Available on line www.jocpr.com

Journal of Chemical and Pharmaceutical Research

J. Chem. Pharm. Res., 2010, 2(6):416-423

ISSN No: 0975-7384
CODEN(USA): JCPRC5

DFT-Based QSAR Prediction of 1-Octanol/Water Partition Coefficient of Adamantine derivatives drugs

Z. Bayat* and M. Zanoozi

Department of Chemistry, Islamic Azad University-Quchan Branch, Iran

ABSTRACT

*A quantitative structure property relationship (QSPR) study was performed to develop a model that relates the structures of 39 ofAdamantine derivatives drugs to simple descriptors. The usefulness of the quantum chemical descriptors, were calculated at the level of the DFT theory using 6-31+G** basis set , and used to represent molecular structures. A subset of the calculated descriptors selected using stepwise regression that used in the QSPR model development. In this study Multiple Linear Regressions (MLR) were employed to model the relationships between molecular descriptors and biological activities of molecules using stepwise method and genetic algorithm as variable selection tools.. Biological activities contain the octanol/water partition coefficient (log P). The final regression equation included four parameters that consisted of Clog P, Mulliken charge, Isotropic parameters and Mass, all of which could be related to log P. Application of the developed model to a testing set of 39 of Adamantine derivatives drugs demonstrates that the new model is reliable with good predictive accuracy and simple formulation. The use of descriptors calculated only from molecular structure eliminates the need for experimental determination of properties for use in the correlation and allows for the estimation of log P for molecules not yet synthesized. The prediction results are in good agreement with the experimental values. Statistical qualities (R_{MAX}= 0.927 , R^2_{MAX}= 0.858 Q^2=0.713at B3LYP/6-31+G**) was obtained by this approach.*

Keywords: partition coefficient octanol- water ($LogP_{o/w}$), Adamantine derivatives, QSAR, DFT, MLR

INTRODUCTION

Diamondoids are classed with organic nanostructures; therefore, adamantane derivatives have become particularly popular with the development of nanotechnologies. The applications of adamantine derivatives are diverse: from antiviral drugs to nanorobots and molecular machines.The octanol-water partition coefficient (log Po/w) is the parameter most widely used to

measure hydrophobicity [1], because it has been shown that this partition system is a good model for many biological processes [2]. Hence, it was deemed advantageous to develop a model to predict partition coefficient using only theoretically derived descriptors. However, using in *vivo* methods to measure the logarithmic values of partition coefficient drug concentration ratios (log Po/w) in humans is not possible, and to do so in animal models is expensive and time consuming. The partition coefficient of a solute between 1-octanol and water was first introduced in 1964 by Hansch and Fujita [3], and since then, many different approaches have been developed in an attempt to estimate this property. Quantitative structure–activity relationship (QSAR) analysis is an effective method in research into rational drug design and the mechanism of drug actions. In addition, it is useful in areas like the design of virtual compound libraries and the computational-chemical optimisation of compounds. QSAR studies can express the biological activities of compounds as a function of their various structural parameters and also describes how the variation in biological activity depends on changes in the chemical structure [4]. Recently, a QSAR study of biological activity has been published by our group [5-7]. If such a relationship can be derived from the structure-activity data, the model equation allows medicinal chemists to say with some confidence which properties are important in the mechanism of drug action. The success of a QSAR study depends on choosing robust statistical methods for producing the predictive model and also the relevant structural parameters for expressing the essential features within those chemical structures. In a QSAR study the model must be validated for its predictive value before it can be used to predict the response of additional chemicals. Validating QSAR with external data (i.e. data not used in the model development), although demanding, is the best method for validation [8-9]. However the availability of an independent external validation set of several compounds is rare in QSAR. Thus, the input data set must be adequately split by experimental design or other splitting procedures into representative training and validation/test sets [10-12]. In the present work, the data splitting was performed randomly and was confirmed by the factor spaces of the descriptors, as in our previous work [13–17]. Finally, the accuracy of the proposed model was illustrated using the following: leave one out, bootstrapping and external test set, cross-validations and chance correlation techniques. Several research groups have modeled the partition coefficient (LogP).As expected; the models typically show good fitting and prediction statistics with less than ten simple descriptors.

EXPERIMENTAL SECTION

Methodology

Data set

The properties data used in this study are the $LogP_{o/w}$ of the set of 39 Adamantine derivatives [17],[18]. The data set was randomly divided into two subsets: the training set containing 38 compounds (80%) and the test set containing ?compounds (20%). The training set was used to build a regression model, and the test set was used to evaluate the predictive ability of the model obtained. The properties data for the complete set of compounds are presented in Table 1, 2.To derive QSAR models, an appropriate representation of the chemical structure is necessary. For this purpose, descriptors of the structure are commonly used.

