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QSAR study on the physico-chemical parameters of barbiturates by using topological indices and MLR method

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In this study the relationship of the Randic' (^{1}X), Balaban (J), Szeged (Sz), Harary (H), Wiener (W), Hyper-Wiener (WW) and Wiener polarity (Wp) with 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 sets method and Polak-Ribiere algorithm with conjugated gradient within Hyper Chem 8.0 environment. The multiple linear regressions (MLR) and backward methods (with significance 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 the used properties. The predictive powers of the models were discussed by using the method of cross-validation. The results have shown that the combination of two descriptors (Wp, W) is excellent for predicting the polarizability, and the descriptor (WW) is useful for modeling and for predicting the molar refractivity and octanol/water partition of the corresponding barbiturates.

Keywords: Barbiturates; QSAR; Polarizability; Molar refractivity; Octanol/water partition coefficient; Multiple linear regressions (MLR); Validation

INTRODUCTION

Barbiturates are a category of compounds that are focal nervous system depressants. Barbiturates overdose leads to weakness of the central nervous system, respiratory and cardiovascular depression and eventual death [1-4]. Barbituric acid derivatives act as central nervous system depressors and are used in medicine as sedative, hypnotic and anticonvulsant drugs with hypnotic or sedative properties depending on the dose administered [5]. Drug therapy is mainly used to reduce the symptoms of acute insomnia while their role in the management of chronic insomnia remains unclear [6,7]. Attention to sleep hygiene is the most important line of treatment and should be tried before any pharmacological approach is considered [8]. The relative activity in a series of barbituric acid substitution derivatives and their lipophilicity has been studied [9]. Quantitative structure – activity relationship (QSAR) has been known as a quantum chemical technique in connection with the biological activity of compounds by their molecular structure and has been used as a predictive tool in drug design [10]. A QSAR analysis of 21 molecules of 1, 2, 3-oxadiazole-2-thiones has been performed using multiple linear regression model [11]. Calculation of the volume distribution of certain pharmaceutical compounds from their structural descriptors has been considered [12]. QSAR studies on the benzylidenebarbiturate derivatives inhibiting the activity of the mushroom tyrosinase have been investigated [13]. QSAR models have been developed to determine the penetration coefficients of barbiturates in biological membranes [14]. 3D QSAR technique has been used to predict biological properties such as toxicity of chemicals [15-18]. The structure-activity relationship in barbiturates and its similarity to other drugs has been traditionally developed to the estimation and prediction of biological activity [19-21]. 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, MATHEMATICAL METHOD AND GRAPHS

The barbiturates discussed in this study consist of 17 derivatives with substitution at 3, and 5, 5 positions. Figure 1 shows the template structure of barbiturates used in the present study.

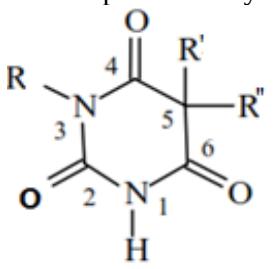

Figure 1.The structural template of barbiturates

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

Compound No	Name of compound	POL	MR	Log P
1	Barbituric acid	11.1	23.23	-1.6
2	1,3-Dimethylpyrimidine-2,4,6-trione	14.22	34.52	-1.4
3	5,5-Dimethylpyrimidine-2,4,6-trione	14.77	32.31	-0.37
4	5-Ethyl-5-methylpyrimidine-2,4,6-trione	16.6	36.91	-0.03
5	5-Ethyl-1-methylpyrimidine-2,4,6-trione	16.6	38.18	-0.37
6	5-Ethyl-5-isopentylpyrimidine-2,4,6-trione	23.14	58	1.86
7	5-sec-Butyl-5-ethyl-1-methylpyrimidine-2,4,6-trione	23.94	56.43	1.42
8	5-Ethyl-5-(pentan-2-yl)pyrimidine-2,4,6-trione	23.94	55.26	1.55
9	5-sec-Butyl-5-ethylpyrimidine-2,4,6-trione	22.11	52.4	1.19
10	5-(Hexan-2-yl)pyrimidine-2,4,6-trione	22.11	50.76	0.88
11	5-Ethyl-5-(Hexan-2-yl)-1,3-dimethylpyrimidine-2,4,6-trione	29.45	69.65	2.44
12	5-Allyl-5-(pentan-2-yl)pyrimidine-2,4,6-trione	25.58	59.9	1.73
13	5-sec-Butyl-5-allylpyrimidine-2,4,6-trione	21.91	50.7	0.94
14	5-Cyclohexenyl-1,5-dimethylpyrimidine-2,4,6-trione	24.01	61.95	1.17
15	5-Ethyl-5-phenylpyrimidine-2,4,6-trione	24.43	57	1.25
16	5-Ethyl-1-methyl-5-phenylpyrimidine-2,4,6-trione	26.26	62.77	1.51
17	5-Ethyl-1,3-dimethyl-5-phenylpyrimidine-2,4,6-trione	27.55	66.8	1.74

