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Combining DFT and QSAR result for predicting the toxicity of a series of substituted phenols

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ABSTRACT

The DFT-B3LYP method, with the basis set 6-31G (d), was employed to calculate some quantum chemical descriptors of 31 substituted phenols compounds. The best descriptors were selected to establish the quantitative structure activity relationship (QSAR) of the toxicity of these compounds to Rana japonica tadpoles by principal components analysis (PCA), to a multiple regression analysis (MLR), to a non-linear regression (RNLM) and to an artificial neural network (ANN). We accordingly propose a quantitative model, and we interpret the activity of the compounds relying on the multivariate statistical analysis. This study shows that the prediction results were in excellent agreement with the experimental value.

Keywords: QSAR model, DFT study, substituted phenols, Tadpoles (*Rana japonica*).

INTRODUCTION

One of the current interests in medicinal chemistry, environmental sciences and toxicology is the ranking of chemical substances with respect to their potential hazardous effects on humans, wild life, aquatic flora and fauna [1]. Quantitative structure–activity relationships (QSARs) and quantitative structure–toxicity relationships (QSTRs) have provided a valuable approach in research on the toxicity of organic chemicals in such studies.

Numerous laboratory aquatic acute toxicity were developed using species belonging to different levels in the food webs as test organisms [2].While a number of studies have focused predominantly on fish and crustaceans, there is limited data pertaining to the effects of these chemicals on amphibians [3]. Amphibian species have shown to be more sensitive bio-indicators of aquatic contaminants than other aquatic vertebrates because they have a permeable skin that readily absorbs substances from the environment. Tadpoles, the larvae of frogs are useful biological materials for performing standardized acute toxicity assessment bioassays [2]. Thus, it is necessary to investigate the adverse effect of industrial materials on the tadpoles for further protecting frogs and aquatic environment.

Phenol and its derivatives have been used for many years in chemical industry. They are used as solvents, propellants, additives, cooling agents and other polymers, for insecticide, herbicides and organic syntheses [4]. Many of these chemicals were released into the environment and accumulated in nearly all environmental compartments, especially in aquatic systems, so it is beneficial to make a deep study of their potential hazard to aquatic organism.

QSAR can predict the bioactivity such as toxicity, mutagenicity and carcinogenicity based on structural parameters of compounds and appropriate mathematical models. With the rapid development of computer science and theoretical quantum chemical study, it can speedily and precisely obtain the quantum chemical parameters of compounds by computation. Moreover, these parameters, which have definite physical meaning, along with the

introduction of the QSAR model can increase the interpretability. So quantum chemical theory is extensively applied in establishing QSAR models [5-7].

The aims of this study are to develop predictive QSAR models for the acute toxic effects of phenol compounds to the tadpoles (*Rana japonica*) using several statistical tools, principal components analysis (PCA), multiple linear regression (MLR), non-linear regression (RNLM) and artificial neural network (ANN) calculations.

MATERIALS AND METHODS

Data sources

Acute toxicity data of 31substituted phenols to*R. japonica* tadpoles were taken from a literature [8]. LC_{50} (mmol/l) heremeans the lethal concentration needed to obtain half mortality for each chemical to *Rana japonica* tadpoles.The table 1 shows the chemical compounds studied and the corresponding experimental toxicities.