Table 1. Experimental values of $LogP_{o/w}$ for Adamantine derivatives training set

Compound	logP		Ref.
		Pred.	
Adamantine	2.69	2.82	[18]
1 3 dimethyl adamantine	3.56	3.51	[18]
1,3,5 -trim ethyl adamantine	3.99	4.34	[18]
1-adamantanol	2.66	1.96	[19]
1-buthyl adamantine	4.31	4.21	[18]
1-ethyl adamantine	3.52	3.43	[18]
1-isopropyl adamantine	3.85	3.83	[18]
1-propyl adamantine	3.92	3.80	[18]
2-buthyl adamantine	4.21	4.08	[18]
2-ethyl adamantine	3.42	3.54	[18]
2-isopropyl adamantine	3.75	3.98	[18]
2-methyl adamantine	3.02	3.22	[18]
2-propyl adamantine	3.81	3.73	[18]
1-bromo adamantine	2.66	3.36	[19]
methyl-(1-adamanthyl) ketone	2.9	3.08	[18]
propyl-(1-adamanthyl) ketone	3.93	4.08	[18]
2-adamantanon	2.31	2.71	[19]
ethyl-(1-adamanthyl)ketone	3.53	3.67	[18]
1-methyladamantane	3.13	3.01	[18]
1- sec butyl adamantine	4.25	4.12	[18]
1-tert-buthyl adamantine	4.29	4.19	[18]
1-amino adamantine	1.11	1.63	[18]
2-amino adamantine	2.44	1.69	[19]
1-carboxcylic acid adamantine	2.36	2.73	[19]
1-aceti acid adamantine	2.29	2.72	[19]
1.3-diacetic acid adamantane	1.89	1.94	[19]
1-adamantanol-3 carboxylic acid	1.12	1.27	[19]
1-adamantyl Ethan amine	3.28	2.41	[19]
3,5 -dimethyl-adamantine 1-amine	3.31	2.84	[18]
2-bromo ethyl adamantine	5.094	4.22	[19]
1-adamantane ethanol	3.227	2.69	[19]
1-ethyl-3-methyl-adamantane	4.35	3.92	[18]
1.3.5.7.tetra methyl adamantine	4.42	4.86	[18]

Table 2. Experimental values of $LogP_{o/w}$ for adamantine derivatives test set

Compound	logP	Pred.	Ref.
1.3 diethyl adamantine	4.35	4.34	[18]
1n-methyl-amino adamantine	1.51	2.06	[18]
1-n-n dimethyl adamantine	1.88	2.49	[18]
2-chloro adamantine	3.865	3.41	[19]
1-chloroadamantane	2.6	2.76	[19]
2-isobuthyl adamantine	4.15	4.20	[18]

Molecular descriptor generation

To derive QSAR models, an appropriate representation of the chemical structure is necessary. For this purpose, descriptors of the structure are commonly used. These descriptors are generally understood as being any term, index or parameter conveying structure information. Commonly used descriptors in the QSAR analysis are presented in Table 2. Some of the descriptors are

obtained directly from the chemical structure, e. g. constitutional, geometrical, and topological descriptors. Other chemical and physicochemical properties were determined by the chemical structure (lipophilicity, hydrophilicity descriptors, electronic descriptors, energies of interaction). In this work, we used Gaussian 03 for ab initio calculations. HF method at 6-31+G** were applied for optimization of adamantine derivatives and calculation of many of the descriptors. At first adamantine derivatives were built by Hyperchem software and some of the descriptors such as surface area, hydration energy, and refractivity were calculated through it. The rest of the descriptors were obtained of Gaussian calculations. A large number of descriptors were calculated by Gaussian package and Hyperchem software. One way to avoid data redundancy is to exclude descriptors that are highly intercorrelated with each other before performing statistical analysis. Reduced multi collinearity and redundancy in the data will facilitate selection of relevant variables and models for the investigated endpoint. Variable-selection for the QSAR modeling was carried out by stepwise linear regression method. A stepwise technique was employed that only one parameter at a time was added to a model and always in the order of most significant to least significant in terms of F-test values. Statistical parameters were calculated subsequently for each step in the process, so the significance of the added parameter could be verified.