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

TOPOLOGICAL INDICES

A topological index is a numeric quantity that is mathematically derived in a direct and unambiguous manner from the structural graph of a molecule. The topological indices (TIs) used for the QSAR analysis were Wiener (W) [22], Szeged (Sz) [23], first order molecular connectivity (^{1}X) [24], Balaban (J) [25], Hyper-Wiener (WW) [26], Wiener polarity (Wp) [27] and Harary (H) [28] indices. All used topological indices were calculated using hydrogen suppressed graph by deleting all carbon-hydrogen, as well as heteroatomic hydrogen bonds from the structure of the barbiturates. The calculations of topological indices used in this paper are well documented. The descriptors were calculated with the chemicalize program [29]. Seven topological indices tested in the present study are listed in Table 2.

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 ^{1}X, J, H, W, Wp, WW and Sz indices as independent variables. Criteria for selection of the best multiple linear regression model were the statistics: squared multiple correlation coefficient (R^2), adjusted correlation coefficient (R^2_{adj}), Fisher ratio (F), root mean square error (RMSE), Durbin-Watson value (DW) and significance (Sig).

Table 2. Barbiturates and their topological indices used in the present study

No.	^{1}X	J	H	W	WW	Wp	Sz
1	4.18	2.08	19.5	84	159	9	144
2	5.04	2.39	27.32	140	281	17	230
3	4.94	2.43	27.57	138	274	17	226
4	5.5	2.73	31.43	177	372	20	279
5	5.57	2.65	31.05	181	388	19	287
6	7.42	2.74	47.51	418	1115	26	576
7	7.41	3.05	49.44	379	903	32	549
8	7.48	2.9	48.43	398	1005	29	556
9	6.98	2.74	44.39	324	761	28	468
10	7.06	2.34	41.92	374	1040	21	518
11	8.84	2.9	63.25	632	1761	38	866
12	7.98	2.77	52.83	472	1233	30	644
13	7.48	2.96	48.65	391	961	29	549
14	7.98	2.2	54.63	458	1179	32	770
15	8.11	2.2	54.4	458	1172	31	756
16	8.54	2.15	59.76	526	1363	35	863
17	8.96	2.11	65.37	598	1564	39	976

RESULTS

Several linear QSAR models involving three-seven 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 four topological descriptors, namely, Hyper Wiener (WW), Szeged (Sz), Harary (H) and Wiener (W) indices. The model is presented below:

Model 1

MR =-14.096-0.037(Sz)+ 0.118(WW)-0.464(W)+3.224(H) (1)

N=17, R=0.991, R^2=0.983, R^2_{adj} = 0.977,

RMSE= 26.346, F=172.333, Sig=0.000, DW=2.102

QSAR models for the polarizability (POL)

The best linear model for polarizability contains four topological descriptors, namely, Wiener polarity (Wp), Hyper Wiener (WW), Randic (^{1}X) and Szeged (Sz) indices.

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

Model 2

POL= -0.676+2.653(^{1}X)+0.179(Wp)-0.011(Sz)+0.005(WW) (2)

N=17, R=0.996, R^2=0.992, R^2_{adj} = 0.989,

RMSE=10.248, F=351.311, Sig=0.000, DW=1.959

QSAR models for octanol/water partition coefficient (logP)

The best linear model for the octanol/water partition coefficient contains three topological descriptors, namely, Hyper Wiener (WW), Szeged (Sz) and Harary (H) indices. The model is presented below:

Model 3

logP =-3.706-0.008(Sz)+0.002(WW)+0.154(H) (3)

N =17, R=0.968, R^2=0.937, R^2_{adj}=0.922,

RMSE=2.594, F=64.046, Sig=0.000, DW=1.978.

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 topological indices and the polarizability, molar refractivity and octanol/water partition coefficient of 17 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.

