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QSAR study for the prediction of physico-chemical parameter of category barbiturate compounds by using descriptors structure

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Topological indices as molecule indices are used in quantitative studies of structure- properties. In this study the relationship between the S1K, X0, X0sol, MW, Se, Ms, BAC , BIC2, Xindex, X3A , CSI, S3K, SRW04, IDDE, nSK ,Ss , SMTIV ,GNar , TIC0, X5v , AECC and UNIP calculated by Dragon to the Polarizability (POL) of 32 barbiturates is represented. The chemical structures of the molecules were optimized using ab initio 6-31G basis sets method and Polak-Ribiere algorithm with conjugated gradient within HyperChem 8.0 environment. The multiple linear regressions (MLR) and Back ward 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 best models for used properties. The predictive powers of the models were discussed by using the method of cross-validation. The results have shown that descriptors (S3K, SRW04, and GNar) could be efficiently used for estimating the polarizability of respect compounds.

Key words: Basis sets method, Polak-Ribiere algorithm, Molecular descriptors, QSAR model, MLR analysis

INTRODUCTION

Barbiturates are a group of compounds that are focal nervous system depressants. Barbiturates overdose leads to weakness of the central nervous system, recessional and cardiovascular depression and finally death [1-4]. The first report of Quantitative Structure–Activity Relationship (QSAR) was reported by Crum-Brown and Fraser that studied the relationship between chemical structure and physiological activity [5]. QSAR has been known as a quantum chemical method in connection with the biological activity of compounds of their molecular structure and has been used as a predictive tool in drug design [6]. The medicinal importance of pyrimidine derivatives such as barbituric acid and thiobarbituric acid plays an essential role across different heterocyclic compounds due to theirantineoplastic[7,8], antiviral [9], the antibiotic [10].

and anti-inflammatory [11] activity. Toxicity of the addictive drugs (barbiturates and thiobarbiturates) by using physical and chemical describers have been proposed [12-15].

QSAR studies on the estimation validation approach of chemical mixture shave been investigated [16]. QSAR studies have been examined using 3D parameters in predicting the biological properties especially molecular toxicity [17-21]. Derivations of barbiturates based on nuclides in a watery environment as a potential anti-cancer agent has been designed [22, 23].

MATERIALS, MATHEMATICAL METHOD,AND GRAPHS

The Polarizability of barbiturates is taken from the quantum mechanics methodology with ab initio 6-31G basis sets method and Polak-Ribiere algorithm with conjugated gradient within HyperChem 8.0 environment. A set of thirty-two essential barbiturates was investigated. Studied barbiturates and their Polarizability are listed in Table 1.

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Table 1. Barbiturates and their polarizability in the present study.

Compounds	No.	POL	Compounds	No.	POL
Barbituric acid	1	11.1	5-Ethyl-1,3-dimethyl-5-phenylpyrimidine-2,4,6-trione	17	27.55
1,3-Dimethylpyrimidine-2,4,6-trione	2	14.22	5-Methylbarbiturate	18	12.14
5,5-Dimethylpyrimidine-2,4,6-trione	3	14.77	5-Ethyl-barbiturate	19	13.42
5-Ethyl-5-methylpyrimidine-2,4,6-trione	4	16.6	Isopropylbarbiturate	20	16.6
5-Ethyl-1-methylpyrimidine-2,4,6-trione	5	16.6	5,5-Diethylbarbiturate	21	18.44
5-Ethyl-5-isopentylpyrimidine-2,4,6-trione	6	23.14	5-Methyl-5-allylbarbiturate	22	18.24
5-Sec-butyl-5-ethyl-1-methylpyrimidine-2,4,6-trione	7	23.94	5-Ethyl-5-propylbarbiturate	23	20.27
5-Ethyl-5-(pentan-2-yl)pyrimidine-2,4,6-trione	8	23.94	5,5-Dipropylbarbiturate	24	22.11
5-Sec-butyl-5-ethylpyrimidine-2,4,6-trione	9	22.11	5,5-Di-i-propylbarbiturate	25	22.11
5-(Hexan-2-yl)pyrimidine-2,4,6-trione	10	22.11	5-Ethyl-5-allylbarbiturate	26	20.08
5-Ethyl-5-(Hexan-2-yl)-1,3-dimethylpyrimidine-2,4,6-trione 11	11	29.45	5-Methyl-5-(3-methylbut-2-enyl) barbiturate	27	21.91
5-Allyl-5-(pentan-2-yl)pyrimidine-2,4,6-trione	12	25.58	5-Ethyl-5-(3-methylbut-2-enyl) barbiturate	28	23.2
5-Sec-butyl-5-allylpyrimidine-2,4,6-trione	13	21.91	5-Ethyl-5-heptylbarbiturate	29	27.61
5-Cyclohexenyl-1,5-dimethylpyrimidine-2,4,6-trione	14	24.01	5-Ethyl-5-pentylbarbiturate	30	23.4
5-Ethyl-5-phenylpyrimidine-2,4,6-trione	15	24.43	Hexethal	31	25.23
5-Ethyl-1-methyl-5-phenylpyrimidine-2,4,6-trione	16	26.26	5-i-Propyl-5-(3-methylbut-2-enyl) barbiturate	32	25.04

