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QSAR models to predict physico-chemical properties of some barbiturate derivatives using molecular descriptors and genetic algorithm- multiple linear regressions

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Abstract

In this study, the relationship between choosing appropriate descriptors by genetic algorithm to the Polarizability (POL), Molar Refractivity (MR) and Octanol/water Partition Coefficient (LogP) of barbiturates is studied. The chemical structures of the molecules were optimized using ab initio 6-31G basis set method and Polak-Ribiere algorithm with conjugated gradient within HyperChem 8.0 environment. Three structural parameters were calculated using a quantum-mechanical method and Polak-Ribiere geometric optimization followed by ab initio 6-31G method. The multiple linear regressions (MLR) and Backward methods (with significant at the 0.05 level) were employed to give the QSAR models. After MLR analysis, we studied the validation of linearity between the molecular descriptors in the made models for the used properties. The predictive powers of the models were discussed using the method of cross-validation. The results have shown that molecular descriptors (MPC08, SIC2, TIC0), (ZM1V, IC2, GNar, UNIP, X3) and (S1K, Mi, SMTIV) could be used for modeling and predicting the MR, LogP and POL of the corresponding barbiturates, respectively.

Keywords: Barbiturates; structure-activity relationship; polarizability; molar refractivity; octanol/waterpartition coefficient; multiple linear regressions (MLR).

Introduction

Barbiturates are a category of compounds that are focal nervous system depressants. Barbiturate overdose leads to weakness of the central nervous system, respiratory and cardiovascular depression and eventually death [1-4]. Barbituric acid derivatives act as central nervous depression and in medicine as a sedative, hypnotic and anticonvulsant drugs with hypnotic or sedative properties depending on the dose administered [5]. The physical and chemical properties of a compound are a function of its molecular structure. Quantitative structure- property relationship (QSPR) empirically define relationship between molecular structure and observed properties, and quantitative structure-activity relationship (QSAR) study define relationship between molecular structure and observed activity. QSAR

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models have been developed to determine the penetration coefficients of barbiturates in biological membranes [6]. QSAR has been known as a quantum chemical technique in connection to the biological activity of compounds by their molecular structure and has been used as a predictive tool in drug design [7]. Activity in biological and pharmaceutical organosulfur molecules and barbiturates has been investigated [8-10]. QSAR models to predict octanol-water partition coefficients (LogP) and vapor pressures of some organic compounds and environmental toxicity of petroleum substances based on neural net interpretation of descriptors derived from quantum mechanical calculations have been researched. The models are cross-validated by dividing the compound set into several equal portions. The results are combined to give a mean predicted property value [11,12]. QSPR studies on the estimation of solubility of 45 barbiturates by using molecular descriptors have been developed [13]. 3D QSAR technique has been used to predict biological properties (toxicity) of chemicals [14-17]. Calculation of the volume distribution of certain pharmaceutical compounds from their structural descriptors has been considered [18]. QSAR studies on the benzylidenebarbiturate derivatives inhibiting the activity of the mushroom tyrosinase have been examined [19]. QSAR technique has been studied in Diarylaniline Analogues as in Vitro Anti-HIV-1 Agents in Pharmaceutical Interest [20].The aim of this study is to provide reliable QSAR models for predicting the polarizability (POL), molar refractivity (MR) and octanol/water partition coefficient (LogP) of barbiturates.

Materials and mathematical methods

The barbiturates discussed in this study consist of 42 derivatives with substitution at 3, 5, and 5 positions. Figure 1 shows the template structure of barbiturates used in the present study. The studied barbiturates and their Polarizability (POL), Molar Refractivity (MR) and Octanol/water Partition Coefficient (LogP) are listed in Table 1.

The polarizability, molar refractivity and octanol/water partition coefficient of barbiturates are taken from the quantum mechanics methodology with ab initio 6-31G basis sets method and Polak- Ribiere algorithm with APHS.