Table1:substituted phenols andtheir observed toxicitiesto R. japonica tadpoles

N°	Name (IUPAC)	pLC_{50}	N°	Name (IUPAC)	pLC_{50}
1	2-Nitrophenol	3.686	**17**	2,6-Dimethylphenol	3.331
2	3- Nitrophenol	3.482	**18**	Salicylaldehyde	3.968
3	4-Nitrophenol	4.052	**19**	4-Hydroxybenzaldehyde	2.804
4	4-Chloro-2-nitrophenol	4.880	**20**	Salicylicacid	2.841
5	2-Nitroresorcinol	3.380	**21**	2-Hydroxy, methyl benzoate	3.303
6	2-Chlorophenol	3.024	**22**	4-Hydroxy, methyl benzoate	3.163
7	4-Chlorophenol	3.308	**23**	Diphenylol propane	4.710
8	2,4-Dichlorophenol	3.996	**24**	Diphenylolsulfoxide	2.853
9	4-Bromophenol	3.619	**25**	1,1-Diphenylol ethane	4.014
10	2-Bromo-4-methylphenol	3.753	**26**	Resorcinol	2.077
11	2-Hydroxy-5-chlorobenzoic acid	3.012	**27**	3-Aminophenol	2.064
12	4-Fluorophenol	2.670	**28**	4-Hydroxyacetophenone	2.509
13	4-Methoxylphenol	2.371	**29**	4-Hydroxy-benzyl aceticacid	2.505
14	2- Methoxylphenol	2.500	**30**	4-Tert-Butylphenol	4.170
15	4-Methylphenol	2.928	**31**	Phenol	2.804
16	2-Methylphenol	2.819	-	-	-

Molecular descriptors

At present, there are a large number of molecular descriptors that can be used in QSAR studies. Once validated, the findings can be used to predict activities of untested compounds.

On the one hand, the computation of electronic descriptors was performed by using Gaussian 03W program [9]. The geometries of 31 substituted phenols were optimized with DFT method at the B3LYP functional and a 6-31G (d) basis set. Then choose some related structural parameters from the results of quantum computation: highest occupied molecular orbital energy E_{HOMO}, lowest unoccupied molecular orbital energy E_{LUMO}, energy gap ΔE, dipole moment μ, total energy E_T, activation energy E_a, and absorption maximum λ_{max}.

On the other hand, ACD/ChemSketch program [10] was employed to calculate the topological descriptors which are: Molar Volume (MV)**,**Molecular Weight (MW), Molar Refractivity (MR)**,**Parachor (Pc)**,** Density (D), Refractive Index (n), Surface Tension (γ) and Polarizability (α).

Statistical analysis

The substituted phenols (1 to 31) were studied by statistical methods based on the principal component analysis (PCA) [11] using the software XLSTAT version 2013 [12]. PCA is a statistical technique useful for summarizing all the information encoded in the structures of the compounds. It is also very helpful for understanding the distribution of the compounds [13]. This is an essentially descriptive statistical method which aims to present, in graphic form, the maximum of information contained in the data table 1 and table 2.

The multiple linear regression (MLR) analysis with descendent selection and elimination of variables was employed to model the structure activity relationships. It is a mathematic technique that minimizes differences between actual and predicted values. It has served also to select the descriptors used as the input parameters inartificial neural network (ANN).

(MLR) and (MNLR) were generated using the software XLSTAT version 2013, to predict toxic effects LC_{50} activities. Equations were justified by the correlation coefficient (R), mean squared error (MSE) [12].

The ANNs analysis was performed with the use of Matlab software version 2009a Neural Fitting tool (nftool) toolbox on a data set of our compounds[14]. A number of individual models of ANN were designed built up and

trained. Three components constitute a neural network: the processing elements or nodes, the topology of the connections between the nodes, and the learning rule by which new information is encoded in the network. While there are a number of different ANN models, the most frequently used type of ANN in QSAR is the three-layered feedforward network [15]. In this type of networks, the neurons are arranged in layers (an input layer, one hidden layer and an output layer). Each neuron in any layer is fully connected with the neurons of a succeeding layer and no connections are between neurons belonging to the same layer.

According to the supervised learning adopted, the networks are taught by giving them examples of input patterns and the corresponding target outputs. Through an iterative process, the connection weights are modified until the network gives the desired results for the training set of data. A backpropagation algorithm is used to minimize the error function. This algorithm has been described previously with a simple example of application [16] and a detail of this algorithm is given elsewhere [17].

RESULTS

A QSAR study was carried for a series of 31 substituted phenols to *R. japonica* tadpoles as reported in [8], in order to determine a quantitative relationship between structure and toxicity. The values of the 15 chemical descriptors as shown in table 2.