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 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 are close to 2 (see eqs.1, 2 and 3) and hence the errors are uncorrelated.

Results and discussion of validation: Multiple linear regression method was 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 models 1, 2 and 3. We obtained by SPSS the Pearson (2) coefficient correlation and collinearity statistics as follows (see Tables 3, 4 and 5). For model 1 the Pearson correlations (WW, W), (WW, H) and (W, H) are near 1, and VIF (WW, H, W, Sz) >10, therefore there is linearity between these descriptors. After removing W and H from this model, we corrected model 1 as follows:

MR=26.298+0.027(WW) (4)

N=17, R=0.968, R^2=0.936, R^2_{adj} = 0.932,

RMSE= 51.4242, F=219.944, Sig=0.000, DW=1.560, Q^2=0. 88.

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

POL=8.822+0.265(Wp)+0.006(WW) (5)

N=17, R=0.986, R^2=0.973, R^2_{adj}= 0.969, RMSE= 14.353, F=248.454, Sig=0.000, DW=0.950, Q^2=0.86.

logP=-1.22+0.002(WW) (6)

N=17, R=0.915, R^2=0.837, R^2_{adj} = 0.826, RMSE= 4.246, F=76.787, Sig=0.000, DW=0.836, Q^2=0.88.

Further we computed Q^2 (Eq. 7) by 50% of the data, randomly, that are positive and less than 1:

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

where the notation indicates that the response is predicted by a model estimated when the i[th] sample was left out from the data set.

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

	Pearson correlations (model 1)				Collinearity statistical		Corrected model	
	H	WW	Sz	W	Tolerance	VIF	VIF	VIF
H	1	0.960	-0.521	-0.974	0.001	698.821	35.953	-
WW		1	-0.405	-0.996	0.000	2.15×10^3	19.135	1
Sz			1	0.381	0.027	37.541	32.103	-
W				1	0.000	4.784×10^3	-	-

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

	Pearson correlations (model 2)				Collinearity statistical		Corrected model	
	Wp	WW	^{1}X	Sz	Tolerance	VIF	VIF	VIF
Wp	1	0.425	-0.682	-0.258	0.058	17.097	9.152	6.283
WW		1	-0.663	-0.427	0.036	27.833	15.60	6.283
^{1}X			1	-0.209	0.019	52.583	-	-
Sz				1	0.042	23.718	22.681	-

Table 5. Correlation between the molecular descriptors (model 3) for octanol/water partition coefficient (logP)

	Pearson correlations (model 3)			Collinearity statistical		Corrected model
	Wp	WW	Sz	Tolerance	VIF	VIF
Wp	1	-0.432	0.718	0.028	35.953	-
WW		1	0.298	0.052	9.135	1
Sz			1	0.031	2.103	-

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

No.	Observed MR	Predicted MR	Residual	No.	Observed POL	Predicted POL	Residual	No.	Observed logP	Predicted logP	Residual
1	23.23	30.59	-7.36	1	11.10	12.21	-1.11	1	-1.60	-0.86	-0.74
2	34.52	33.89	0.63	2	14.22	15.10	-0.88	2	-1.40	-0.59	-0.81
3	32.31	33.70	-1.39	3	14.77	15.06	-0.29	3	-0.37	-0.61	0.24
4	36.91	36.35	0.56	4	16.60	16.47	0.13	4	-0.03	-0.39	0.37
5	38.18	36.78	1.40	5	16.60	16.31	0.29	5	-0.37	-0.35	-0.02
6	58.00	56.43	1.57	6	23.14	22.74	0.40	6	1.86	1.27	0.59
7	56.43	50.70	5.73	7	23.94	23.00	0.94	7	1.42	0.79	0.63
8	55.26	53.46	1.80	8	23.94	22.87	1.07	8	1.55	1.02	0.53
9	52.40	46.86	5.54	9	22.11	21.04	1.07	9	1.19	0.48	0.71
10	50.76	54.40	-3.64	10	22.11	20.94	1.17	10	0.88	1.10	-0.22
11	69.65	73.89	-4.24	11	29.45	30.00	-0.55	11	2.44	2.71	-0.27
12	59.90	59.62	0.28	12	25.58	24.55	1.03	12	1.73	1.53	0.20
13	50.70	52.27	-1.57	13	21.91	22.57	-0.66	13	0.94	0.92	0.02
14	61.95	58.16	3.79	14	24.01	24.74	-0.73	14	1.17	1.41	-0.24
15	57.00	57.98	-0.98	15	24.43	24.43	0.00	15	1.25	1.39	-0.14
16	62.77	63.13	-0.36	16	26.26	26.69	-0.43	16	1.51	1.82	-0.31
17	66.80	68.56	-1.76	17	27.55	29.02	-1.47	17	1.74	2.27	-0.53