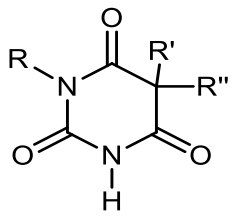

Figure 1. The structural template of barbiturates

Table 1. Barbiturates and their polarizability, molar refractivity and octanol/water partition coefficient

No.	Compounds	POL	LogP	MR
1	Barbituric acid	11.1	-1.6	23.23
2	1,3-Dimethylpyrimidine-2,4,6-trione	14.22	-1.4	34.52
3	5,5-Dimethylpyrimidine-2,4,6-trione	14.77	-0.37	32.31
4	5-Ethyl-5-methylpyrimidine-2,4,6-trione	16.6	-0.03	36.91
5	5-Ethyl-1-methylpyrimidine-2,4,6-trione	16.6	-0.37	38.18
6	5-Ethyl-5-isopentylpyrimidine-2,4,6-trione	23.14	1.86	58
7	5-Sec-butyl-5-ethyl-1-methylpyrimidine-2,4,6-trione	23.94	1.42	56.43
8	5-Ethyl-5-(pentan-2-yl)pyrimidine-2,4,6-trione	23.94	1.55	55.26
9	5-Sec-butyl-5-ethylpyrimidine-2,4,6-trione	22.11	1.19	52.4
10	5-(Hexan-2-yl)pyrimidine-2,4,6-trione	22.11	0.88	50.76
11	5-Ethyl-5-(Hexan-2-yl)-1,3-dimethylpyrimidine-2,4,6-trione	29.45	2.44	69.65
12	5-Allyl-5-(pentan-2-yl)pyrimidine-2,4,6-trione	25.58	1.73	59.9
13	5-Sec-butyl-5-allylpyrimidine-2,4,6-trione	21.91	0.94	50.7
14	5-Cyclohexenyl-1,5-dimethylpyrimidine-2,4,6-trione	24.01	1.17	61.95
15	5-Ethyl-5-phenylpyrimidine-2,4,6-trione	24.43	1.25	57
16	5-Ethyl-1-methyl-5-phenylpyrimidine-2,4,6-trione	26.26	1.51	62.77
17	5-Ethyl-1,3-dimethyl-5-phenylpyrimidine-2,4,6-trione	27.55	1.74	66.8
18	5-Methylbarbiturate	12.14	-0.72	30.55
19	5-Ethyl-barbiturate	13.42	-0.57	34.83
20	Isopropylbarbiturate	16.6	-0.59	37.29
21	5,5-Diethylbarbiturate	18.44	0.43	41.51
22	5-Methyl-5-allylbarbiturate	18.24	0.21	41.55
23	5-Ethyl-5-propylbarbiturate	20.27	0.82	46.11
24	5,5-Dipropylbarbiturate	22.11	1.24	51.58
25	5,5-Di-i-propylbarbiturate	22.11	1.09	50.61
26	5-Ethyl-5-allylbarbiturate	20.08	0.61	46.15
27	5-Methyl-5-(3-methylbut-2-enyl) barbiturate	21.91	0.71	51.51
28	5-Ethyl-5-(3-methylbut-2-enyl) barbiturate	23.2	0.81	57.61
29	5-Ethyl-5-heptylbarbiturate	27.61	2.41	64.51
30	5-Ethyl-5-pentylbarbiturate	23.4	1.32	56.81
31	Hexethal	25.23	1.71	61.41
32	5-i-Propyl-5-(3-methylbut-2-enyl) barbiturate	25.04	1.15	62.15
33	5-t-Butyl-5-(3-methylbut-2-enyl) barbiturate	26.87	1.58	66.63
34	5-Ethyl-5-octylbarbiturate	28.9	2.51	70.61
35	5-Ethyl-5-nonylbarbiturate	30.74	2.9	75.21
36	Cyclopropane-spirobarbiturate	13.45	-1.17	32
37	Cyclobutane-spirobarbiturate	15.28	-0.77	36.6
38	Cyclopentane-spirobarbiturate	17.12	-0.38	41.2
39	Cyclohexane-spirobarbiturate	18.95	0.02	45.8
40	Cycloheptane-spirobarbiturate	20.79	0.42	50.4
41	5-Allyl-5-phenylbarbiturate	25.52	0.37	67.28
42	5,5-Diphenylbarbiturate	29.87	0.24	82.27

