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QSAR modeling of anxiolytic activity taking into account the presence of keto- and enol-tautomers by balance of correlations with ideal slopes

Research Article

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Abstract: Optimal descriptors calculated with simplified molecular input line entry system (SMILES) have been examined as a tool for prediction of anxiolytic activity. Descriptors calculated with SMILES (a) of keto-isomers; (b) of enol-isomers; and (c) of both keto-isomers together with enol-isomers have been studied. Three approaches have been compared: 1. classic 'training-test' system 2. balance of correlations and 3. balance of correlations with ideal slopes. The best statistical characteristics for the external validation set took place for optimal descriptors calculated with SMILES of both keto-form and enol-form (*i.e.*, molecular structure was represented in the format: 'SMILES of keto-form . SMILES of enol-form') by means of balance of correlations with ideal slopes. The predictive potential of this model was checked with three random splits.

Keywords: *QSAR • SMILES • Tautomerism • Anxiolytic activity • Balance of correlation*

1. Introduction

Tautomerism is an important phenomenon in chemistry and biochemistry. By taking this phenomenon into account one can improve the statistical characteristics of the quantitative structure – activity relationships (QSAR), which are used for prediction of the biochemical behaviour of substances.

Anxiolytic agents are widely used in medicine. The search for new anxiolytic agents is an important problem. QSAR prediction of the anxiolytic activity is possible [1]. These calculations can be useful in both practice and theory.

QSAR analysis has both many aims and approaches [2-8]. The validation of a QSAR model becomes a very important aspect of the QSAR analysis [9-11]. In the present study we have used the probabilistic approach to validate a model calculated with the simplified molecular input line entry system (SMILES) [12,13]. In other words, models were examined with three random splits into sub-training, calibration, and validation sets.

The aim of the present study is the estimation of SMILES-based optimal descriptors as a tool to predict anxiolytic activity.

2. Experimental procedure

2.1. Method

A group of 67 pyrido[1,2-a]benzimidazole derivatives and their anxiolytic activities (pIC50 values measured in the absence of γ-aminobutyric acid) were taken from [1]. The

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Supplementary materials section contains the molecular structures of these compounds.

Three versions of the SMILES-based optimal descriptors [13-15] were examined:

$$DCW(Threshold) = F(A) \quad (1)$$

$$DCW(Threshold) = F(B) \quad (2)$$

$$DCW(Threshold) = F(A,B) \quad (3)$$

where F is a mathematical function; A is SMILES for the keto-form of a given substance; B is SMILES for the enol-form of a given substance, and Threshold is a parameter that is used to classify SMILES attributes into two categories, *i.e*., rare or active [12,13]. Rare attributes do not contain sound information and bring noise to the model. In order to avoid this influence of the rare (noise) SMILES attributes, one can fix zero value of the correlation weight of each rare attribute (Eq. 4).

Thus, Eq. 1 is the model for anxiolytic activities that is based on the keto-form of compounds, Eq. 2 is the model that is based on the enol-form, and finally Eq. 3 is the model that is based on both the keto- and enol-forms.

Three approaches to the calculation of optimal descriptors were examined. These are the classic training set – validation set scheme [14,15], the balance of correlations [12,13], and the balance of correlations with ideal slopes [16,17].

Classic scheme (CS). We have used optimal SMILES-based descriptors, which are calculated with the correlation weights (descriptor of correlation weights = DCW) as follows

$$DCW(Threshold) = \sum_{k=1}^{E} W({}^1S_k) + \sum_{k=1}^{E-1} W({}^2S_k) + \sum_{k=1}^{E-2} W({}^3S_k) \quad (4)$$

where ${}^1S_k$, ${}^2S_k$,${}^3S_k$ are one-, two-, and three-element SMILES attributes. The majority of SMILES elements contain one character (*e.g*. 'C', 'c', 'N', etc.). There are SMILES elements which contain two characters (*e.g*. 'Cl', 'Br', '@@', *etc*.). In other words, the SMILES element encodes some part of the string which cannot be divided. However, the CORAL software used in this study (http://www.insilico.eu/CORAL/) reserves a standard twelve characters for a SMILES attribute and four positions in the standard string for each element, because, generally, a SMILES element can involve three ('Na+'), four ('[O-]'), or even larger numbers of characters ('[Cu+2]') [18-20]. Fortunately, the majority of attributes can be expressed by combining four (or less) characters. $W({}^xS_k)$ is the correlation weight for a SMILES attribute (x=1,2,3).

The process of calculating ${}^1S_k$, ${}^2S_k$,${}^3S_k$ can be represented by the scheme:

ABCDE → A+B+C+D+E (^1S_k)
ABCDE → AB+BC+CD+DE (^2S_k)
ABCDE → ABC+BCD+CDE (^3S_k)

For instance, SMILES = 'CCCN' is represented by nine strings. Table 1 shows strings encoded with ${}^1S_k$, ${}^2S_k$, and ${}^3S_k$ for the above SMILES. Thus, each SMILES is converted in a group of SMILES attributes (Table 1). When the preparation of all attributes which occur in all substances is completed, the system of building up the model is provided with the list of SMILES attributes for which the correlation weights $W({}^xS_k)$ should be calculated. It is to be noted that each SMILES attribute is a representation of some molecular fragment.

Using the Monte Carlo method, one can calculate the $W({}^xS_k)$ values that produce the maximum correlation coefficient between DCW(Threshold) and the pIC_{50} for the training set. Having numerical data for optimal $W({}^xS_k)$, one can calculate DCW(Threshold) for all compounds (*i.e*., both for the training set and validation set). By the least squares method one can calculate a model of pIC_{50}:

$$pIC50 = C0 + C1 * DCW(Threshold) \quad (5)$$

The predictive potential of the model calculated with Eq. 5 should be checked with the external validation set.

