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Short Communication

CORAL: QSPR model of water solubility based on local and global SMILES attributes

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HIGHLIGHTS

- ▶ The CORAL software for the building up of QSPR/QSAR models is suggested.
- ▶ The SMILES is used as the representation of the molecular structure.
- ▶ The CORAL model for water solubility is described in detail.

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ABSTRACT

Water solubility is an important characteristic of a chemical in many aspects. However experimental definition of the endpoint for all substances is impossible. In this study quantitative structure–property relationships (QSPRs) for negative logarithm of water solubility–log S (mol L^{-1}) are built up for five random splits into the sub-training set (≈55%), the calibration set (≈25%), and the test set (≈20%). Simplified molecular input-line entry system (SMILES) is used as the representation of the molecular structure. Optimal SMILES-based descriptors are calculated by means of the Monte Carlo method using the CORAL software (http://www.insilico.eu/coral). These one-variable models for water solubility are characterized by the following average values of the statistical characteristics: $n_{\text{sub\_train}} = 725–763$; $n_{\text{calib}} = 312–343$; $n_{\text{test}} = 231–261$; $r^2_{\text{sub\_train}} = 0.9211 \pm 0.0028$; $r^2_{\text{calib}} = 0.9555 \pm 0.0045$; $r^2_{\text{test}} = 0.9365 \pm 0.0073$; $s_{\text{sub\_train}} = 0.561 \pm 0.0086$; $s_{\text{calib}} = 0.453 \pm 0.0209$; $s_{\text{test}} = 0.520 \pm 0.0205$. Thus, the reproducibility of statistical quality of suggested models for water solubility confirmed for five various splits.

1. Introduction

The solubility of liquids and solids in water is a very important molecular property that affects their biological activity (Huuskonen, 2000; Tetko et al., 2001; Roy and Saha, 2003; Yan and Gasteiger, 2003). Quantitative structure – property/activity relationships (QSPRs/QSARs) based on various molecular descriptors (Furtula and Gutman, 2011; Melagraki and Afantitis, 2011; Mullen et al., 2011; Ojha et al., 2011) are a possible tool to predict physicochemical properties (Huuskonen, 2000; Tetko et al., 2001; Yan and Gasteiger, 2003) as well as biological activity (Marino et al., 2002; Toropov and Toropova, 2002; Peruzzo et al., 2003; Melagraki and Afantitis, 2011; Mullen et al., 2011; Ojha et al., 2011) for substances which have not been examined in the experiment.

Recently, the CORAL software (http://www.insilico.eu/coral) has been suggested as a tool of the QSPR/QSAR analyses of various endpoints (Toropov et al., 2011; Toropova et al., 2011a,b,c). The software is building up models for various endpoints with representation of the molecular structure by simplified molecular input-line entry system (SMILES) (Weininger, 1990). The aim of the present study is the estimation of the software as a tool to build up QSPR models of water solubility.

2. Method

Data on water solubility of 1311 substances, i.e. their CAS number, SMILES, and values of negative logarithm of water solubility – log S (mol L^{-1}) were taken from the web site of Virtual Computational Chemistry Laboratory (http://www.vcclab.org/lab/alogps/). These substances were distributed by means of five random splits into the sub-training set (≈55%), calibration set (≈25%), and test set (≈20%).

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Table 1
Definitions of the *BOND*, *NOSP*, and *HALO* attributes.

=	#	@	Comments
Calculation of the BOND index			
0	0	0	There are no double, triple, or stereo chemical bonds
0	0	1	The molecule contains only stereo chemical bonds
0	1	0	The molecule contains only triple bonds
0	1	1	The molecule contains triple and stereo chemical bonds
1	0	0	The molecule contains only double bonds
1	0	1	The molecule contains double bonds and stereo chemical bonds
1	1	0	The molecule contains double and triple bonds
1	1	1	The molecule contains double, triple, and stereo chemical bonds

