445$, $q^2 = 0.1217$, $s = 0.026$, $F = 6$ (sub-training set)
$n = 5$, $r^2 = 0.9040$, $s = 0.017$ (calibration set)
$n = 5$, $r^2 = 0.9951$, $s = 0.020$
$(r_2 - r_0^2)/r^2 = 0.1202 < 0.1$ [26]
$(r^2 - r'^2_0)/r^2 = 0.0644 < 0.1$ [26]
$k = 0.9909$; $0.85 < k < 1.15$ [26]
$k' = 1.0091$; $0.85 < k' < 1.15$ [26]
Average $R^2_{\mathrm{m}} = 0.6970 > 0.5$ [27,28]
$\Delta R^2_{\mathrm{m}} = 0.0922 < 0.2$ [27,28]
Y-randomization $R^2 \approx 0.48$ [29] (test set)
$n = 5$, $r^2 = 0.7394$, $s = 0.041$ (validation set)

Table 1
Structures of *N*-benzylsalicylthioamides studied, experimental half-wave potentials in 0.1 M $NaClO_4$ in acetonitrile (vs. Ag/0.01 M $AgNO_3$/1 M $NaClO_4$), and the SMILES notation.



Compound	R^1	R^2	$E_{1/2}^{expr.}$ (V)	SMILES
1			1.167	S=C(NCc1ccccc1)c2ccccc2O
2		3-CH_3	1.165	S=C(NCc1cccc(C)c1)c2ccccc2O
3		3-Cl	1.190	Clc2cc(CNC(=S)c1ccccc1O)ccc2
4		4-CH_3	1.169	S=C(NCc1ccc(C)cc1)c2ccccc2O
5		4-Cl	1.154	Clc2ccc(CNC(=S)c1ccccc1O)cc2
6		4-F	1.187	S=C(NCc1ccc(F)cc1)c2ccccc2O
7		4-OCH_3	1.117	S=C(NCc1ccc(OC)cc1)c2ccccc2O
8		4-*tert*-butyl	1.175	S=C(NCc1ccc(cc1)C(C)(C)C)c2ccccc2O
9		3,4-Cl_2	1.203	Clc2ccc(CNC(=S)c1ccccc1O)cc2Cl
10	4-OCH_3		1.132	S=C(NCc1ccccc1)c2ccc(cc2O)OC
11	5-Cl		1.216	Oc2ccc(Cl)cc2C(=S)NCc1ccccc1
12	4-CH_3		1.137	S=C(NCc1ccccc1)c2ccc(C)cc2O
13	5-Br	3-Br	1.220	Oc2ccc(Br)cc2C(=S)NCc1cccc(Br)c1
14	4-OCH_3	3-Cl	1.125	Clc2cc(CNC(=S)c1ccc(OC)cc1O)ccc2
15	4-CH_3	3-NO_2	1.190	S=C(NCc1cccc(c1)[N+](O-])=O)c2ccc(C)cc2O
16	4-Cl	4-Br	1.205	Brc2ccc(CNC(=S)c1ccc(Cl)cc1O)cc2
17	5-Br	4-Br	1.192	Oc2ccc(Br)cc2C(=S)NCc1ccc(Br)cc1
18	3-CH_3	4-Cl	1.230	Clc2ccc(CNC(=S)c1cccc(C)c1O)cc2
19	5-Cl	4-F	1.235	Oc2ccc(Cl)cc2C(=S)NCc1ccc(F)cc1
20	4-CH_3	4-CH_3	1.125	S=C(NCc1ccc(C)cc1)c2ccc(C)cc2O
21	5-NO_2	4-CH_3	1.231	S=C(NCc1ccc(C)cc1)c2cc(ccc2O)[N+](O-])=O
22	5-Cl	3,4-Cl_2	1.244	Clc2ccc(CNC(=S)c1cc(Cl)ccc1O)cc2Cl
23	5-Br	3,4-Cl_2	1.218	Oc2ccc(Br)cc2C(=S)NCc1ccc(Cl)c(Cl)c1
24	4-CH_3	4-*tert*-butyl	1.155	S=C(NCc1ccc(cc1)C(C)(C)C)c2ccc(C)cc2O