Balance of correlations (BC). The classic scheme can lead to overtraining (overfitting), *i.e*., a situation when high correlation for the training set is accompanied by poor correlation for the validation set. The correlation balance is aimed to avoid the overtraining. The essence of the method is the following: (a) the training set should be split into a sub-training set and calibration set; (b) instead of the Monte Carlo optimization of the correlation coefficient between DCW(Threshold) and pIC_{50}, one can use the Monte Carlo optimization with the target function calculated as

$$BC = R + R' - abs(R-R')*0.1 \quad (6)$$

where R and R' are the correlation coefficients for the sub-training set and calibration set, respectively. In fact, the calibration set is a preliminary validation set. A low value of the correlation coefficient for the calibration set leads to a decrease of BC. In fact, the search for the maximum of BC as calculated with Eq. 6 is an attempt to obtain the same correlation coefficients for the sub-training set and the calibration set.

Table 1. Example of SMILES attributes (^1S_k, ^2S_k, and ^3S_k) for SMILES represented by "CCCN"

^1S_k	^2S_k	^3S_k
Cxxxxxxxxxx*		
Cxxxxxxxxxx	CxxxCxxxxxxx	
Cxxxxxxxxxx	CxxxCxxxxxxx	CxxxCxxxCxxx
Nxxxxxxxxxx	CxxxNxxxxxxx	CxxxCxxxNxxx

*) The 'x' is used to indicate the vacant place in the string of symbols used for representation of a SMILES attribute.

Balance of correlations with ideal slopes (IS). Good correlations between DCW(Threshold) and pIC_{50} can take place for considerably different slopes in plots of pIC_{50}(experiment) versus pIC_{50}(calculated) for the sub-training set and calibration set. Fig. 1 shows this situation. In order to avoid this situation, one can use the following target function for the Monte Carlo optimization:

$$IS = BC - [abs(C0)+abs(C0')+abs(C1-C1')] *0.005 \quad (7)$$

where C0 and C0' are intercepts for the sub-training set and calibration set, respectively, and C1 and C1' are slopes for the sub-training and calibration set (the C0, C0', C1, C1' are calculated by the least squares method). In fact, the optimization with the target function that is calculated with Eq. 7 is an attempt to obtain intercepts for the sub-training set and the calibration set which are equal to zero, as well as identical slopes for the sub-training set and the calibration set. Unfortunately, this is an ideal situation which can be obtained only approximately [16,17].

The coefficients of 0.1 (Eq. 6) and 0.005 (Eq. 7) were defined empirically. This shows that the correlation coefficients provide a larger contribution to the quality of the model. However, the influence of the intercepts (C0, and C0') and slopes (C1, and C1') is also relevant, because the models which have been calculated with Eq. 7 are more accurate (Table 2) than models based on the balance of correlations (Eq. 6). Using 0.1 or even 0.01 instead of 0.005 leads to ineffective optimization based on the target function calculated with Eq. 7.

The algorithm of the Monte Carlo optimization that is used for all three approaches mentioned above (*i.e.*, CS, BC, and IS) was described in [21].

3. Results and Discussion

Table 2 shows the statistical quality of the models. One can see that models calculated with a separate keto-form (*i.e.*, using Eq. 1) or with a separate enol-form (*i.e.*, using Eq. 2) have similar statistical quality for the external test set. However, statistical quality of the

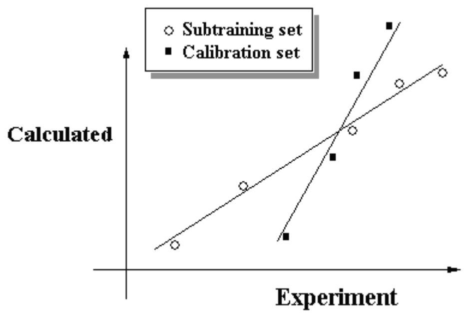


Figure 1. Good correlations which are accompanied by different slopes for the sub-training set and the calibration set in plots of experiment versus calculated values of an endpoint.

model calculated by taking into account the molecular architecture of both forms (*i.e.*, using Eq. 3) is superior. In addition, the models calculated with the CS scheme have modest statistical quality (the range of r^2_{test} is 0.6747-0.8063); the statistical quality of the models calculated with BC is better (the range of r^2_{test} is 0.7069-0.8567); and the statistical quality of models calculated with IS is the best (the range of r^2_{test} is 0.7974-0.8763).

Fig. 2 shows diagrams of the observed correlation coefficients for sub-training, calibration, and test sets for the range of the threshold 1-20 (in the case of the CS, the diagram contains data for the training and test sets, since the calibration set is not used). One can see the best predictions (maximum r^2_{test}) are obtained with IS for all three splits, but the optimal threshold values are different. These are 5,6, and 8 for split 1, split 2, and split 3, respectively.

The best model arises for split 3. This model is calculated as follows:

$$pIC_{50} = 2.2888(\pm0.1307) + 0.05654(\pm0.00142)* *DCW(8) \quad (8)$$

n=32, r^2=0.6291, q^2=0.5805, s=0.630, F=51 (sub-training set)

n=23, r^2=0.7242, s=0.677, F=55 (calibration set)

n=12, r^2=0.8750, s=0.490, F=70 (validation set)

Table 3 contains the values of pIC_{50} found experimentally and calculated with Eq. 8. Table 4 shows an example of the calculation of DCW(8). Fig. 3 depicts the model graphically. The *Supplementary materials* section contains data on correlation weights for the calculation of the DCW(8).

Table 2. Average correlation coefficients for the pIC_{50} models (external validation sets) obtained with three probes of the Monte Carlo optimization [F(A) is the model based on keto-form; F(B) is the model based on enol-form; and F(A,B) is the model calculated by taking into account both the keto-form and the enol-form]. The best models are indicated in bold text.