TOPOLOGICAL INDICES

A topological index is a numeric amount that is mathematically obtained in a direct and unambiguous method from the structural graph of a molecule. Descriptors of the structure of drugs were computed by standard molecular modeling. Hyperchem 8 for Windows operating system was used. Geometry optimization was performed using molecular mechanics ab initio 6-31G force field method and was followed by quantum chemical calculations according to ab initio 6-31Gmethod.In addition, the set of structural descriptors was completed with Dragon 5.5 software.[23]The list of descriptors is presented in Table (2, 3)

REGRESSION ANALYSES

n the present work, linear regression analyses were performed using SPSS-16 (SPSS Inc., Chicago, IL, USA)) and method Back ward step wise regression routine implemented in SPSS to develop the linear model for the prediction of Polarizability. The Polarizability (POL) is used as the dependent variable S1K, X0, X0sol,MW, Se, Ms, BAC,BIC2, Xindex, X3A,CSI, S3K, SRW04,IDDE,nSK,Ss,SMTIV,GNar,TIC0, X5v, AECC and UNIP indices as the independent variables. Criteria for selection of the best multiple linear regression models were the statistics: squared multiple correlation coefficients (R^2), adjusted correlation coefficient (R^2_{adj}), Fisher ratio (F), root mean square error (RMSE), Durbin-Watson value (DW) and significant (Sig).

Table 2. List of structural parameters employed in present study

Abbreviation	Description
S1K	1-path Kier alpha-modified shape index
MW	Molecular weight
X0sol	solvation connectivity index of order 0
X0	connectivity index of order 0
Se	sum of atomic Sanderson electronegativities (scaled on Carbon atom)
Ms	mean first ionization potential (scaled on Carbon atom)
BAC	Balaban centric index
BIC2	Bond Information Content index (neighborhood symmetry of 2-order)
Xindex	Balaban X index
X3A	average connectivity index of order 3
CSI	eccentric connectivity index
S3K	3-path Kier alpha-modified shape index
SRW04	self-returning walk count of order 4
IDDE	mean information content on the distance degree equality
nSK	number of non-H atoms
Ss	sum of first ionization potentials (scaled on Carbon atom)
SMTIV	Schultz Molecular Topological Index by valence vertex degrees
GNar	Narumi geometric topological index
TIC0	Total Information Content index (neighborhood symmetry of 0-order)
X5v	valence connectivity index of order 5
AECC	average eccentricity
UNIP	unipolarity

Table 3. List of barbiturates studied and structural parameters.