Table 2:Values of the obtained parameters of the studied substituted phenols

	MW	MR (cm^3)	MV (cm^3)	Pc (cm^3)	n	γ (dyne/cm)	D (g/cm^3)	α (cm^3)	E_T (Ua)	E_{HOMO} (ev)	E_{LUMO} (ev)	ΔE (ev)	μ (debye)	Ea (ev)	λ_{max} (nm)
1	139.109	34.670	99.70	277.70	1.612	60.20	1.395	13.740	-13941.11	-6.80	-2.71	4.089	3.616	3.951	313.82
2	139.109	34.670	99.70	277.70	1.612	60.20	1.395	13.740	-13940.86	-6.80	-2.46	4.340	3.566	3.947	314.15
3	139.109	34.670	99.70	277.70	1.612	60.20	1.395	13.740	-13940.92	-6.93	-2.22	4.703	5.341	3.901	317.81
4	173.554	39.570	111.60	313.60	1.626	62.20	1.554	15.680	-26455.81	-8.91	-2.98	5.921	2.670	3.949	313.99
5	155.108	36.560	98.10	292.70	1.667	79.20	1.580	14.490	-15988.98	-6.46	-2.45	4.001	5.052	3.897	318.14
6	128.556	33.020	99.80	258.10	1.575	44.70	1.287	13.090	-20887.12	-6.26	-0.36	5.899	0.933	5.311	233.43
7	128.556	33.020	99.80	258.10	1.575	44.70	1.287	13.090	-20886.88	-6.53	-0.43	6.099	2.213	5.262	235.63
8	163.001	37.920	111.70	294.00	1.593	47.80	1.458	15.030	-33401.86	-6.36	-0.76	5.601	1.070	5.122	242.08
9	173.007	35.820	104.00	272.70	1.604	47.20	1.662	14.200	-78383.27	-6.44	-0.43	6.008	2.136	5.196	238.64
10	187.034	40.640	120.30	310.40	1.590	44.30	1.554	16.110	-79454.18	-6.01	-0.32	5.690	1.327	5.180	239.34
11	172.566	39.950	112.30	320.20	1.629	66.00	1.536	15.840	-26022.21	-6.34	-1.78	4.556	1.075	5.142	241.11
12	112.102	28.120	92.00	229.40	1.523	38.50	1.217	11.150	-11074.19	-6.42	-0.33	6.092	1.828	5.346	231.92
13	124.137	34.810	111.80	278.90	1.534	38.60	1.109	13.800	-11490.39	-6.25	-0.09	6.165	0.289	5.370	230.88
14	124.137	34.810	111.80	278.90	1.534	38.60	1.109	13.800	-11490.76	-5.53	0.32	5.849	2.735	5.218	237.61
15	108.138	32.950	104.10	259.90	1.545	38.80	1.038	13.060	-9442.88	-5.75	0.07	5.816	1.334	5.368	230.97
16	108.138	32.950	104.10	259.90	1.545	38.80	1.038	13.060	-9442.89	-5.83	0.16	5.989	1.672	5.438	227.99
17	122.164	37.780	120.40	297.50	1.540	37.20	1.014	14.970	-10513.54	-5.72	0.29	6.005	1.486	5.405	229.40
18	122.121	34.880	99.50	267.30	1.618	52.00	1.226	13.830	-11458.08	-6.50	-1.58	4.919	4.766	3.870	320.42
19	122.121	34.880	99.50	267.30	1.618	52.00	1.226	13.830	-11458.17	-6.50	-1.45	5.045	3.386	3.984	311.18
20	138.121	35.060	100.30	284.40	1.615	64.40	1.375	13.900	-13507.29	-6.29	-1.37	4.926	0.715	4.928	251.59
21	152.147	39.900	125.70	327.10	1.547	45.70	1.209	15.820	-14577.62	-6.18	-1.24	4.944	1.146	4.950	250.46
22	152.147	39.900	125.70	327.10	1.547	45.70	1.209	15.820	-14577.50	-6.32	-0.93	5.394	1.344	5.166	239.98
23	228.286	68.590	199.40	526.50	1.603	48.50	1.144	27.190	-19923.54	-5.58	-0.32	5.262	3.078	5.141	241.18
24	234.271	63.390	155.10	480.80	1.752	92.20	1.500	25.130	-29601.63	-5.82	-1.09	4.734	5.256	2.172	570.85
25	214.260	63.960	182.90	486.70	1.616	50.10	1.171	25.350	-18853.05	-5.53	-0.32	5.207	3.048	5.148	240.86
26	110.111	30.010	86.20	237.30	1.612	57.10	1.275	11.890	-10420.42	-5.78	0.20	5.978	1.355	5.250	236.16
27	109.126	23.370	90.10	248.10	1.637	57.40	1.210	12.830	-9879.54	-5.32	0.40	5.717	2.740	5.448	227.58
28	136.148	38.160	119.30	307.40	1.552	43.90	1.140	15.120	-12528.92	-6.35	-1.23	5.115	2.610	4.189	296.00
29	152.147	39.240	115.30	320.60	1.596	59.80	1.319	15.550	-14577.48	-5.98	-0.13	5.850	0.460	5.286	234.57
30	150.218	46.520	154.50	370.30	1.513	32.90	0.971	18.440	-12654.31	-5.76	0.08	5.839	1.334	5.357	231.46
31	94.111	28.130	87.80	222.20	1.553	40.90	1.071	11.150	-8372.09	-6.48	0.003	6.483	1.598	5.482	226.19