	Classic scheme			Balance of correlations			Balance of correlations with Ideal Slopes		
Split	F(A)	F(B)	F(A,B)	F(A)	F(B)	F(A,B)	F(A)	F(B)	F(A,B)
1	0.6246	0.6362	0.6747	0.6510	0.6603	0.7069	0.7277	0.7291	0.7974
2	0.6132	0.5771	0.7650	0.6346	0.5535	0.7687	0.6240	0.6204	0.8029
3	0.7889	0.7841	0.8063	0.7997	0.7993	0.8567	0.8566	0.7763	0.8763

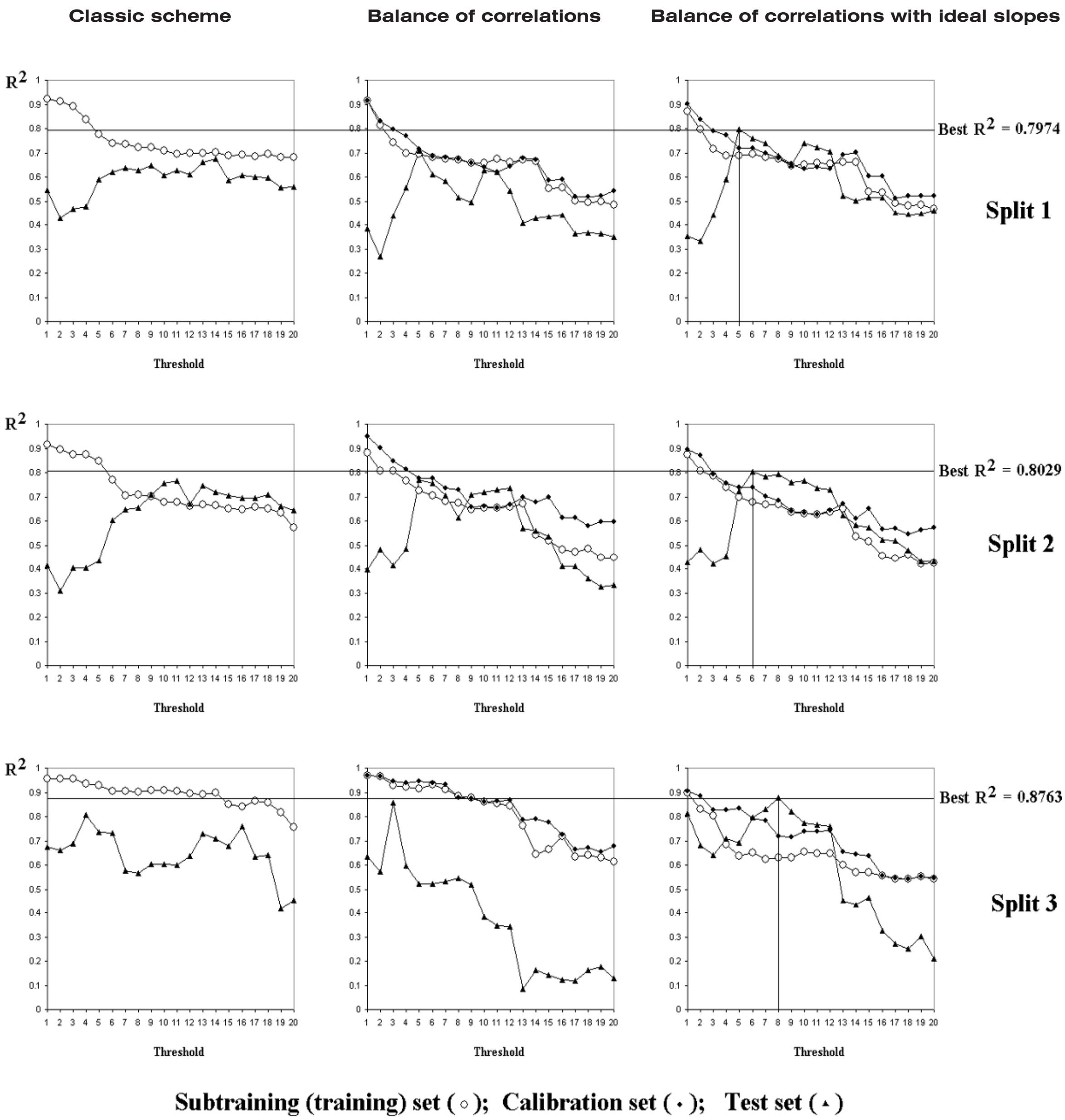


Figure 2. Diagrams of correlation coefficients versus the Threshold values for three random splits. One can see that the balance of correlations with ideal slopes gives the maximum correlation coefficient between DCW and pIC_{50} for the validation sets. The descriptors were calculated with Eq. 3

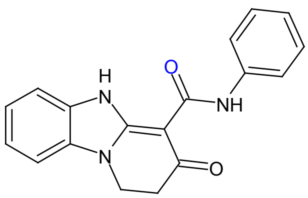
Table 3. Values of anxiolytics activity (pIC_{50}) from experiments and calculated with Eq. 8. The molecular structure is represented in the format 'SMILES of keto-form . SMILES of enol-form'.