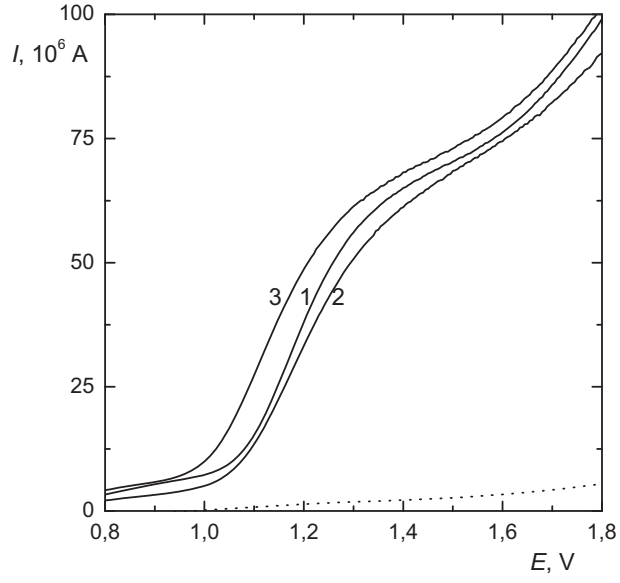


Fig. 1. DC voltammetry of (1) *N*-benzyl-2-hydroxy-salicylthioamide, (2) *N*-(3-chlorobenzyl)-2-hydroxy-thiobenzamide, and (3) *N*-benzyl-2-hydroxy-4-methoxy-thiobenzamide in 0.1 M $NaClO_4$ in acetonitrile (dot line). ($c = 2 \times 10^{-4}$ M, $A = 14$ mm^2, $v = 0.01$ V s^{-1}, 1226 rpm, *E* vs. Ag/0.01 M $AgNO_3$/1 M $NaClO_4$).

Table 2
The splits of examined compounds into the sub-training, calibration, test, and validation sets.

	Set			
	Sub-training	Calibration	Test	Validation
Split 1	5, 6, 8, 9, 12, 14, 15, 20, 22	3, 10, 19, 23, 24	2, 7, 13, 17, 21	1, 4, 11, 16, 18
Split 2	1, 3, 4, 5, 8, 11, 13, 14, 18	6, 7, 12, 19, 24	2, 9, 10, 21, 22	15, 16, 17, 20, 23
Split 3	5, 9, 12, 15, 19, 20, 21	1, 4, 6, 14, 16, 18, 24	2, 7, 13, 17, 23	3, 8, 10, 11, 22

c) Split 3

$$E_{1/2}(\mathrm{V}) = 0.7265(\pm 0.1068) + 0.0245(\pm 0.0056) \times \mathrm{DCW}(3,53) \quad (5)$$

$n = 7$, $r^2 = 0.8378$, $q^2 = 0.6981$, $s = 0.018$, $F = 26$ (sub-training set)
$n = 7$, $r^2 = 0.8519$, $s = 0.054$ (calibration set)
$n = 5$, $r^2 = 0.9110$, $s = 0.065$
$(r^2 - r_0^2)/r^2 = 0.0154 < 0.1$ [26]
$(r^2 - r'^2_0)/r^2 = 0.0006 < 0.1$ [26]
$k = 0.9967$; $0.85 < k < 1.15$ [26]
$k' = 1.0032$; $0.85 < k' < 1.15$ [26]
Average $R_m^2 = 0.8468 > 0.5$ [27,28]
$\Delta R_m^2 = 0.0874 < 0.2$ [27,28]
Y-randomization $R^2 \approx 0.43$ [29] (test set)
$n = 5$, $r^2 = 0.9439$, $s = 0.014$ (validation set)

The criteria were taken in the literature: $(r^2 - r_0^2)/r^2 < 0.1$, $(r^2 - r'^2_0)/r^2 < 0.1$, $0.85 < k \approx k' < 1.15$ according to [26]; Average R_m^2 should be larger than 0.5 and ΔR_m^2 should be less than 0.2 according to [27,28]; and Y-randomization R^2 (correlation coefficient) should be reduced after random shifting of endpoint values in the test set [29]. One can see, that all three models are quite good according to above criteria [26–29]. Moreover, statistical quality of prediction for "invisible" validation sets also is quite good for all splits.