Comp. No.	S1K	MW	X0sol	X0	Se	Ms	BAC	BIC2	Xindex	X3A	CSI
1	6.074	128.1	6.853	6.853	14.07	3.61	10	0.733	0.817	0.201	63
2	8.049	156.16	8.594	8.594	19.84	3.23	26	0.651	0.822	0.21	89
3	8.049	156.16	8.646	8.646	19.84	3.3	26	0.651	0.837	0.203	85
4	9.039	170.19	9.353	9.353	22.72	3.15	27	0.711	0.819	0.197	100
5	9.039	170.19	9.301	9.301	22.72	3.11	27	0.828	0.797	0.198	104
6	13.015	226.31	12.345	12.35	34.25	2.76	43	0.671	0.731	0.183	186
7	13.015	226.31	12.508	12.51	34.25	2.76	55	0.721	0.807	0.181	162
8	13.015	226.31	12.345	12.35	34.25	2.76	43	0.671	0.771	0.175	182
9	12.046	212.28	11.422	11.42	31.37	2.63	32	0.755	0.703	0.195	168
10	12.02	212.28	11.422	11.42	31.37	2.81	30	0.726	0.689	0.189	198
11	16.004	268.4	14.793	14.79	42.91	2.56	72	0.654	0.763	0.182	252
12	13.752	238.32	13.052	13.05	35.25	2.77	46	0.779	0.761	0.172	195
13	11.761	210.26	11.638	11.64	29.49	2.94	42	0.761	0.794	0.17	151
14	12.153	236.3	12.629	12.63	33.37	2.67	26	0.791	0.571	0.183	212
15	11.648	232.26	12.466	12.47	29.6	2.79	18	0.719	0.571	0.171	210
16	12.621	246.29	13.337	13.34	32.49	2.72	27	0.758	0.575	0.174	223
17	13.597	260.32	14.207	14.21	35.37	2.65	38	0.694	0.58	0.176	236
18	7.06	142.13	7.724	7.724	16.95	3.43	17	0.754	0.818	0.209	76
19	8.049	156.16	8.431	8.431	19.84	3.26	18	0.778	0.789	0.193	91
20	9.039	170.19	9.301	9.301	22.72	3.11	27	0.75	0.783	0.182	102
21	10.032	184.22	10.06	10.06	25.6	3.02	30	0.671	0.811	0.184	111
22	9.774	182.2	10.06	10.06	23.72	3.13	28	0.798	0.784	0.19	129
23	11.025	198.25	10.768	10.77	28.49	2.91	31	0.675	0.784	0.18	140
24	12.02	212.28	11.475	11.48	31.37	2.82	34	0.635	0.766	0.175	153
25	12.02	212.28	11.801	11.8	31.37	2.86	54	0.574	0.823	0.163	133
26	10.767	196.23	10.768	10.77	26.6	3.02	31	0.811	0.784	0.18	140

27	11.761	210.26	11.638	11.64	29.49	2.89	40	0.742	0.722	0.193	175
28	12.756	224.29	12.345	12.35	32.37	2.81	43	0.76	0.731	0.183	186
29	15.007	254.37	13.596	13.6	40.02	2.6	35	0.581	0.643	0.19	299
30	13.015	226.31	12.182	12.18	34.25	2.73	33	0.634	0.713	0.185	211
31	14.011	240.34	12.889	12.89	37.14	2.66	34	0.607	0.677	0.188	253
32	13.752	238.32	13.215	13.22	35.25	2.75	56	0.727	0.747	0.174	197