ID	SMILES	DCW(8)	Expr	Calc
	Sub-training set			
P1	O=C(Nc1ccccc1)C3=C4Nc2ccccc2N4CCC3=O.O=C(Nc1ccccc1)C=3c4nc2ccccc2n4CCC=3O	88.1308382	8.040	7.268
P4	Clc4ccccc4NC(=O)C2=C3Nc1ccccc1N3CCC2=O.Clc4ccccc4NC(=O)C=2c3nc1ccccc1n3CCC=2	81.8014747	7.920	6.911
P8	COc4ccccc4NC(=O)C2=C3Nc1ccccc1N3CCC2=O.COc4ccccc4NC(=O)C=2c3nc1ccccc1n3CCC=2O	81.8824544	6.000	6.915
P9	Clc4cccc(Cl)c4NC(=O)C2=C3Nc1ccccc1N3CCC2=O.Clc4cccc(Cl)c4NC(=O)C=2c3nc1ccccc1n3CCC=2O	81.7637028	6.490	6.908
P14	NC(=O)C2=C3Nc1ccccc1N3CCC2=O.NC(=O)C=2c3nc1ccccc1n3CCC=2O	67.7360730	5.620	6.116
P16	S=C(Nc1ccccc1)C3=C4Nc2ccccc2N4CCC3=O.S=C(Nc1ccccc1)C=3c4nc2ccccc2n4CCC=3O	86.6191127	6.440	7.183
P19	O=C(Sc1ccccc1)C3=C4Nc2ccccc2N4CCC3=O.O=C(Sc1ccccc1)C=3c4nc2ccccc2n4CCC=3O	89.6077880	7.540	7.352
P21	Fc4ccccc4NC(=O)C2=C3Nc1ccccc1N3C=CC2=O.Fc4ccccc4NC(=O)c2c3nc1ccccc1n3ccc2O	134.4648060	9.640	9.886
P23	Oc1ccc(cc1)NC(=O)C3=C4Nc2ccccc2N4CCC3=O.Oc1ccc(cc1)NC(=O)C=3c4nc2ccccc2n4CCC=3O	88.0426091	7.340	7.263
P25	Nc4ccccc4NC(=O)C2=C3Nc1ccccc1N3CCC2=O.Nc4ccccc4NC(=O)C=2c3nc1ccccc1n3CCC=2O	72.7510016	7.300	6.399
P26	CN(C)c1ccc(cc1)NC(=O)C3=C4Nc2ccccc2N4CCC3=O.CN(C)c1ccc(cc1)NC(=O)C=3c4nc2ccccc2n4CCC=3O	75.2744925	6.570	6.542
P28	CN(C)c4ccccc4NC(=O)C2=C3Nc1ccccc1N3CCC2=O.CN(C)c4ccccc4NC(=O)C=2c3nc1ccccc1n3CCC=2O	76.4201682	5.000	6.607
P29	CN(C)c4ccc(NC(=O)C2=C3Nc1ccccc1N3CCC2=O)c(F)c4.CN(C)c4ccc(NC(=O)C=2c3nc1ccccc1n3CCC=2O)c(F)c4	64.4565559	6.920	5.931
P30	CN(C)c4ccc(NC(=O)C2=C3Nc1ccccc1N3CCC2=O)c(C)c4.CN(C)c4ccc(NC(=O)C=2c3nc1ccccc1n3CCC=2O)c(C)c4	59.7550663	5.400	5.665
P31	O=C(Nc1ccncc1)C3=C4Nc2ccccc2N4CCC3=O.O=C(Nc1ccncc1)C=3c4nc2ccccc2n4CCC=3O	77.6569524	6.800	6.676
P33	O=C(Nc1ccccn1)C3=C4Nc2ccccc2N4CCC3=O.O=C(Nc1ccccn1)C=3c4nc2ccccc2n4CCC=3O	85.8202534	7.230	7.138
P36	Fc4cnccc4NC(=O)C2=C3Nc1ccccc1N3CCC2=O.Fc4cnccc4NC(=O)C=2c3nc1ccccc1n3CCC=2O	94.1884845	7.280	7.610
P37	Clc4ncccc4NC(=O)C2=C3Nc1ccccc1N3CCC2=O.Clc4ncccc4NC(=O)C=2c3nc1ccccc1n3CCC=2O	86.2527330	7.170	7.162
P38	O=C(NCc1ccncc1)C3=C4Nc2ccccc2N4CCC3=O.O=C(NCc1ccncc1)C=3c4nc2ccccc2n4CCC=3O	83.2318150	7.190	6.991
P43	O=C(Nc1ccncc1)C3=C4Nc2ccccc2N4C=CC3=O.O=C(Nc1ccncc1)c3c4nc2ccccc2n4ccc3O	81.0926322	6.590	6.871
P45	Oc1cc2NC3=C(C(=O)CCN3c2cc1)C(=O)Nc4ccccc4.Oc1cc2nc3C(=C(O)CCn3c2cc1)C(=O)Nc4ccccc4	88.8405337	7.390	7.308
P47	Fc4ccccc4NC(=O)C2=C3Nc1c(OC)cccc1N3CCC2=O.Fc4ccccc4NC(=O)C=2c3nc1c(OC)cccc1n3CCC=2O	99.0822515	8.110	7.887
P48	Fc4cccc(F)c4NC(=O)C2=C3Nc1c(OC)cccc1N3CCC2=O.Fc4cccc(F)c4NC(=O)C=2c3nc1c(OC)cccc1n3CCC=2O	98.9914751	6.810	7.882
P49	COc1cc2NC3=C(C(=O)CCN3c2cc1)C(=O)Nc4ccccc4.COc1cc2nc3C(=C(O)CCn3c2cc1)C(=O)Nc4ccccc4	86.1286565	7.400	7.155
P52	Fc4ccccc4NC(=O)C2=C3Nc1c(cccc1C)N3CCC2=O.Fc4ccccc4NC(=O)C=2c3nc1c(cccc1C)n3CCC=2O	97.8295180	7.020	7.816
P53	Fc4ccccc4NC(=O)C2=C3Nc1cc(ccc1N3CCC2=O)C(F)(F)F.Fc4ccccc4NC(=O)C=2c3nc1cc(ccc1n3CCC=2O)C(F)(F)F	75.3170896	6.740	6.544
P55	Fc4cccc(F)c4NC(=O)C2=C3Nc1c(Cl)cccc1N3CCC2=O.Fc4cccc(F)c4NC(=O)C=2c3nc1c(Cl)cccc1n3CCC=2O	104.5503841	8.960	8.196