Molecular descriptors

HyperChem (Version 8.0) was used to draw the molecular structures. Ab initio 6-31G basis sets were applied to optimize the structures. Calculation of molecular descriptors for each compound of data set has been followed using the Dragon 5.5

software. Totally, 1065 different molecular descriptors were calculated for each compound. In order to decrease the redundancy existing in the descriptors data matrix, the correlations of descriptors with each other and with Polarizability (POL), Molar Refractivity (MR) and Octanol/water Partition Coefficient (LogP) of the molecules are examined, and collinear descriptors (R > 0.9) are detected. Those of the descriptors which have the pair wise correlation coefficient above 0.9 and having the lower correlation with Polarizability (POL), Molar Refractivity (MR) and Octanol/water Partition Coefficient (LogP) values are removed from the data matrix. They were excluded in the pre-reduction step and 81 descriptors were left for variable selection.

Genetic algorithm

Choosing best descriptors molecular forQSAR studies is difficult, because there are no absolute rules that govern this choice. In this study, genetic algorithm- multiple linear regressions (MLR) were employed to give the QSAR model.The genetic algorithmprogram is implemented in Matlab (R2010 a) software [21]. The list of choosing best descriptors by genetic algorithm-based multiple linear regression forphysico-chemical parameters of some barbiturate derivatives are presented in Table 2.

Table 2. List of choosing best descriptors by genetic algorithm- multiple linear regression

Abbreviation	Description	Block
ZM1V	first Zagreb index by valence vertex degrees	Topological indices
IC2	Information Content index (neighborhood symmetry of 2 order)	Information indices
GNar	Narumi geometric topological index	Topological indices
UNIP	unipolarity	Topological indices
X3	connectivity index of order 3	Connectivity indices
MPC08	molecular path count of order 8	Walk and path counts
SIC2	Structural Information Content index (neighborhood symmetry of 2 order)	Information indices
TIC0	Total Information Content index (neighborhood symmetry of 0-order)	Information indices
S1K	1-path Kier alpha-modified shape index	Topological indices
Ms	mean first ionization potential (scaled on Carbon atom)	Constitutional indices
SMTIV	Schultz Molecular Topological Index by valence vertex degrees	Topological indices

Regression analyses

In the present work, linear regression analyses were performed using SPSS-16 (SPSS Inc., Chicago, IL, USA)). The Polarizability (POL), Molar Refractivity (MR) and Octanol/water Partition Coefficient (LogP) were used as dependent variables and ZM1V, IC2, GNar, UNIP, X3, MPC08, SIC2, TIC0, S1K, Ms, AECC, CENT, CSI, Ss, PCR, PCD, BIC1, X1v, SCBO, X5Av, IAC and SNar descriptors as independent

variables. Criteria for selection of the best multiple linear regression model were the statistics: squared multiple correlation coefficient ($\boldsymbol{R^2}$), adjusted correlation coefficient ($\boldsymbol{R^2_{adj}}$), Fisher ratio (F), root mean square error (RMSE), Durbin-Watson value (DW) and significance (Sig).

Results

Several linear QSAR models involving three- Twenty-four descriptors were established and the strongest multivariable correlations were identified by the backward stepwise regression routine implemented in SPSS used to develop the linear model for the prediction of polarizability, molar refractivity and octanol/water partition coefficient.

QSAR models for molar refractivity (MR)

The best linear model for molar refractivity contains five descriptors, namely, CENT, MPC08, SIC2, TIC0and AECC descriptors. The model is presented below:

Model 1

MR= 4.437+ 0.050 (CENT) + 0.171 (MPC08) + 9.509 (SIC2) + 0.667 (TIC0) -1.118 (AECC) (1)

N=42 R=0.996 R^2=0.993 R^2_{adj} = 0.991 RMSE=38.70 F= 955.742 Sig=0.000 DW=1.860

QSAR models for the polarizability (POL)

The best linear model for polarizability contains seven descriptors, namely, S1K, Mi, CSI, Ss, SMTIV, TIC0 and AECC indices.