Comp. No.	S3K	SRW04	IDDE	nSK	Ss	SMTIV	GNar	TIC0	X5v	AECC	UNIP
1	1.419	66	1.585	9	32.5	968	1.82	25.351	0.23	3.667	16
2	1.203	86	2.732	11	35.5	1330	1.76	34.446	0.438	4.273	20
3	1.203	90	2.732	11	36.25	1324	1.74	34.446	0.397	4.091	19
4	1.321	96	2.752	12	37.75	1568	1.76	38.482	0.452	4.417	21
5	1.45	92	2.918	12	37.33	1582	1.77	38.482	0.562	4.583	23
6	2.565	124	2.983	16	44.08	2986	1.78	53.106	1.208	6.125	34
7	1.738	128	3.75	16	44.08	2712	1.75	53.106	1.104	5.375	31
8	2.091	124	3.078	16	44.08	2858	1.78	53.106	1.007	6	32
9	2.96	110	3.64	15	39.5	2624	1.82	49.606	0.689	5.867	33
10	2.947	110	3.374	15	42.17	2774	1.82	49.606	1.002	6.867	34
11	2.373	150	3.392	19	48.58	4050	1.76	63.232	1.724	6.947	43
12	2.355	130	3.41	17	47.08	3397	1.79	54.692	1.2	6.059	35
13	1.761	118	3.24	15	44.08	2559	1.77	47.604	0.809	5.333	28
14	1.757	144	3.572	17	45.42	3438	1.91	52.691	1.629	6.118	36
15	1.696	140	3.146	17	47.42	3724	1.95	48.087	1.149	6.059	35
16	1.723	150	3.281	18	48.92	4096	1.92	51.836	1.355	6.111	38
17	1.742	160	3.471	19	50.42	4482	1.89	55.467	1.546	6.158	41
18	1.285	76	1.895	10	34.33	1142	1.78	30.126	0.324	4	18
19	1.504	82	2.914	11	35.83	1376	1.8	34.446	0.387	4.364	20
20	1.773	92	2.689	12	37.33	1610	1.77	38.482	0.443	4.5	22
21	1.408	102	2.931	13	39.25	1826	1.77	42.322	0.508	4.538	23
22	1.567	102	3.085	13	40.75	1981	1.77	40.068	0.546	5.231	24
23	1.771	108	3.182	14	40.75	2158	1.79	46.019	0.886	5.286	26
24	2.137	114	3.107	15	42.25	2512	1.8	49.606	1.16	5.4	29
25	1.62	122	2.84	15	42.92	2372	1.74	49.606	0.59	4.733	27
26	1.677	108	3.182	14	42.25	2266	1.79	43.908	0.703	5.286	26
27	2.378	118	3.006	15	43.42	2775	1.77	47.604	0.916	6.133	32
28	2.455	124	2.983	16	44.92	3104	1.78	51.191	0.984	6.125	34
29	3.475	132	3.684	18	46.75	4306	1.83	59.909	1.371	8.556	48
30	2.565	120	3.108	16	43.75	3060	1.82	53.106	1.106	6.875	35
31	2.991	126	3.735	17	45.25	3638	1.83	56.537	1.246	7.706	41
32	2.511	134	3.175	17	46.75	3441	1.76	54.692	1.044	6.118	36

QSAR MODELS FOR THE POLARIIZABILITY (POL)

The best linear model for Polarizability contains eight descriptors, namely, Se, Ms, Xindex, S3K, SRW04,GNar, AECC and UNIP indices. The regression parameters of the best eight descriptors correlation model are gathered in equation (1).

Model.I.

POL= -67.609+0.333 Se -5.949Ms +40.940 Xindex +1.806 S3K +0.211 SRW04 +27.225 GNar +0.908 AECC+0.118 UNIP (1)

N=32 $R=0.998 R^2=0.996 R^2_{adj} = 0.995$

RMSE=9.285 F=818.517 Sig=0.000 DW=2.181

This model produced a root mean square error (RMSE) of 9.285, a squared correlation coefficient of 0.996, and the adjusted correlation coefficient

(adjusted r- squared) was calculated as 0.995. The result is therefore very satisfactory.

DISCUSSION

We studied the relationship between descriptors structural to the Polarizability of 32 barbiturates. In this study, to find the best model for predict the parameters mentioned, we will use the following sections.

Multicollinearity

Multiple linear regression is one of the most complex statistical techniques that are usually used for data whose level of their measurement is spatial (distance). Multivariate regression is a method for the collective and individual participation of two or more independent variables in the variations of a dependent variable since the basic task of science is the prediction and explanation of phenomena. The word of collinearity indicates that the two variables are close to a linear combination of each other. When there are more than two variables in the model, the term is changed to "multicollinearity". Test multicollinearity as a basis the variance inflation factor (VIF) value of multicollinearity test results using SPSS. If the VIF value lies between1-10, then there is no multicollinearity, and if the VIF<1 or >10, then there is multicollinearity.

In all our final models, the multicollinearity has existed, because the values of correlations between independent variables are near to one and VIFs value lies between 1 and 10.

Verification and validity of models

In this section, it emphasizes the validation of regression models on the Durbin-Watson and unstandardized predicted and residual values. The Durbin-Watson is used to evaluate the correlated residuals. The Durbin-Watson statistic is between 0 and 4 that its middle point is 2. In our model, the value of Durbin-Watson statistic is 2(See eq.1) and hence the errors are uncorrelated.