P58	Fc4cccc(F)c4NC(=O)C2=C3Nc1cc(Cl)ccc1N3CCC2=O.Fc4cccc(F)c4NC(=O)C=2c3nc1cc(Cl)ccc1n3CCC=2O	103.6759025	8.200	8.146
P60	Fc4ccccc4NC(=O)C2=C3Nc1cc(F)ccc1N3CCC2=O.Fc4ccccc4NC(=O)C=2c3nc1cc(F)ccc1n3CCC=2O	101.8920635	8.720	8.046
P61	Fc4cccc(F)c4NC(=O)C2=C3Nc1cc(F)ccc1N3CCC2=O.Fc4cccc(F)c4NC(=O)C=2c3nc1cc(F)ccc1n3CCC=2O	101.8012871	8.200	8.041
P63	Fc4cccc(F)c4NC(=O)C2=C3Nc1c(ccc(F)c1F)N3CCC2=O.Fc4cccc(F)c4NC(=O)C=2c3nc1c(ccc(F)c1F)n3CCC=2O	101.3254463	8.960	8.014
P65	Fc4cccc(F)c4NC(=O)C2=C3Nc1c(cc(F)cc1F)N3CCC2=O.Fc4cccc(F)c4NC(=O)C=2c3nc1c(cc(F)cc1F)n3CCC=2O	100.4509647	7.520	7.964
	Calibration set			
P5	Fc4ccccc4NC(=O)C2=C3Nc1ccccc1N3CCC2=O.Fc4ccccc4NC(=O)C=2c3nc1ccccc1n3CCC=2O	102.6413963	8.770	8.088
P6	COc1ccc(cc1)NC(=O)C3=C4Nc2ccccc2N4CCC3=O.COc1ccc(cc1)NC(=O)C=3c4nc2ccccc2n4CCC=3O	85.3307319	7.390	7.110
P7	COc1cccc(c1)NC(=O)C3=C4Nc2ccccc2N4CCC3=O.COc1cccc(c1)NC(=O)C=3c4nc2ccccc2n4CCC=3O	86.2052135	7.590	7.159
P10	Fc4cccc(F)c4NC(=O)C2=C3Nc1ccccc1N3CCC2=O.Fc4cccc(F)c4NC(=O)C=2c3nc1ccccc1n3CCC=2O	102.5506199	8.550	8.083
P11	O=C(NC1CCCCC1)C3=C4Nc2ccccc2N4CCC3=O.O=C(NC1CCCCC1)C=3c4nc2ccccc2n4CCC=3O	85.3196446	6.850	7.109
P12	O=C(NC1CCC1)C3=C4Nc2ccccc2N4CCC3=O.O=C(NC1CCC1)C=3c4nc2ccccc2n4CCC=3O	92.8600262	7.520	7.535
P13	O=C(NC1CC1)C3=C4Nc2ccccc2N4CCC3=O.O=C(NC1CC1)C=3c4nc2ccccc2n4CCC=3O	96.6302170	7.800	7.748
P15	O=C(OCC)C2=C3Nc1ccccc1N3CCC2=O.O=C(OCC)C=2c3nc1ccccc1n3CCC=2O	71.1054957	6.170	6.306
P17	CN(c1ccccc1)C(=O)C3=C4Nc2ccccc2N4CCC3=O.CN(c1ccccc1)C(=O)C=3c4nc2ccccc2n4CCC=3O	68.3790025	5.000	6.152
P20	O=C(Nc1ccccc1)C3=C4Nc2ccccc2N4C=CC3=O.O=C(Nc1ccccc1)c3c4nc2ccccc2n4ccc3O	91.5665180	7.620	7.462
P22	O=C(O)c1ccc(cc1)NC(=O)C3=C4Nc2ccccc2N4CCC3=O.O=C(O)c1ccc(cc1)NC(=O)C=3c4nc2ccccc2n4CCC=3O	65.5834716	5.000	5.994
P24	Nc1ccc(cc1)NC(=O)C3=C4Nc2ccccc2N4CCC3=O.Nc1ccc(cc1)NC(=O)C=3c4nc2ccccc2n4CCC=3O	71.5913527	4.890	6.334
P27	CN(C)c1cccc(c1)NC(=O)C3=C4Nc2ccccc2N4CCC3=O.CN(C)c1cccc(c1)NC(=O)C=3c4nc2ccccc2n4CCC=3O	76.1489741	7.430	6.591
P32	O=C(Nc1cccnc1)C3=C4Nc2ccccc2N4CCC3=O.O=C(Nc1cccnc1)C=3c4nc2ccccc2n4CCC=3O	86.7475832	7.290	7.190
P34	Clc4cnccc4NC(=O)C2=C3Nc1ccccc1N3CCC2=O.Clc4cnccc4NC(=O)C=2c3nc1ccccc1n3CCC=2O	71.5269520	6.660	6.330
P39	O=C(NCc1cccnc1)C3=C4Nc2ccccc2N4CCC3=O.O=C(NCc1cccnc1)C=3c4nc2ccccc2n4CCC=3O	92.3224458	6.820	7.505
P42	O=C(Nc1ccncn1)C3=C4Nc2ccccc2N4CCC3=O.O=C(Nc1ccncn1)C=3c4nc2ccccc2n4CCC=3O	77.8758430	6.320	6.689
P50	Fc4ccccc4NC(=O)C2=C3Nc1cc(OC)ccc1N3CCC2=O.Fc4ccccc4NC(=O)C=2c3nc1cc(OC)ccc1n3CCC=2O	98.2077699	8.210	7.838
P51	Cc4cccc1c4NC2=C(C(=O)CCN12)C(=O)Nc3ccccc3.Cc4cccc1c4nc2C(=C(O)CCn12)C(=O)Nc3ccccc3	98.6620685	8.000	7.863
P59	Clc1ccc2NC3=C(C(=O)CCN3c2c1)C(=O)Nc4ccccc4.Clc1ccc2nc3C(=C(O)CCn3c2c1)C(=O)Nc4ccccc4	86.0089241	6.760	7.148
P62	Fc4ccccc4NC(=O)C2=C3Nc1c(ccc(F)c1F)N3CCC2=O.Fc4ccccc4NC(=O)C=2c3nc1c(ccc(F)c1F)n3CCC=2O	101.4162227	8.850	8.019
P64	Fc4ccccc4NC(=O)C2=C3Nc1c(cc(F)cc1F)N3CCC2=O.Fc4ccccc4NC(=O)C=2c3nc1c(cc(F)cc1F)n3CCC=2O	100.5417411	7.700	7.969
P66	Fc4ccccc4NC(=O)C2=C3Nc1ccc(F)c(F)c1N3CCC2=O.Fc4ccccc4NC(=O)C=2c3nc1ccc(F)c(F)c1n3CCC=2O	92.6339461	6.070	7.523