The regression parameters of the best four descriptors correlation model are gathered in equation (2):

Model 2

POL= 25.409 +1.807(S1K) -7.074(Mi) +0.057(CSI)+0.392(Ss)- 0.001(SMTIV) -0.354(TIC0) - 1.732(AECC) (2)

N=42 R=0.998 R^2= 0.997R^2_{adj} = 0.996 RMSE= 12.248 F=1440 Sig= 0.000 DW= 1.921

QSAR models for octanol/water partition coefficient (LogP)

The best linear model for the octanol/water partition coefficient contains fifteen descriptors, namely, ZM1V, PCR, PCD, BIC1, X1v, Mi, IC2, SIC0, X3, SCBO, GNar, X5Av, IAC, UNIP and SNar descriptors. The model is presented below:

Model 3

LogP= 71.570-0.061(ZM1V)-31.478(PCR)+ 0.642(PCD) +13.232(BIC1) + 3.580(X1v) -7.269 (Mi) - 0.864(IC2) + 19.969(SIC0)+ 0.307(X3) + 0.649(SCBO) - 11.728(GNar) + 53.294(X5Av) - 0.294(IAC) -0.030(UNIP)-1.346(SNar) (3)

N=42 R=0.996 R^2= 0.991 R^2_{adj} = 0.987 RMSE= 1.798 F= 200.793 Sig=0.000 DW=2.641

These models produced a squared correlation coefficient close to 1, and the results of other statistical parameters are also very satisfactory.

Discussion

We studied the relationship between the molecular descriptors and the polarizability, molar refractivity and octanol/water partition coefficient of 42 barbiturates. In this study, to find the best model to predict the parameters mentioned, we will use the following sections.

Multicollinearity

Multicollinearity test is a basis of the variance inflation factor (VIF) value of multicollinearity test results using SPSS. If the VIF value lies between 1 and 10, then there is no multicollinearity; if the VIF<1 or >10, then there is multicollinearity. In all our final models there is multicollinearity, because the values of the correlations

between independent variables are close to 1 and the VIF value does not lie between 1 and 10.

We studied the linearity between the molecular descriptors in the models 1, 2 and 3. We obtained by SPSS the Pearson coefficient correlation and collinearity statistics as follows (see Tables 3, 4 and 5). For model 1 the Pearson correlations (CENT, MPC08) are near 1, and VIF (CENT) >10, therefore there is linearity between these descriptors. After removing CENT from this model, we corrected model 1 as follows:

MR= 12.990 +0.365(MPC08) +10.726(SIC2) +1.087(TIC0) (4)

N=42 R= 0.990 R^2= 0.980 R^2_{adj} =0.979 RMSE= 49.64 F= 625.455 Sig=0.000 DW= 1.350Q^2= 0. 883

Similarly to model 1 we obtained the corrected models 2 and 3 as follows:

POL= 19.562 + 0.888(S1K) - 4.274(Mi) + 0.001(SMTIV) (5)

N=42 R= 0.992 R^2=0.984 R^2_{adj} = 0.982 RMSE=18.821 F=766.419 Sig=0.000 DW=1.063 Q^2= 0. 896

LogP = 4.151 - 0.024(ZM1V) + 0.421 (IC2) - 2.784 (GNar) + 0.069(UNIP) + 0.700(X3) (6)

N=42 R= 0.946 R^2=0.894 R^2_{adj} = 0.880 RMSE = 2.959 F=60.980 Sig=0.000 DW= 2.013 Q^2=0.844

Table 3. Correlation between the molecular descriptors (model 1) for molar refractivity (MR)

Pearson correlations (model 1)						**Collinearity statistical**		**Corrected model**
	SIC2	AECC	MPC08	CENT	TIC0	Tolerance	VIF	VIF
SIC2	1.000					0.767	1.304	1.243
AECC	0.213	1.000				0.158	6.313	-
MPC08	0.114	0.476	1.000			0.204	4.895	1.378
CENT	-0.089	-0.537	-0.847	1.000		0.041	24.356	-
TIC0	0.094	-0.065	0.520	-0.741	1.000	0.095	10.574	1.575

Table 4. Correlation between the molecular descriptors (model 2) for the polarizability (POL)