N	O	S	P	Comments
Calculation of the NOSP index				
0	0	0	0	Nitrogen, oxygen, sulfur, and phosphorus are absent
0	0	0	1	The molecule contains only phosphorus
0	0	1	0	The molecule contains only sulfur
0	0	1	1	The molecule contains sulfur and phosphorus
0	1	0	0	The molecule contains only oxygen
0	1	0	1	The molecule contains oxygen and phosphorus
0	1	1	0	The molecule contains oxygen and sulfur
0	1	1	1	The molecule contains oxygen, sulfur, and phosphorus
1	0	0	0	The molecule contains only nitrogen
1	0	0	1	The molecule contains nitrogen and phosphorus
1	0	1	0	The molecule contains nitrogen and sulfur
1	0	1	1	The molecule contains nitrogen, sulfur, and phosphorus
1	1	0	0	The molecule contains nitrogen and oxygen
1	1	0	1	The molecule contains nitrogen, oxygen and phosphorus
1	1	1	0	The molecule contains nitrogen, oxygen, and sulfur
1	1	1	1	The molecule contains nitrogen, oxygen, sulfur, and phosphorus

F	Cl	Br	Comments
Calculation of the HALO index			
0	0	0	Fluorine, chlorine and bromine are absent
0	0	1	The molecule contains only bromine
0	1	0	The molecule contains only chlorine
0	1	1	The molecule contains chlorine and bromine
1	0	0	The molecule contains only fluorine
1	0	1	The molecule contains fluorine and bromine
1	1	0	The molecule contains fluorine and chlorine
1	1	1	The molecule contains fluorine, chlorine, and bromine

Table 2
Example of calculation DCW(1,35) for SMILES = "CC(N)=O" DCW(1,35) = 14.2270.

Structural attribute (*SA*)	*W*(*SA*)
S_k	
`C..........`	−0.5615
`C..........`	−0.5615
`(..........`	−2.6250
`N..........`	−1.3760
`(..........`	−2.6250
`=..........`	−1.2520
`O..........`	1.0665
SS_k^*	
`C...C.......`	−4.1925
`C...(.......`	−0.4385
`N...(.......`	−0.8165
`N...(.......`	−0.8165
`=...(.......`	−0.0635
`O...=.......`	−0.0675
SSS_k^*	
`C...C...(...`	1.3740
`N...(...C...`	3.2500
`(...N...(...`	4.9395
`N...(...=...`	−3.5605
`O...=...(...`	−0.8770
`NOSP1100`	13.3125
`HAL00000`	6.1845
`BOND100`	3.9335

* The bracket of '(' is inserted instead of ')', since both brackets are representation of the same phenomenon of branching of molecular skeleton; SS_k and SSS_k are ordered according ASCII codes in order to avoid situation where the same attributes are indicated by two various manner (e.g. AB and BA or ABC and CBA), thus instead of '`(...N.......`' and '`N...).......`' we have the only '`N...(.......`'.

The SMILES-based optimal descriptors were calculated with scheme developed for QSAR models of toxicity in rats (Toropov et al., 2011):

$$DCW(T, N_{epoch}) = \sum W(S_k) + \sum W(SS_k) + \sum W(SSS_k) + W(BOND) + W(NOSP) + W(HALO) \quad (1)$$

where S_k, SS_k, and SSS_k are local SMILES attributes (fragments) which are involving one, two, and three SMILES element, respectively. The SMILES element can be one symbol, e.g. '*C*', '*c*', '*N*', '=', '#', etc., or several symbols which cannot be considered separately, e.g. 'Cl', 'Br', '11%', etc. (Weininger, 1990); *BOND*, *NOSP*, and *HALO* are global molecular features which are calculated with SMILES (Toropova et al., 2011d). Table 1 shows the schemes of calculation of *BOND*, *NOSP*, and *HALO*.