Continued **Table 3.** Values of anxiolytics activity (pIC_{50}) from experiments and calculated with Eq. 8. The molecular structure is represented in the format 'SMILES of keto-form . SMILES of enol-form'.

ID	SMILES	DCW(8)	Expr	Calc
	Validation set			
P2	Clc1ccc(cc1)NC(=O)C3=C4Nc2ccccc2N4CCC3=O.Clc1ccc(cc1)NC(=O)C=3c4nc2ccccc2n4CCC=3O	83.4281413	6.210	7.002
P3	Clc1cccc(c1)NC(=O)C3=C4Nc2ccccc2N4CCC3=O.Clc1cccc(c1)NC(=O)C=3c4nc2ccccc2n4CCC=3O	84.3026229	6.920	7.052
P18	O=C(Oc1ccccc1)C3=C4Nc2ccccc2N4CCC3=O.O=C(Oc1ccccc1)C=3c4nc2ccccc2n4CCC=3O	83.4242062	6.700	7.002
P35	Cc4cnccc4NC(=O)C2=C3Nc1ccccc1N3CCC2=O.Cc4cnccc4NC(=O)C=2c3nc1ccccc1n3CCC=2O	70.8855742	5.150	6.294
P40	O=C(Nc1cncn1)C3=C4Nc2ccccc2N4CCC3=O.O=C(Nc1cncn1)C=3c4nc2ccccc2n4CCC=3O	84.4369984	6.440	7.059
P41	O=C(Nc1nccn1)C3=C4Nc2ccccc2N4CCC3=O.O=C(Nc1nccn1)C=3c4nc2ccccc2n4CCC=3O	84.5618052	7.270	7.067
P44	Fc4ccccc4NC(=O)C2=C3Nc1c(O)cccc1N3CCC2=O.Fc4ccccc4NC(=O)C=2c3nc1c(O)cccc1n3CCC=2O	98.1968569	7.980	7.837
P46	Fc4ccccc4NC(=O)C2=C3Nc1cccc(O)c1N3CCC2=O.Fc4ccccc4NC(=O)C=2c3nc1cccc(O)c1n3CCC=2O	98.1968569	7.850	7.837
P54	Fc4ccccc4NC(=O)C2=C3Nc1c(Cl)cccc1N3CCC2=O.Fc4ccccc4NC(=O)C=2c3nc1c(Cl)cccc1n3CCC=2O	104.6411605	8.150	8.201
P56	Clc1cc2NC3=C(C(=O)CCN3c2cc1)C(=O)Nc4ccccc4.Clc1cc2nc3C(=C(O)CCn3c2cc1)C(=O)Nc4ccccc4	84.2260659	7.180	7.048
P57	Fc4ccccc4NC(=O)C2=C3Nc1cc(Cl)ccc1N3CCC2=O.Fc4ccccc4NC(=O)C=2c3nc1cc(Cl)ccc1n3CCC=2O	103.7666789	8.290	8.152
P67	Fc4cccc(F)c4NC(=O)C2=C3Nc1ccc(F)c(F)c1N3CCC2=O.Fc4cccc(F)c4NC(=O)C=2c3nc1ccc(F)c(F)c1n3CCC=2O	92.5431697	7.180	7.517

Table 4. Example of DCW(8) calculation for a substance (P1) which is represented by the SMILES: O=C(Nc1ccccc1)C3=C4Nc2ccccc2N4CCC3=O. O=C(Nc1ccccc1)C=3c4nc2ccccc2n4CCC=3O DCW(8) = 88.1308382



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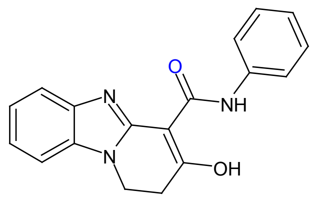
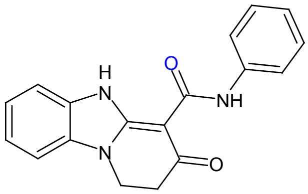