Pearson correlations (model 2)						**Collinearity statistical**	**Corrected model**
	SMTIV	Mi	Ss	S1K	Tolerance	VIF	VIF
SMTIV	1.000				0.095	10.525	4.241
Mi	0.121	1.000			0.158	6.340	6.331
Ss	-0.773	0.037	1.000		0.087	11.526	-
S1K	-0.079	0.651	-0.258	1.000	0.124	8.063	7.527

Table 5. Correlation between the molecular descriptors (model 3) for theoctanol/water partition coefficien(LogP)

Pearson correlations (model 3)									**Collinearity Statistical**		**Corrected model**
	X3	IC2	PCR	GNar	UNIP	BIC1	ZM1V	X1v	Tolerance	VIF	VIF
X3	1.000								0.069	14.399	6.509
IC2	-0.030	1.000							0.208	4.806	1.541
PCR	0.192	0.016	1.000						0.089	11.188	-
GNar	-0.052	0.587	-0.072	1.000					0.463	2.162	1.809
UNIP	0.350	0.287	-0.344	0.181	1.000				0.067	14.833	2.522
BIC1	0.026	-0.797	-0.264	-0.364	-.145	1.000			0.089	11.239	-
ZM1V	-0.617	-0.019	-0.798	-0.088	0.053	0.077	1.000		0.040	24.716	6.247
X1v	-0.378	-0.539	0.362	-0.248	-0.839	0.500	-0.163	1.000	0.025	40.420	-

Validation

The success of any QSAR model depends on the accuracy of the input data, selection of appropriate descriptors, statistical tools and validation of the developed model. In this section, for verification and validity of the regression models, we will focus on the Durbin-Watson statistics and unstandardized predicted and residual values. The Durbin-Watson statistics ranges in value from 0 to 4. A value near 2 indicates non-autocorrelation. In all our models, the value of Durbin-Watson statistics is close to 2 (see eqs.1, 2 and 3) and hence the errors are uncorrelated.

Also for the predictive power of the model, squared cross- validation coefficient for leave –one- out (Q^2LOO) was used. The Q^2LOO value (Eq. 7) computed from 50 % of randomly chosen data was found to be positive and smaller than one.

$$\mathbf{Q^2 = 1 - \frac{\sum(Y_i - \hat{Y}_{i|i})^2}{\sum(Y_i - \bar{Y})^2} Q^2 \leq 1} \qquad (7)$$

In the equation (7), the notation i|i indicates that the quantity is predicted by a model estimated when the i-th sample was left out from the training set.

The Q^2_{LOO} values of the LogP,POL and MR calculated 0.844, 0.896 and 0.883 respectively.

Regular residuals

The residual is the difference between the observed and predicted values. Comparison between predicted and observed values of polarizability, molar refractivity and octanol/water partition coefficient of the barbiturates is shown in Table 6. Figures 2-4 show the linear correlation between the observed and the predicted polarizability, molar refractivity and octanol/water partition coefficient of barbiturates values obtained using equations (4-6), respectively.

Table 6. Comparison between predicted and observed values of models calculated validation of POL, MR and LogP of the corresponding barbiturates

No.	**Observed POL**	**Predicted POL**	**Residual**	**Observed MR**	**Predicted MR**	**Residual**	**Observed LogP**	**Predicted LogP**	**Residual**
1	11.1	10.94	0.16	23.23	23.06	0.18	-1.6	-1.55	-0.05
2	14.22	14.85	-0.63	34.52	31.78	2.74	-1.4	-0.35	-1.06
3	14.77	14.54	0.23	32.31	31.78	0.53	-0.37	-0.32	-0.05
4	16.6	16.41	0.19	36.91	37.50	-0.59	-0.03	0.16	-0.19
5	16.6	16.61	-0.01	38.18	38.81	-0.63	-0.37	0.31	-0.68