RESULTS AND DISCUSSION

Validation

Multiple linear regression methods were used for all QSAR analyses. A good QSAR model should have both suitable relativity and good predictability. We studied the validation of linearity between the molecular descriptors in the model IWe obtained by SPSS the Pearson coefficient correlation and collinearity statistics as follow Tables (4).

For modelI the Pearson correlation (Se, Xindex), (Se, Ms), (Xindex, GNar) is near one, and VIF(Se), VIF (Xindex) and VIF (Ms), VIF (GNar)>10, therefore there is a linearity between (Se, Xindex), (Se, Ms) and (Xindex, GNar). After removed Se from this modelsix indices GNar, S3K, Ms, Xindex, AECC and SRW04 remains the Pearson correlation (Xindex, GNar) is near one, and VIF (Xindex), VIF(GNar))>10, therefore there is a linearity between Xindex and GNar. After removed Xindex from this model, we corrected model Ias follows:

POL= 11.273 +2.098 S3K +0.185 SRW04-8.613GNar

N=32; R=0.991R^2=0.983 R^2_{adj} = 0.981 RMSE=15.060 F=540.809 Sig=0.000 DW=1.893 Q^2=0.933 (2)

Furthermore, we have computed Q^2 (Eq.3) by 50% of data, randomly, that is positive and less than one.

$$Q^2 = 1 - \frac{\sum(Y_i - \hat{Y}_{i|i})^2}{\sum(Y_i - \bar{Y})^2} Q^2 \leq 1 \qquad (3)$$

Where the notation i|i indicates that the response is predicted by a model estimated when the ith sample was left out from the training set.

Table 4. Correlation between the molecular descriptors (model I)

Collinearity	Statistical								Corrected	Model
	UNIP	GNar	S3K	Xindex	Ms	AECC	SRW04	Se	Tolerance	VIF
UNIP	1.000								.012	82.488
GNar	.175	1.000							.058	17.323
S3K	-.244	.403	1.000						.066	15.196
Xindex	.403	.869	.391	1.000					.014	70.370
Ms	-.526	-.396	.048	-.648	1.000				.024	41.846
AECC	-.371	.261	.001	.360	-.242	1.000			.039	25.949
SRW04	-.161	.505	.768	.662	-.231	.478	1.000		.016	62.593
Se	.499	-.517	-.338	-.840	.805	-.360	-.670	1.00	.006	179.436

Collinearity	Statistical						Corrected	Model	
	GNar	S3K	Ms	Xindex	AECC	SRW04	Tolerance	VIF	VIF
GNar	1.000						.080	12.527	1.325
S3K	.264	1.000					.100	10.002	1.275
Ms	.015	.540	1.000				.072	13.869	-
Xindex	.938	.224	.083	1.000			.048	20.701	-
AECC	.024	-.764	-.109	.125	1.000		.083	12.105	-
SRW04	.257	.699	.828	.347	-.393	1.000	.071	14.042	1.638

Regular residuals

The residual is the difference between the observed and predicted values .Comparison between predicted and observed values of Polarizability, barbiturates show in Table (5). Figures (1) show the linear correlation between the observed and the predicted Polarizability of barbiturates values obtained using equation (2).

Table 5. Comparison between predicted and observed values of models calculated validation of POL respect barbiturates.

No.	Observed POL	Predicted POL	Residual	No.	Observed POL	PredictedPOL	Residual
1	11.1	10.800	0.300	17	27.55	28.188	-0.638
2	14.22	14.577	-0.357	18	12.14	12.660	-0.520
3	14.77	15.480	-0.710	19	13.42	14.073	-0.653
4	16.6	16.656	-0.056	20	16.6	16.718	-0.118
5	16.6	16.041	0.559	21	18.44	17.801	0.639
6	23.14	24.226	-1.086	22	18.24	18.134	0.106
7	23.94	23.497	0.443	23	20.27	19.534	0.736
8	23.94	23.231	0.709	24	22.11	21.299	0.811
9	22.11	22.166	-0.056	25	22.11	22.278	-0.168
10	22.11	22.138	-0.028	26	20.08	19.336	0.744
11	29.45	28.809	0.641	27	21.91	22.836	-0.926
12	25.58	24.791	0.789	28	23.2	23.995	-0.795
13	21.91	21.542	0.368	29	27.61	27.166	0.444
14	24.01	25.090	-1.080	30	23.4	23.202	0.198
15	24.43	23.939	0.491	31	25.23	25.119	0.111
16	26.26	26.085	0.175	32	25.04	26.116	-1.076