Principal component analysis

The totality of the descriptors encoding the 31 molecules was submitted to a principal components analysis (PCA) [18,19].The first three principal axes are sufficient to describe the information provided by the data matrix. Indeed, the percentages of variance are 43.12%; 25.80% and 11.65% for the axes F1, F2 and F3, respectively. The total information is estimated to a percentage of 80.57%.

The principal component analysis (PCA) [20] was conducted to identify the link between the different variables. Bold values are different from 0 at a significance level of p= 0.05. Correlations between the sexteen descriptors are shown in table 3 as a correlation matrix and in Figure 1 these descriptors are represented in a correlation circle.

The Pearson correlation coefficients are summarized in the following table 3. The obtained matrix provides information on the negative or positive correlation between variables.

Table 3: Correlation matrix (Pearson (n)) between different obtained descriptors

	pLC_{50}	MW	MR	MV	Pc	n	γ	D	α	E_T	E_{HOMO}	E_{LUMO}	ΔE	μ	Ea	λ_{max}
pLC_{50}	**1**															
MW	0.545	**1**														
MR	0.493	**0.892**	**1**													
MV	0.474	**0.790**	**0.951**	**1**												
Pc	0.453	**0.884**	**0.987**	**0.962**	**1**											
n	0.117	**0.526**	0.340	0.093	0.347	**1**										
γ	0.027	**0.444**	0.253	0.003	0.273	**0.932**	**1**									
D	0.259	**0.456**	0.041	-0.176	0.016	**0.672**	**0.676**	**1**								
α	0.458	**0.889**	**0.987**	**0.954**	**0.996**	**0.381**	0.276	0.030	**1**							
E_T	-0.313	**-0.496**	-0.175	-0.105	-0.126	-0.218	-0.061	**-0.649**	-0.163	**1**						
E_{HOMO}	-0.431	0.009	0.209	0.324	0.248	-0.145	-0.231	**-0.479**	0.261	0.097	**1**					
E_{LUMO}	-0.431	-0.222	-0.033	0.141	-0.017	**-0.474**	**-0.595**	**-0.594**	0.005	0.007	**0.749**	**1**				
ΔE	-0.224	-0.340	-0.253	-0.105	-0.267	**-0.567**	**-0.664**	**-0.421**	-0.248	-0.084	0.144	**0.764**	**1**			
μ	0.305	0.256	0.244	0.090	0.234	**0.613**	**0.555**	0.274	0.262	0.065	-0.187	**-0.531**	**-0.611**	**1**		
Ea	-0.214	**-0.363**	-0.288	-0.061	-0.263	**-0.718**	**-0.741**	**-0.445**	-0.272	0.000	**0.393**	**0.709**	**0.677**	**-0.791**	**1**	
λ_{max}	0.101	**0.429**	**0.378**	0.152	**0.357**	**0.741**	**0.744**	**0.387**	**0.372**	-0.037	-0.218	**-0.501**	**-0.535**	**0.707**	**-0.948**	**1**