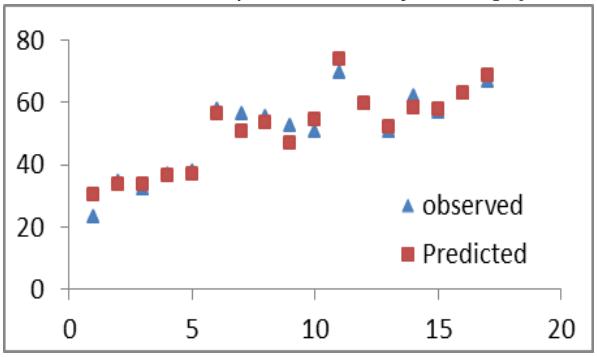

Fig. 2. Comparison between observed and predicted values of molar refractivity (MR) calculated by the MLR method.

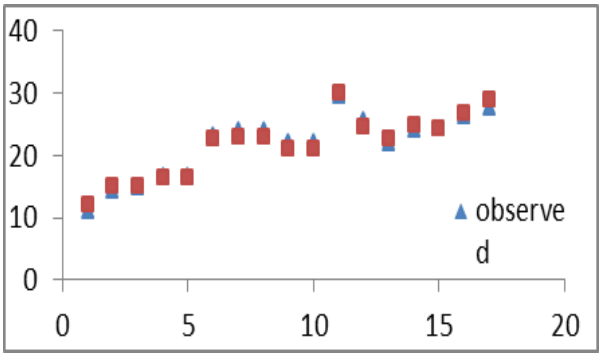

Fig. 3. Comparison between observed and predicted values of polarizability calculated by the MLR method.

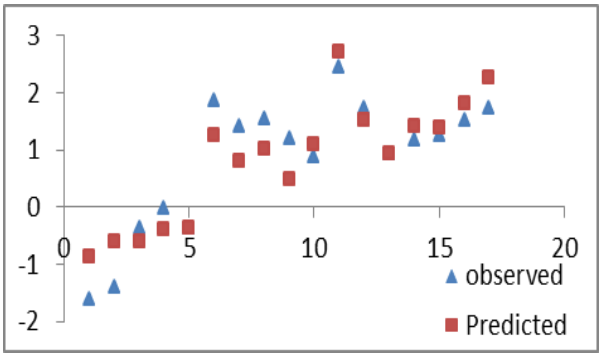

Fig. 4. Comparison between predicted and observed values of logP calculated by the MLR method.

CONCLUSIONS

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 alone were developed. MLR model proved to be a useful tool in the prediction of POL, MR and log P. Cross-validation as the evaluation technique was designed to evaluate the quality and predictive ability of the MLR model. The obtained results showed that two topological indices (WW and Wp) could be used successfully for predicting POL, and Hyper-Wiener index (WW) is a good topological index for modeling logP and MR.