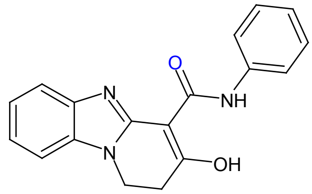
B

SMILES attribute with one element, ^1S_k	$W(^1S_k)$	SMILES attribute with two elements, ^2S_k	$W(^2S_k)$	SMILES attribute with three elements, ^3S_k	$W(^3S_k)$
Oxxxxxxxxxxx	1.2719842				
=xxxxxxxxxxx	-2.2014019	Oxxx=xxxxxxx	-2.1994232		
Cxxxxxxxxxxx	-0.3206889	Cxxx=xxxxxxx	0.3667137	Oxxx=xxxCxxx	0.0000000
(xxxxxxxxxxx	-0.8829287	Cxxx(xxxxxxx	-1.4836818	=xxxCxxx(xxx	2.1374485
Nxxxxxxxxxxx	-2.0876386	Nxxx(xxxxxxx	3.7006953	Nxxx(xxxCxxx	1.4792241
cxxxxxxxxxxx	-0.7405851	cxxxNxxxxxxx	-1.5267925	cxxxNxxx(xxx	0.0000000
1xxxxxxxxxxx	5.8997748	cxxx1xxxxxxx	1.4457884	Nxxxcxxx1xxx	-2.3039632
cxxxxxxxxxxx	-0.7405851	cxxx1xxxxxxx	1.4457884	cxxx1xxxcxxx	1.8464055
cxxxxxxxxxxx	-0.7405851	cxxxcxxxxxxx	-1.0453451	cxxxcxxx1xxx	-2.1506885
cxxxxxxxxxxx	-0.7405851	cxxxcxxxxxxx	-1.0453451	cxxxcxxxcxxx	1.2647377
cxxxxxxxxxxx	-0.7405851	cxxxcxxxxxxx	-1.0453451	cxxxcxxxcxxx	1.2647377
cxxxxxxxxxxx	-0.7405851	cxxxcxxxxxxx	-1.0453451	cxxxcxxxcxxx	1.2647377
1xxxxxxxxxxx	5.8997748	cxxx1xxxxxxx	1.4457884	cxxxcxxx1xxx	-2.1506885
(xxxxxxxxxxx	-0.8829287	1xxx(xxxxxxx	0.2671641	cxxx1xxx(xxx	1.3956548
Cxxxxxxxxxxx	-0.3206889	Cxxx(xxxxxxx	-1.4836818	Cxxx(xxx1xxx	1.0026046
3xxxxxxxxxxx	5.9294417	Cxxx3xxxxxxx	-1.0581548	3xxxCxxx(xxx	0.8880894
=xxxxxxxxxxx	-2.2014019	=xxx3xxxxxxx	-0.2418664	Cxxx3xxx=xxx	-0.7277957
Cxxxxxxxxxxx	-0.3206889	Cxxx=xxxxxxx	0.3667137	Cxxx=xxx3xxx	0.7038408
4xxxxxxxxxxx	0.6960386	Cxxx4xxxxxxx	-0.9386474	=xxxCxxx4xxx	-1.2726292
Nxxxxxxxxxxx	-2.0876386	Nxxx4xxxxxxx	0.4028821	Nxxx4xxxCxxx	-1.7787158
cxxxxxxxxxxx	-0.7405851	cxxxNxxxxxxx	-1.5267925	cxxxNxxx4xxx	-1.7385920
2xxxxxxxxxxx	5.6377804	cxxx2xxxxxxx	2.6149517	Nxxxcxxx2xxx	-1.7110720
cxxxxxxxxxxx	-0.7405851	cxxx2xxxxxxx	2.6149517	cxxx2xxxcxxx	2.1285531
cxxxxxxxxxxx	-0.7405851	cxxxcxxxxxxx	-1.0453451	cxxxcxxx2xxx	2.5239971
cxxxxxxxxxxx	-0.7405851	cxxxcxxxxxxx	-1.0453451	cxxxcxxxcxxx	1.2647377
cxxxxxxxxxxx	-0.7405851	cxxxcxxxxxxx	-1.0453451	cxxxcxxxcxxx	1.2647377
cxxxxxxxxxxx	-0.7405851	cxxxcxxxxxxx	-1.0453451	cxxxcxxxcxxx	1.2647377
2xxxxxxxxxxx	5.6377804	cxxx2xxxxxxx	2.6149517	cxxxcxxx2xxx	2.5239971

Continued Table 4. Example of DCW(8) calculation for a substance (P1) which is represented by the SMILES: O=C(Nc1ccccc1)C3=C4Nc2ccccc2N4CCC3=O.O=C(Nc1ccccc1)C=3c4nc2ccccc2n4CCC=3O DCW(8) = 88.1308382



A



B

SMILES attribute with one element, ^1S_k	$W(^1S_k)$	SMILES attribute with two elements, ^2S_k	$W(^2S_k)$	SMILES attribute with three elements, ^3S_k	$W(^3S_k)$
Nxxxxxxxxxxx	-2.0876386	Nxxx2xxxxxxx	1.0975444	cxxx2xxxNxxx	0.7788656
4xxxxxxxxxxx	0.6960386	Nxxx4xxxxxxx	0.4028821	4xxxNxxx2xxx	-1.8247358
Cxxxxxxxxxxx	-0.3206889	Cxxx4xxxxxxx	-0.9386474	Nxxx4xxxCxxx	-1.7787158
Cxxxxxxxxxxx	-0.3206889	CxxxCxxxxxxx	0.5510065	CxxxCxxx4xxx	2.2541704
Cxxxxxxxxxxx	-0.3206889	CxxxCxxxxxxx	0.5510065	CxxxCxxxCxxx	-2.1154130
3xxxxxxxxxxx	5.9294417	Cxxx3xxxxxxx	-1.0581548	CxxxCxxx3xxx	-0.4492216
=xxxxxxxxxxx	-2.2014019	=xxx3xxxxxxx	-0.2418664	Cxxx3xxx=xxx	-0.7277957
Oxxxxxxxxxxx	1.2719842	Oxxx=xxxxxxx	-2.1994232	Oxxx=xxx3xxx	-1.8742464
.xxxxxxxxxxx	6.3036180	Oxxx.xxxxxxx	2.0704994	=xxxOxxx.xxx	1.2961041
Oxxxxxxxxxxx	1.2719842	Oxxx.xxxxxxx	2.0704994	Oxxx.xxxOxxx	0.0000000
=xxxxxxxxxxx	-2.2014019	Oxxx=xxxxxxx	-2.1994232	=xxxOxxx.xxx	1.2961041
Cxxxxxxxxxxx	-0.3206889	Cxxx=xxxxxxx	0.3667137	Oxxx=xxxCxxx	0.0000000
(xxxxxxxxxxx	-0.8829287	Cxxx(xxxxxxx	-1.4836818	=xxxCxxx(xxx	2.1374485
Nxxxxxxxxxxx	-2.0876386	Nxxx(xxxxxxx	3.7006953	Nxxx(xxxCxxx	1.4792241
cxxxxxxxxxxx	-0.7405851	cxxxNxxxxxxx	-1.5267925	cxxxNxxx(xxx	0.0000000
1xxxxxxxxxxx	5.8997748	cxxx1xxxxxxx	1.4457884	Nxxxcxxx1xxx	-2.3039632
cxxxxxxxxxxx	-0.7405851	cxxx1xxxxxxx	1.4457884	cxxx1xxxcxxx	1.8464055
cxxxxxxxxxxx	-0.7405851	cxxxcxxxxxxx	-1.0453451	cxxxcxxx1xxx	-2.1506885
cxxxxxxxxxxx	-0.7405851	cxxxcxxxxxxx	-1.0453451	cxxxcxxxcxxx	1.2647377
cxxxxxxxxxxx	-0.7405851	cxxxcxxxxxxx	-1.0453451	cxxxcxxxcxxx	1.2647377
cxxxxxxxxxxx	-0.7405851	cxxxcxxxxxxx	-1.0453451	cxxxcxxxcxxx	1.2647377
1xxxxxxxxxxx	5.8997748	cxxx1xxxxxxx	1.4457884	cxxxcxxx1xxx	-2.1506885
(xxxxxxxxxxx	-0.8829287	1xxx(xxxxxxx	0.2671641	cxxx1xxx(xxx	1.3956548
Cxxxxxxxxxxx	-0.3206889	Cxxx(xxxxxxx	-1.4836818	Cxxx(xxx1xxx	1.0026046
=xxxxxxxxxxx	-2.2014019	Cxxx=xxxxxxx	0.3667137	=xxxCxxx(xxx	2.1374485
3xxxxxxxxxxx	5.9294417	=xxx3xxxxxxx	-0.2418664	Cxxx=xxx3xxx	0.7038408
cxxxxxxxxxxx	-0.7405851	cxxx3xxxxxxx	6.1923868	cxxx3xxx=xxx	1.9870684
4xxxxxxxxxxx	0.6960386	cxxx4xxxxxxx	1.7015689	4xxxcxxx3xxx	-1.4351969
nxxxxxxxxxxx	-1.1419529	nxxx4xxxxxxx	2.9733890	nxxx4xxxcxxx	2.3494223
cxxxxxxxxxxx	-0.7405851	nxxxcxxxxxxx	-1.5660261	cxxxnxxx4xxx	4.0961712
2xxxxxxxxxxx	5.6377804	cxxx2xxxxxxx	2.6149517	nxxxcxxx2xxx	4.4522769
cxxxxxxxxxxx	-0.7405851	cxxx2xxxxxxx	2.6149517	cxxx2xxxcxxx	2.1285531
cxxxxxxxxxxx	-0.7405851	cxxxcxxxxxxx	-1.0453451	cxxxcxxx2xxx	2.5239971
cxxxxxxxxxxx	-0.7405851	cxxxcxxxxxxx	-1.0453451	cxxxcxxxcxxx	1.2647377
cxxxxxxxxxxx	-0.7405851	cxxxcxxxxxxx	-1.0453451	cxxxcxxxcxxx	1.2647377
cxxxxxxxxxxx	-0.7405851	cxxxcxxxxxxx	-1.0453451	cxxxcxxxcxxx	1.2647377
2xxxxxxxxxxx	5.6377804	cxxx2xxxxxxx	2.6149517	cxxxcxxx2xxx	2.5239971
nxxxxxxxxxxx	-1.1419529	nxxx2xxxxxxx	-0.0017811	nxxx2xxxcxxx	0.8517795
4xxxxxxxxxxx	0.6960386	nxxx4xxxxxxx	2.9733890	4xxxnxxx2xxx	-1.9961987
Cxxxxxxxxxxx	-0.3206889	Cxxx4xxxxxxx	-0.9386474	nxxx4xxxCxxx	2.9259553
Cxxxxxxxxxxx	-0.3206889	CxxxCxxxxxxx	0.5510065	CxxxCxxx4xxx	2.2541704
Cxxxxxxxxxxx	-0.3206889	CxxxCxxxxxxx	0.5510065	CxxxCxxxCxxx	-2.1154130
=xxxxxxxxxxx	-2.2014019	Cxxx=xxxxxxx	0.3667137	CxxxCxxx=xxx	-2.2971478
3xxxxxxxxxxx	5.9294417	=xxx3xxxxxxx	-0.2418664	Cxxx=xxx3xxx	0.7038408
Oxxxxxxxxxxx	1.2719842	Oxxx3xxxxxxx	-1.4111115	Oxxx3xxx=xxx	2.1204695