Bold values are different from 0 at a level significant for $p < 0.05$; At a very significant for $p < 0.01$
At a highly significant to $p < 0.001$

Correlation circle

Principal component analysis (PCA) was also performed to detect the connection between the different variables.

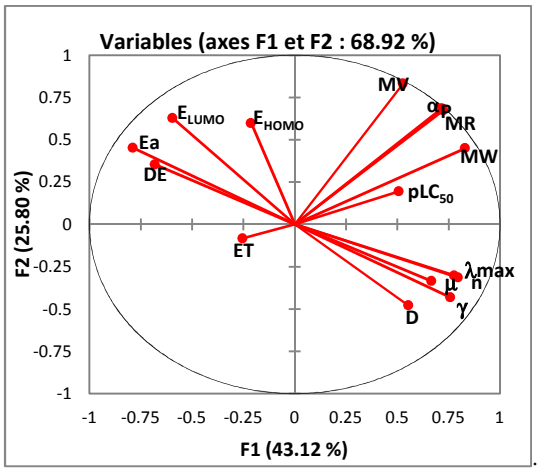

Figure 1: Correlation circle

Multiple linear regressions

To establish quantitative relationships between toxicity pLC_{50} and selected descriptors, our array data were subjected to a multiple regression linear and were nonlinear. Only variables whose coefficients are significant were retained.

Multiple linear regression of the variable toxicity (MLR)

Many attempts have been made to develop a relationship with the indicator variable of toxicity pLC_{50}, but the best relationship obtained by this method is only one corresponding to the linear combination of several descriptors selected: Molar Refractivity (MR), Molar Volume (MV)**,** Refractive Index (n), Surface Tension (γ),Polarizability (α), energy E_{HOMO}, energy E_{LUMO},dipole moment (μ), activation energy (E_a), and absorption maximum (λ_{max}).

The resulting equation is:

$$\mathbf{pLC_{50}} = -83.845 + 0.120\times\mathbf{MR} + 0.187\times\mathbf{MV} + 43.479\times\mathbf{n} - 6.824\ 10^{-02}\times\boldsymbol{\gamma} - 1.579\times\boldsymbol{\alpha} - 0.516\times\mathbf{E_{HOMO}} - 0.614\times\mathbf{E_{LUMO}} + 0.270\times\boldsymbol{\mu} + 2.208\times\mathbf{Ea} + 1.764\ 10^{-02}\times\boldsymbol{\lambda_{max}} \quad \text{(Equation 1)}$$

For our 31 compounds, the correlation between experimental toxicity and calculated one based on this model is quite significant (Figure 2) as indicated by statistical values:

N = 31 **R = 0.937** **R^2 = 0.879** **RMSE = 0.305**

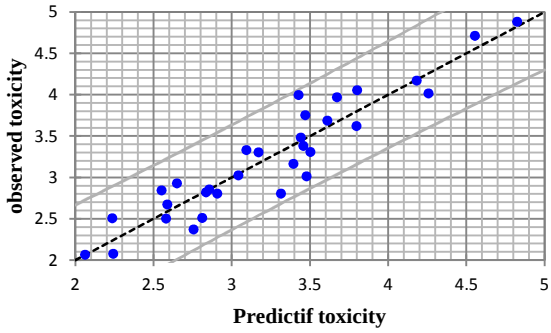

Figure 2: Graphical representation of calculated and observed toxicity by MLR.

The figure 2 shows a very regular distribution of toxicity values depending on the experimental values.