6	23.14	23.68	-0.54	58.00	57.21	0.79	1.86	1.20	0.66
7	23.94	23.28	0.66	56.43	55.92	0.51	1.42	1.74	-0.32
8	23.94	23.49	0.45	55.26	56.48	-1.22	1.55	1.25	0.30
9	22.11	22.85	-0.74	52.40	53.98	-1.58	1.19	0.83	0.36
10	22.11	22.27	-0.16	50.76	53.30	-2.54	0.88	0.83	0.05
11	29.45	28.74	0.71	69.65	69.44	0.21	2.44	2.84	-0.40
12	25.58	24.89	0.69	59.90	60.16	-0.26	1.73	1.45	0.29
13	21.91	21.18	0.73	50.70	50.15	0.55	0.94	0.71	0.23
14	24.01	23.96	0.05	61.95	64.78	-2.83	1.17	1.70	-0.53
15	24.43	23.42	1.01	57.00	59.16	-2.16	1.25	0.58	0.67
16	26.26	25.12	1.14	62.77	65.08	-2.31	1.51	1.33	0.19
17	27.55	26.85	0.70	66.80	69.71	-2.91	1.74	1.78	-0.04
18	12.14	12.84	-0.70	30.55	28.34	2.21	-0.72	-0.69	-0.03
19	13.42	14.79	-1.37	34.83	33.94	0.89	-0.57	-0.49	-0.08
20	16.6	16.65	-0.05	37.29	38.67	-1.38	-0.59	-0.41	-0.18
21	18.44	18.23	0.21	41.51	41.91	-0.40	0.43	0.31	0.12
22	18.24	17.76	0.48	41.55	41.01	0.54	0.21	0.26	-0.05
23	20.27	20.06	0.21	46.11	46.67	-0.56	0.82	0.47	0.35
24	22.11	21.85	0.26	51.58	50.83	0.75	1.24	0.53	0.71
25	22.11	21.47	0.64	50.61	50.17	0.44	1.09	0.58	0.51
26	20.08	19.52	0.56	46.15	46.00	0.15	0.61	0.54	0.07
27	21.91	21.70	0.21	51.51	51.39	0.12	0.71	0.80	-0.09
28	23.2	23.41	-0.21	57.61	56.18	1.43	0.81	1.09	-0.28
29	27.61	28.06	-0.45	64.51	65.77	-1.26	2.41	2.12	0.29
30	23.4	23.92	-0.52	56.81	56.07	0.75	1.32	1.18	0.14
31	25.23	25.94	-0.71	61.41	61.31	0.10	1.71	1.62	0.09
32	25.04	25.04	0.00	62.15	60.32	1.83	1.15	1.27	-0.12
33	26.87	26.64	0.23	66.63	64.20	2.43	1.58	1.37	0.21
34	28.9	30.31	-1.41	70.61	69.48	1.13	2.51	2.70	-0.19
35	30.74	32.67	-1.93	75.21	73.15	2.06	2.9	3.35	-0.45
36	13.45	13.80	-0.35	32.00	30.88	1.12	-1.17	-1.06	-0.11
37	15.28	15.61	-0.33	36.60	36.65	-0.05	-0.77	-0.53	-0.25
38	17.12	17.35	-0.23	41.20	43.41	-2.21	-0.38	-0.35	-0.03
39	18.95	19.12	-0.17	45.80	48.54	-2.74	0.02	-0.11	0.13
40	20.79	20.88	-0.09	50.40	55.05	-4.65	0.42	0.13	0.29
41	25.52	24.92	0.60	67.28	62.28	5.00	0.37	0.61	-0.24
42	29.87	29.37	0.50	82.27	78.45	3.82	0.24	0.50	-0.26

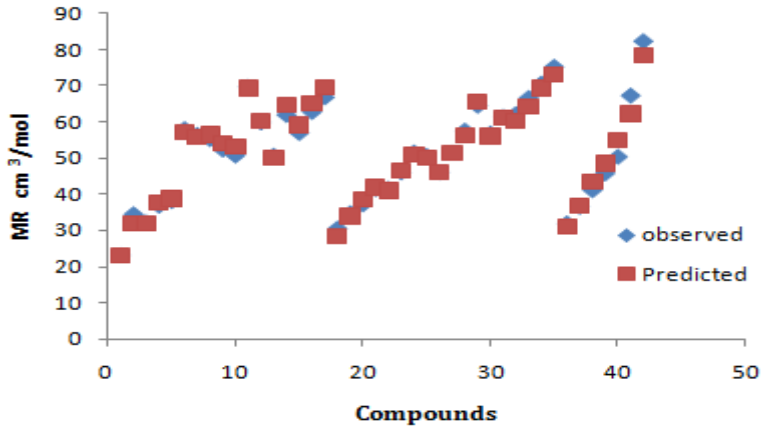

Figure 2. Comparison between observed and predicted values of molar refractivity calculated by the MLR method