A group of runs of the Monte Carlo optimization gives possibility to classify molecular fragments extracted from SMILES into the following categories: (i) a promoter of increase for an endpoint if its correlation weight is positive in all runs; (ii) a promoter of decrease for an endpoint if its correlation weights is negative in all runs; and (iii) a fragment with undefined role if its correlation weight has both positive and negative values in several runs. Analysis of correlation weights for a group of runs of the Monte Carlo optimization for three various splits shows that there are stable promoters of $E_{1/2}$ increase (Table 3). These are (i) branching indicated by "("; (ii) presence of cycles indicated by "1" and "2"; (iii) presence of double bonds indicated by "="; (iv) presence chlorine indicated by "Cl"; (v) presence nitrogen indicated by "N"; (vi) presence of sulfur indicated by "S"; and (vii) presence of aromatic carbon indicated by "c". Promoters of $E_{1/2}$ decrease are (i) presence of carbon of sp3 indicated by "C"; and (ii) presence of oxygen indicated by "O". Thus, suggested models have mechanistic interpretation of SMILES-fragments. In fact, half-wave potential can be examined as a complex mathematical function of presence of functional groups which can be involved in redox reactions. The above list of stable promoters of increase/decrease of half-wave potentials contains functional groups of this type. However the branching and presence of cycles are not functional groups of such type, consequently, it is interesting to note their influence upon the half-wave potentials of examined class of organic compounds (*N*-benzylsalicylthioamides).

Table 3
Types and correlation weights of SMILES attributes which are used for calculation with Eq. (1): *i* is the indicator of promoter of $E_{1/2}$ increase, *d* is the indicator of promoter of $E_{1/2}$ decrease, *u* is the indicator of SMILES-fragment with undefined role.

Type of S_k	S_k	CW(S_k)	Number of SMILES attributes in		
			Sub-training set	Calibration set	Test set
Split 1					
i	(	0.30712	9	5	5
u	+	0.0	1	0	1
u	−	0.0	1	0	1
i	1	2.80500	9	5	5
i	2	2.30200	9	5	5
i	=	1.93550	9	5	5
d	C	−0.48694	9	5	5
u	F	0.0	1	1	0
u	Br	0.0	0	1	2
i	Cl	0.68850	4	3	0
i	N	2.52456	9	5	5
d	O	−2.08625	9	5	5
i	S	2.34900	9	5	5
u	[	0.0	1	0	1
i	c	2.55356	9	5	5
Split2					
i	(	1.00850	9	5	5
u	+	0.0	0	0	1
u	−	0.0	0	0	1
i	1	5.11550	9	5	5
i	2	4.36788	9	5	5
i	=	4.42913	9	5	5
d	C	−1.28094	9	5	5
u	F	0.0	0	2	0
u	Br	0.0	1	0	0
i	Cl	1.59800	5	1	2
i	N	4.33750	9	5	5
d	O	−3.20200	9	5	5
i	S	4.73212	9	5	5
u	[	0.0	0	0	1
i	c	3.97175	9	5	5
Split3					
i	(	0.33706	7	7	5
u	+	0.0	2	0	0
u	−	0.0	2	0	0
i	1	0.99575	7	7	5
i	2	1.17275	7	7	5
i	=	2.69475	7	7	5
d	C	−0.57175	7	7	5
u	F	0.0	1	1	0
u	Br	0.0	0	1	3
i	Cl	0.34888	3	3	1
i	N	2.17244	7	7	5
d	O	−2.39262	7	7	5
i	S	0.91494	7	7	5
u	[	0.0	2	0	0
i	c	0.90556	7	7	5

4. Conclusions

The CORAL software is able to be an efficient tool to build up a robust model for QSER of 24 *N*-benzylsalicylthioamides, as the correlation equation between structure descriptor (descriptor of correlation weights based on SMILES) versus half-wave potential was calculated and tested. The predictive potential of the applied approach was tested with three random splits into the sub-training, calibration, test, and validation sets. The substances, which are distributed in the validation set, are not involved in the building up the models, i.e. the predictability of the CORAL models are demonstrated. The SMILES attributes, which are promoters of increase and decrease of the half-wave potential, were identified.

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