Multiple nonlinear regression of the variable toxicity (MNLR)

We have also used the technique of nonlinear regression model to improve the structure toxicity in a quantitative way, taking into account several parameters. This is the most common tool for the study of multidimensional data. We have applied it to Table 2 containing 31 molecules associated with fifteen variables.

The resulting equation is:

$\mathbf{pLC_{50}}$ = -6120.617-2.693×**MW**+31.461×**MR** - 6.417×**MV**+3.391×**Pc**+3617.980×**n** - 5.450×**γ**+ 255.840×**D**-73.418×**α**+5.645 10^{-04}×$\mathbf{E_T}$+ 14.777×$\mathbf{E_{HOMO}}$-8.314×$\mathbf{E_{LUMO}}$-0.179×**μ** +565.393×$\mathbf{E_a}$ + 6.520×$\boldsymbol{\lambda_{max}}$+4.780 10^{-03}×$\mathbf{MW^2}$ - 0.571×$\mathbf{MR^2}$+1.451 10^{-02}×$\mathbf{MV^2}$ -2.967 10^{-03}×$\mathbf{Pc^2}$ - 1159.813×$\mathbf{n^2}$ + 2.644 10^{-02}×$\boldsymbol{\gamma^2}$ - 33.243×$\mathbf{D^2}$+3.593×$\boldsymbol{\alpha^2}$+3.775 10^{-09}×$\mathbf{E_T^2}$ + 0.548×$\mathbf{E_{HOMO}^2}$ - 0.379×$\mathbf{E_{LUMO}^2}$+0.686×$\mathbf{\Delta E^2}$+4.954 10^{-02}×$\boldsymbol{\mu^2}$- 35.131×$\mathbf{E_a^2}$-4.497 10^{-03}×$\boldsymbol{\lambda^2_{max}}$(Equation 2)

The obtained parameters describing the topological and the electronic aspects of the studied molecules are:

N = 31 R = 0.998 R^2 = 0.996

The toxicity value pLC_{50} predicted by this model is somewhat similar to that observed. The figure3 shows a very regular distribution of toxicity values based on the observed values.

With MLNR was obtained significantly better correlation coefficient R = 0. 998.

As part of this conclusion, we can say that the toxicity values obtained from nonlinear regression are highly correlated to that of the observed toxicity comparing to results obtained by MLR method.

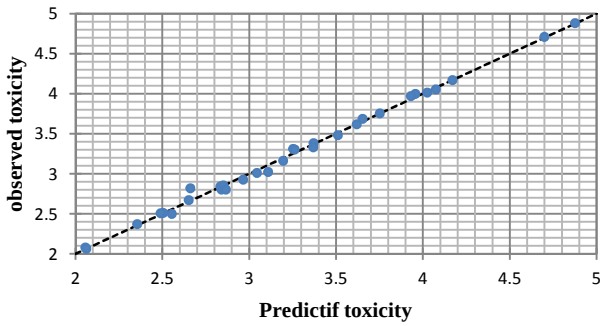

Figure 3: Graphical representation of calculated and observed toxicity by MNLR.

Artificial neural networks ANN

Neural networks (ANN) can be used to generate predictive models of quantitative structure–activity relationships (QSAR) between a set of molecular descriptors obtained from the MLR and observed activity. The ANN calculated toxicity model was developed using the properties of several studied compounds. The correlation between ANN calculated and experimental toxicity values are very significant as illustrated in figure 4 and as indicated by R and R^2 values.

N = 31 R = 0.956 R^2 = 0.915 RMSE = 0.038

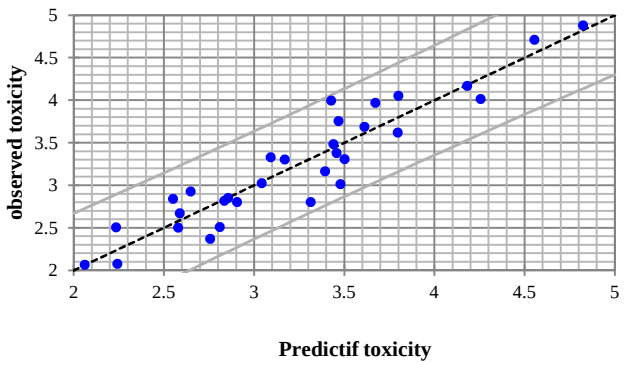

Figure 4: Correlations of observed and predicted activities calculated using ANN

The statistic of the three steps of the calculation by the ANNs: training, validation and test are illustrated in table 4.