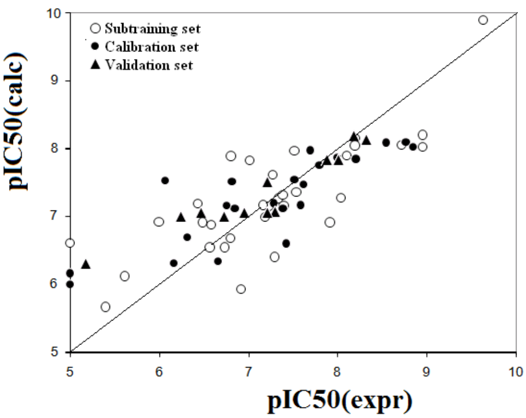


Figure 3. Graphical representation of the model calculated with Eq. 8.

The anxiolytic activity of different substances is important [1,22-28]; however, the QSAR analysis of this endpoint is carried out in few studies [1,22-24]. The statistical characteristics of the model of pIC_{50} described in [1] are the following: n=67, r^2=0.951, s=0.246, F=140. In other words, external validation is absent in this work [1]. The model has been built by the multiple linear regression analysis (MLRA) method with eight descriptors. However, the external checking of an MLRA model can help avoid overtraining [9]. The statistical characteristics of the best model for anxiolytic activity which has been obtained using parameters from quantum chemistry and neural networks [22] are the following: n=33, r^2 = 0.8305, s=0.5700 (training set), and n=15, r^2=0.8154, s=0.7242 (test set). The model of anxiolytic activity based on the PLS method [23] is characterised by n=47, r^2=0.866 (training set) and n=7, r^2=0.681 (test set). The QSAR model for anxiolytic agents described in Ref. 24 is characterized by q^2=0.58, *i.e.*, the statistical quality of this model is similar to the statistical quality of Eq. 8. Thus, one can consider the statistical quality of the model calculated with Eq. 8 and the statistical quality of the above-mentioned models [1,22-24] to be similar, in spite of differences in the approaches used.

4. Conclusions

1. The SMILES-based optimal descriptors calculated with the balance of correlations (which is a system consisting of the sub-training set, the calibration set, and the external test set) yield better predictions of anxiolytic activity than the descriptors calculated with the “classic scheme” (which is a system consisting of the training set and test set, without the calibration set);

2. The optimal SMILES-based descriptors calculated by taking into account intercepts and slopes in the sub-training set and in the calibration set improves the accuracy of the prediction of the anxiolytics activity obtained by the balance of correlations. This is carried out without taking into account the intercepts and the slopes;

3. The SMILES-based descriptors calculated by taking into account both the keto-form and the enol-form of substances yield better prediction of the anxiolytic activity than the descriptors which are calculated using only one of the two aforementioned forms.

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