The descriptors for each substance are calculated with the correlation weights, i.e. $W(S_k)$, $W(SS_k)$, $W(SSS_k)$, *W*(*BOND*), *W*(*NOSP*), and *W*(*HALO*). The numerical values for the correlation weights are calculated with the Monte Carlo method optimization procedure. The target function (TF) of the procedure is the following (Toropov et al., 2010):

$$TF = R + R' - |R - R'| \cdot R_w - (|C_o - C'_0| + |C_1 - C'_1|) \cdot R_c \quad (2)$$

where *R* and *R*' are correlation coefficients between $DCW(T{,}N_{epoch})$ and an endpoint for sub-training set and calibration set, respectively; C_0, C_1, C'_0, and C'_1 are regression coefficients for the sub-training set and calibration set, respectively; $R_w = 0.1$ and $R_c = 0.01$ are empirical constants; *T* is the threshold in order to classify SMILES attributes into two categories: rare (noise) and active (i.e. not rare). Correlation weights for rare attributes are assumed equal to zero, i.e. they are not involved in the modeling process; N_{epoch} is the number of epochs of the Monte Carlo optimization. In the present study $T = 1$ and $N_{epoch} = 35$ were used. Table 2 contains example of representation of molecular structure by the described local and global attributes extracted from SMILES.

3. Results and discussion

Table 3 contains the statistical quality of models of water solubility for five various splits into the sub-training set, calibration set, and test set. These splits have been selected by taking into account the measure of their identity expressed as percentage (Table 4). The identity of two splits is calculated as ratio of the number of identical substances which have the same status for a couple splits to total number of compounds. Two substances are identical if they have the same status in two splits, i.e. both are in sub-training set (or both are in the calibration set or both are in the test set). Table 4 contains the identity for all pairs of five splits examined in this study. It should be noted there are not pairs of splits with the identity larger than 45%. Studies of groups of various splits into the training and test sets gradually become a general principle of the QSPR/QSAR analyses (Roy et al., 2008; Puzyn et al., 2011). We deem that suggested principle of maximal dissimilarity of splits can be used for the QSPR/QSAR analyses as an alternative of existing

Table 3
Comparison of the statistical quality of the CORAL models for water solubility for five various splits with the statistical quality of four models for water solubility which are described in the literature.

Split	N_{act}	n_{sub_train}	$r^2_{sub\_train}$	s_{sub_train}	F_{sub_train}	n_{calib}	r^2_{calib}	s_{calib}	N_{test}	r^2_{test}	s_{test}	R^2_m
1	712	736	0.9231	0.565	8814	314	0.9543	0.453	261	0.9381	0.511	0.8963
2	703	725	0.9230	0.560	8666	343	0.9493	0.479	243	0.9303	0.530	0.9144
3	731	728	0.9173	0.574	8051	324	0.9614	0.425	259	0.9412	0.508	0.9158
4	722	763	0.9242	0.548	9278	312	0.9526	0.473	236	0.9263	0.554	0.9024
5	724	756	0.9182	0.557	8462	324	0.9600	0.435	231	0.9465	0.495	0.9403

Reference	n_{sub_train}	$r^2_{sub\_train}$	s_{sub_train}	F_{sub_train}	n_{calib}	r^2_{calib}	s_{calib}	N_{test}	r^2_{test}	s_{test}
Huuskonen (2000)	884	0.94	0.47	–	413	0.92	0.60	21	0.91	0.63
Tetko et al. (2001)	879	0.95	0.47	–	412	0.92	0.60	21	0.90	0.64
Liu and So (2001)	1033	0.86	0.70	–	258	0.86	0.71	21	0.79	0.93
Yan and Gasteiger (2003)	797	0.93	0.50	–	496	0.92	0.59	21	0.85	0.77

N_{act} is the number of SMILES attributes which are involved in the modeling process; n is the number of substances in a set; r^2 is square of correlation coefficient; s is mean square error; F is Fischer F-ratio; R^2_m is the metric of predictability: R^2_m should be larger than 0.5 (Ojha et al., 2011).

Table 4
The identity (%) of pairs of splits. The identity is defined as identity (%) = 100 * (number of identical substances/1311).