REFERENCES

1. N. Kiyosawa, K. Tanaka, J. Hirao, K. Ito, N. Niino, K. Sakuma, M. Kanbori, T. Yamoto, S. Manabe, N. Matsunuma, *Arch.Toxicol*., **78**, 435 (2004).
2. R. Lal, S. Faiz, R.K. Garg, K.S. Baweja, J. Guntupalli, K.W. Finkel, *Am. J. Kidney Dis.*, **48**, 13 (2006).
3. B.J. Pleuvry, *Anaesth. Intensive. Care*, **5**, 252 (2004).
4. M. Fryer, *Anaesth. Intensive Care*, **5**, 317 (2004).
5. E.A. Mamina, V.V. Bolotov, *Pharm. Chem. J.*, **38**, 53 (2004).
6. C. M. Morin, *Psychosom. Med*., **62**, 483 (2000).
7. M. Hirshkowitz, Essentials of neuropsychiatry and clinical neurosciences (4 ed.). In: S. C. Yudofsky, R. E. Hales, eds., Arlington, Virginia, USA, American Psychiatric Publishing, p. 315, 2004.
8. H.E. Flamer. *Med. J. Aust.*, **162**, 603 (1995).
9. R. Ray, J.D. Sharma, S.N. Limaye, *Asian J. Chem.*, **19**, 3382 (2007).
10. M.J.S. Dewar, E.G. Zoebisch, E.F. Healy, J.J.P. Stewart, *J. Am. Chem. Soc*., **107**, 3902, (1985).
11. Z. Almi, S. Belaidi, T. Lanez, N. Tchouar, *Int. lett. Chem. Phys. Astron*., **37**, 113 (2014).
12. M.H. Fatemi, Z. Ghorbannezhad, *J. Serb. Chem. Soc.*, **76**, 1003 (2011).
13. R.L. Sawant, G.D. Jadhav, P.D. Lanke, J.B. Wadekar, *Drug Design & Discovery*, **4**, 1077 (2013).
14. C. Hansch, A.R. Steward, S.M. Anderson, D. Bentley, *J. Med. Chem*., **11**, 1 (1967).
15. R.D. Crammer III, D.E. Paterson J.D. Bunce, *J. Am. Chem. Soc*., **110**, 5959 (1988).
16. G. Klebe, U. Abraham, T. Mietzner, *J. Med. Chem*., **37**, 4130 (1994).
17. A.N. Jain, K. Koile, D. Chapman, *J. Med. Chem.*, **37**, 2315 (1994).
18. B.D. Silverman, D.E. Platt, *J .Med. Chem*., **39**, 2129 (1996).
19. G. Bravi, E. Gancia and A. Zaliani, *J. Comput-Aided. Mol. Des*., **11**, 62 (1997).
20. C. Hansch, A. Kurup, R Garg, H. Gao, *Chem.Rev*., **101**, 619 (2001).
21. S.C. Basak, Topological Indices and Related Descriptors in QSAR and QSPR in: J. Devillers, A. T. Balaban (eds.), Gordon and Breach, Amsterdam. 563, 1999.
22. P.V. Khadikar, N.V. Deshpande, P.P. Kale, A. Dobrynin, I. Gutman, G. Dömötör, *J. Chem. Inf. Comput. Sci*., **35**, 547 (1995).
23. I. Gutman, S. Klavžar, *J. Chem. Inf. Comput. Sci.* **35**, 1011 (1995).
24. M. Randić, *J. Math. Chem*., **7**, 155 (1991).
25. A. T. Balaban, *Chem. Phys. Lett.*, **89**, 399 (1982).
26. I. Gutman, *Croat. Chem. Acta*, **77**, 61 (2004).
27. M. Liu, B. Liu, *MATCH. Commun. Math. Comput. Chem.* **66**, 293 (2011).
28. C. K. Das, B. Zhou, N. Trinajstic, *J. Math. Chem.*, **1**, 1369 (2009).
29. Web search engine developed by ChemAxon; software available at http:// www.Chemicalize.Org.

QSAR ИЗСЛЕДВАНЕ НА ФИЗИКОХИМИЧНИТЕ ПАРАМЕТРИ НА БАРБИТУРАТИ С ИЗПОЛЗВАНЕ НА ТОПОЛОГИЧНИ ИНДЕКСИ И МЕТОДА НА МНОГОКРАТНАТА ЛИНЕЙНА РЕГРЕСИЯ

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(Резюме)

В настоящата статия е изследвана зависимостта на топологичните индекси Randic (^{1}X), Balaban (J), Szeged (Sz), Harary (H), Wiener (W), Hyper-Wiener (WW) и Wiener полярност (Wp) от поляризуемостта (POL), моларния коефициент на пречупване (MR) и разпределителния коефициент между октанол и вода (logP) на барбитурати. Химичните структури са оптимизирани с помощта на *ab initio* 6-31G базисен метод и алгоритъма на Polak-Ribiere със спрегнат градиент в Hyper Chem 8.0 обкръжение. За получаване на QSAR моделите са използвани методите на многократна линейна регресия и обратните методи (със значимост на 0.05 ниво). След анализ чрез многократна линейна регресия е изследвана линейността при молекулните дескриптори в най-добрите модели. Прогнозната сила на моделите е обсъдена по метода на кръстосаното валидиране. Резултатите показват, че съчетанието от два дескриптора (Wp, W) е подходящо за предсказване на поляризуемостта, а дескрипторът (WW) е подходящ за моделиране и предсказване на моларния коефициент на пречупване и разпределителния коефициент между октанол и вода на барбитуратите.