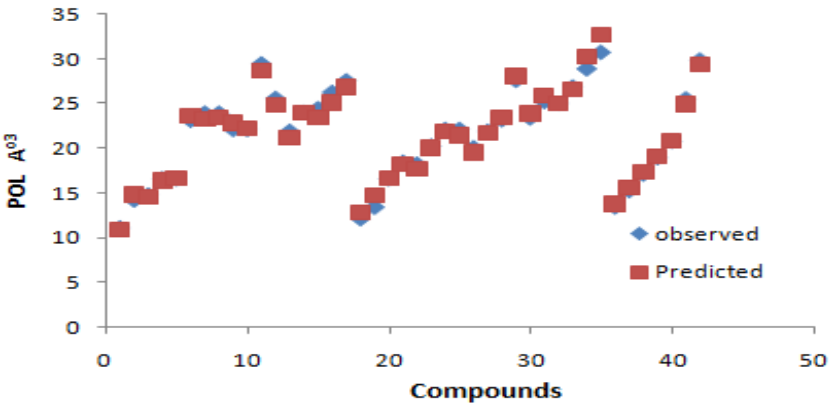

Figure 3. Comparison between observed and predicted values of polarizability calculated by the MLR method

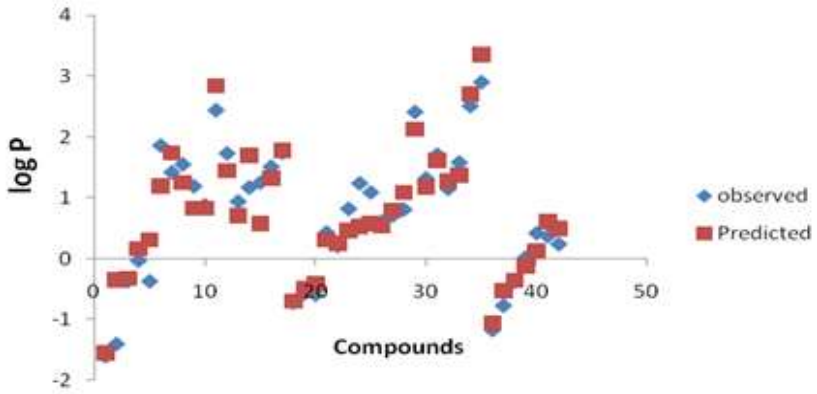

Figure 4. Comparison between predicted and observed values of LogP calculated by the MLR method

Conclusion

In this study, multiple linear regressions as a simple and very fast technique were applied to build a quantitative relation between the molecular structures and polarizability (POL), molar refractivity (MR) and octanol/water partition coefficient (Log P) of barbiturate derivatives. Stepwise and genetic algorithm, were used as powerful methods to select the best descriptors.

QSAR models for prediction of the polarizability (POL), molar refractivity (MR) and octanol/water partition coefficient (Log P) for a training set of barbiturates using MLR based on topological descriptors calculated from molecular structure were developed. The MLR model proved to be a useful tool in the prediction of POL, MR and LogP. Cross-validation as the evaluation technique was designed to evaluate the quality and predictive ability of the MLR model. The obtained results showed that MPC08, SIC2, and TIC0 descriptors could be used successfully for predicting molar refractivity. The polarizability of barbiturates can be better modeled using a combination of the S1K, Mi, and SMTIV descriptors. ZM1V, IC2, GNar, UNIP, and X3descriptorscould beused for modeling and predicting the Log P of respect compounds. These descriptors are classified in topological, constitutional, walk and path counts, information, and connectivity indices.

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