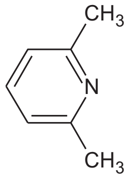
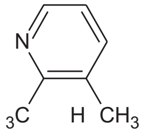
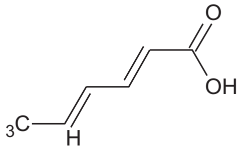
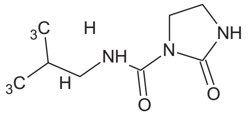
	Split 1	Split 2	Split 3	Split 4	Split 5
Split 1	100	38.8	41.6	43.1	44.4
Split 2	38.8	100	40.7	41.6	42.3
Split 3	41.6	40.7	100	44.2	43.0
Split 4	43.1	41.6	44.2	100	43.7
Split 5	44.4	42.3	43.0	43.7	100

algorithms of the splitting of data into the training and test sets (Roy et al., 2008; Puzyn et al., 2011).

Table 3 contains the statistical characteristics of the models (which are calculated with the same data) for water solubility obtained with the CORAL software together with the statistical characteristics of the models described in the literature (Huuskonen, 2000; Liu and So, 2001; Tetko et al., 2001 and Yan and Gasteiger, 2003). Statistical characteristics of models for other data on water solubility are: (i) various organic compounds, $n = 193$, $r^2 = 0.946$ (Roy and Saha, 2003); (ii) drug-like compounds, $n_{train} = 97$, $r^2_{train} = 0.759$, $n_{test} = 48$, $r^2_{test} = 0.719$ (Duchowicz et al., 2008); and (iii) perfluorinated chemicals: $n = 20$, $r^2 = 0.763$ (Bhhatarai and Gramatica, 2011). Comparison of the statistical quality of models calculated with the CORAL software and the above-mentioned models described in the literature shows that the CORAL models for water solubility are quite good. However, there are substances (Table 5) for which our models give poor prediction. We deem there are two indicators of the poor prediction: (i) symmetry and (ii) the possibility of intramolecular and intermolecular hydrogen bonds.

The CORAL software has been used as a tool of the QSPR/QSAR analyses of several endpoints (Toropov et al., 2010; García et al., 2011; Garro et al., 2011; Mullen et al., 2011; Toropova et al.,

Table 5
Examples of substances for which the CORAL software gives poorest prediction (outliers).

CAS	Structure	Split 1 Δlog S[a]	Split 2 Δlog S	Split 3 Δlog S	Split 4 Δlog S	Split 5 Δlog S
108-48-5		2.505[b]	2.390[b]	2.630[b]	2.413[b]	2.609[b]
583-61-9		2.178[b]	1.935[c]	2.267[b]	2.199[b]	2.356[b]
110-44-1		−1.421[c]	−1.781[b]	−1.807[c]	−1.624[b]	−1.780[b]
30979-48-7		−2.175[c]	−2.183[c]	−2.663[b]	−2.464[b]	−2.532[b]

[a] Δlog S = log S (experiment)−log S(calculated).

[b] Substance is in the sub-training set.

[c] Substance is in the calibration set.

2011a,b,c,d; Ibezim et al., 2012), however water solubility has been examined as target endpoint first time. We believe that presented results (Table 3) indicate that the CORAL can be used as a tool for the QSPR modeling of this endpoint.

4. Conclusions

The CORAL software can be used as a tool for QSPR analysis of the water solubility. We suppose that the reproducibility of the statistical quality of the models for five various splits into the sub-training set, calibration set, and test set is an important advantage of the suggested approach. The suggested measurement of identity for splits (Table 4) can be a criterion for practical definition of group of really different splits for a robust QSPR/QSAR analyses. Four substances are stable outliers for the CORAL models (Table 5).

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Appendix A. Supplementary material

Supplementary materials section contains five splits of examined compounds into the sub-training, calibration, and test sets and technical details of the CORAL method that was used to build up the models. One can check up reproducibility of described approach, using the supplementary materials and the CORAL software available on the Internet (http://www.insilico.eu/coral/). Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.chemosphere.2012.07.035.

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