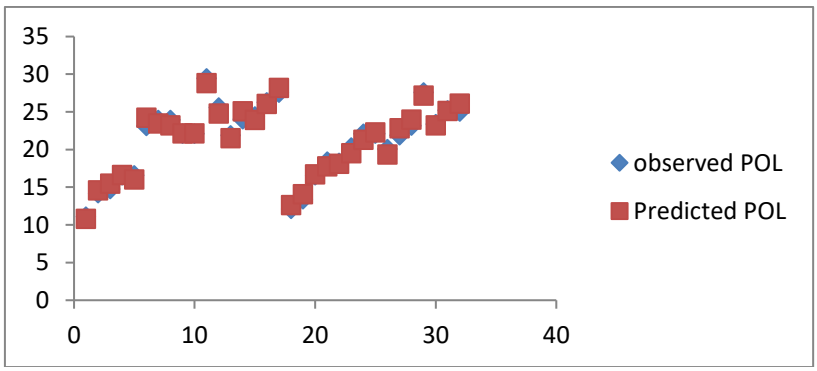

Fig .1. Comparison between the predicted and observed of models calculated validationof Polarizability by MLR method.

QSAR STUDIES AND PREDICTIONS OF PROPERTIES BASED ON IT

As mentioned in the second part, it can investigate the Quantitative Structure-Activity Relationship (QSAR) using the graph theory and obtain the appropriate index that correlates with the desired properties. In this section of the research, it is possible to predict properties using the findings of the first part of the study and determine the appropriate indicators of each property by applying the index to the desired state. So, for this purpose, choose ten combinations of barbiturates such as (5-t-Butyl-5-(3-methylbut-2-enyl) barbiturate, 5-Ethyl-5-octylbarbiturate,5-Ethyl-5-nonylbarbiturate, Cyclopropane-spirobarbiturate, Cyclobutane- Spiro barbiturate, Cyclopentane- Spiro barbiturate, Cyclohexane- Spiro barbiturate, Cycloheptane-spirobarbiturate,5-Allyl-5-phenylbarbiturate,and 5,5-Diphenylbarbiturate)and then was found a suitable index using the obtained results(Equation2) for molecular, computational and Physico-chemical properties. Thus, the S3K,SRW04 and GNarindicesare considered to the Polarizability and the results are shown in the Table 6.

Table 6. Comparison between predicted and HyperChem values of models calculated validation of POL for ten compounds of barbiturates.

.Compound No.	POL (Hyper)	POL(Pre)	Δ[POL(Hyper) –POL(Pre)]
		S3K, SRW04,GNar	S3K, SRW04,GNar
1. 5-t-Butyl-5-(3-methylbut-2-enyl) barbiturate	26.87	29.15	-2.28
2. 5-Ethyl-5-octylbarbiturate	28.9	29.22	-0.32
3.5-Ethyl-5-nonylbarbiturate	30.74	31.39	-0.65
4. Cyclopropane-spirobarbiturate	13.45	14.53	-1.08
5. Cyclobutane-spirobarbiturate	15.28	17.21	-1.93
6. Cyclopentane-spirobarbiturate	17.12	18.23	-1.11
7. Cyclohexane-spirobarbiturate	18.95	19.06	-0.11
8. Cycloheptane-spirobarbiturate	20.79	20.81	-0.02
9. 5-Allyl-5-phenylbarbiturate	25.52	25.55	-0.03
10.5,5-Diphenylbarbiturate	29.87	30.63	-0.76

CONCLUSIONS

In the present study, a set of 22 descriptors is adopted to build a model to describe Polarizability of 32 barbiturates. Results show that MLR model based on selected molecular descriptors showed a high degree of correlation between Polarizability observed and calculated. Cross-validation as the evaluation technique has been designed to evaluate the quality and predictive ability of the MLR model. The obtained results showed that (S3K, SRW04, and GNar) indices are the good descriptors structural for predicting POL.

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