Table 4: Values obtained by ANNs

	Samples	RMSE	R	R^2
Training	21	0.038	0.957	0.914
Validation	5	0.210	0.955253	0.938
Test	5	0.106	0.976	0.977

R: correlation coefficient; R^2: determination coefficient; RMSE: root mean square error.

DISCUSSION

Principal component analysis

* The Polarizability (α) is strongly correlated with the Parachor (Pc) for r=0.996 and p <0.05 at a significant level.
* The Energy of activation (E_a) is highly negatively correlated with the maximum of absorption (λ_{max})for r= -0.948 and p < 0.05 at a significant level.

Table 5: Observed values and calculated values of pLC_{50} according to different methods

N°	pLC_{50} (obs.)	pLC_{50} (calc.)		
		MLR	NMLR	ANN
1	3,686	3,613	3,653	3,668
2	3,482	3,442	3,512	3,519
3	4,052	3,802	4,076	3,991
4	4,880	4,825	4,876	4,313
5	3,380	3,459	3,371	2,779
6	3,024	3,044	3,110	3,241
7	3,308	3,503	3,254	3,197
8	3,996	3,428	3,957	3,763
9	3,619	3,799	3,620	3,622
10	3,753	3,470	3,754	3,583
11	3,012	3,480	3,045	2,939
12	2,670	2,589	2,654	2,352
13	2,371	2,757	2,357	2,980
14	2,500	2,580	2,556	2,625
15	2,928	2,650	2,966	2,911
16	2,819	2,836	2,662	2,904
17	3,331	3,094	3,369	3,151
18	3,968	3,674	3,931	3,279
19	2,804	3,315	2,842	3,012
20	2,841	2,552	2,835	2,950
21	3,303	3,171	3,264	3,146
22	3,163	3,396	3,197	3,158
23	4,710	4,555	4,699	4,561
24	2,853	2,857	2,853	2,971
25	4,014	4,258	4,026	4,148
26	2,077	2,244	2,057	2,281
27	2,064	2,063	2,064	1,998
28	2,509	2,812	2,507	2,630
29	2,505	2,237	2,490	2,293
30	4,170	4,183	4,172	4,030
31	2,804	2,908	2,866	2,596

Correlation circle

The principal component analysis revealed from the correlation circle (Figure 1) shows that the F1 axis (43.12% of the variance) is clearly connected to the molecular weight (MW), while the axis F2 (25.80% of the variance) is located by the other parameters of topologic and energetic.

Statistical analysis

The obtained squared correlation coefficient (R^2) value is 0.914 for this data set of substituted phenols. It confirms that the multiple nonlinear regression (MNLR)results were the best to build the quantitative structure activity relationship models.

In this part, we investigated the best linear QSAR regression equations established in this study. Based on this result, a comparison of the quality of the CPA, MLR and ANN models shows that the MNLR models have substantially better predictive capability because the MNLR approach gives better results than MLR and ANN. MNLR was able to establish a satisfactory relationship between the molecular descriptors and the activity of the studied compounds. Comparison of key statistical terms like R or R^2 of different models obtained by using different statistical tools and different descriptors has been shown in table 5.

CONCLUSION

In this work we have investigated the QSAR regression to predict the toxicity of substituted phenols.

The study of the quality of the MLR, MNLR and ANN models show that the MNLR result has substantially better predictive capability than the other methods. With MNLR approach, we have established a relationship between several descriptors and inhibition values pLC_{50} of several organic compounds based on substituted phenols in satisfactory manners.

Finally, we can conclude that studied descriptors, which are sufficiently rich in chemical, electronic and topological information to encode the structural feature may be used with other descriptors for the development of predictive QSAR models.

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