Table 2. The calculated descriptors used in this study

Descriptors	Symbol	Abbreviation	Descriptors	Symbol	Abbreviation
Quantum chemical descriptors	Molecular Dipole Moment	MDP	Quantum chemical descriptors	difference between LUMO and HOMO	E_{GAP}
	Molecular Polarizability	MP		Hardness [η=1/2 (HOMO+LUMO)]	H
	Natural Population Analysis	NPA		Softness (S=1/ η)	S
	Electrostatic Potentialc	EP		Electro negativity [χ= -1/2 (HOMO–LUMO)]	*X*
	Highest Occupied Molecular Orbital	HOMO		El Electro philicity ($\omega=\chi^2/2\eta$)	Ω
	Lowest Unoccupied Molecular Orbital	LUMO		MullikenlChargeg	MC
	Partition Coefficient	Log P		Molecule surface area	SA
Chemical properties	Mass	M	Chemical properties	Hydration Energy	HE
	Molecule volume	V		Refractivity	REF

RESULTS AND DISCUSSION

In a QSAR study, generally, the quality of a model is expressed by its fitting ability and prediction ability, and of these the prediction ability is the more important. In order to build and test the model, a data set of 39 compounds was separated into a training set of 33 compounds, which were used to build the model and a test set of 6 compounds, which were applied to test the built model. With the selected descriptors, we have built a linear model using the training set data, and the following equation was obtained:

LogP=0.101(±0.040)σ_5+0.011(±0.004)M+3.836(±0.959)MC $_4$+0.700(±0.070) LogP+0.707(±1.3990)

Q^2=0.713R=0 .927 R^2=0.858

In this equation, N is the number of compounds, R^2 is the squared correlation coefficient, Q^2 isthe squared cross-validation coefficient, and F is the Fisher F statistic. The figures in parentheses are the standard deviations. The built model was used to predict the test set data andthe prediction results are given in Table 1.As can be seen from Table 1, the calculated values for the $LogP_{o/w}$ are in good agreement with those of the experimental values. The predicted values for $LogP_{o/w}$ for the compounds in the training and test sets using equation $LogP_{o/w}$ were plotted against the experimental $LogP_{o/w}$ values in Figure 1.and the comparison between $LogP_{o/w}$ using prediction and the experimental .A plot of the residual for the predicted values of RI for both the training and test sets against the experimental $LogP_{o/w}$ values are shown in Figure 2. As can be seen the model did not show any proportional and systematic error, because the propagation of the residuals on both sides of zero are random. The real usefulness of QSAR models is not just their ability to reproduce known data, verified by their fitting power (R^2), but is mainly their potential for predictive application. For this reason the model calculations were performed by maximising the explained variance in prediction, verified by the cross-validated correlation coefficient,Q^2.This indicates that the obtainedregression model has a good internal and external predictive power.

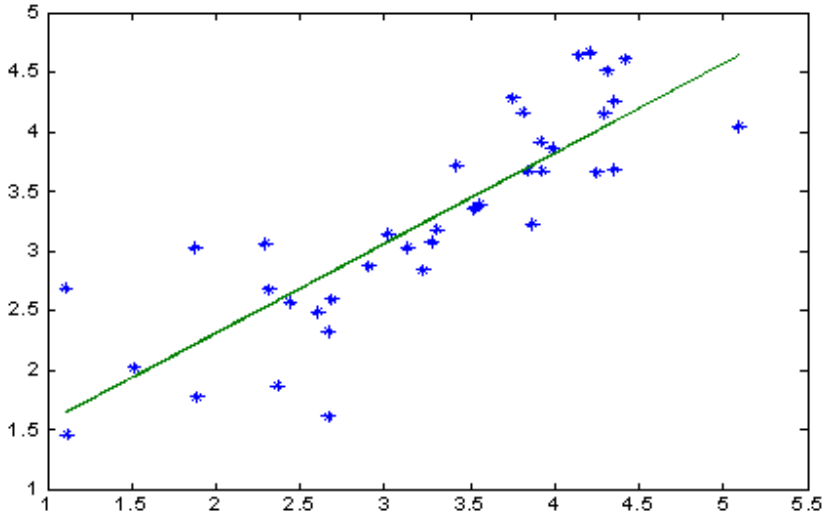


Figure1. The predicted versus the experimental $LogP_{o/w}$ by MLR.

Also, in order to assess the robustness of the model, the chance correlation test was applied in this study. The dependent variable vector ($LogP_{o/w}$) was randomly shuffled and The new QSAR models (after several repetitions) would be expected to have low R^2 and R values (Table 3). If the opposite happens then an acceptable QSAR model cannot be obtained for the specific modeling method and data.

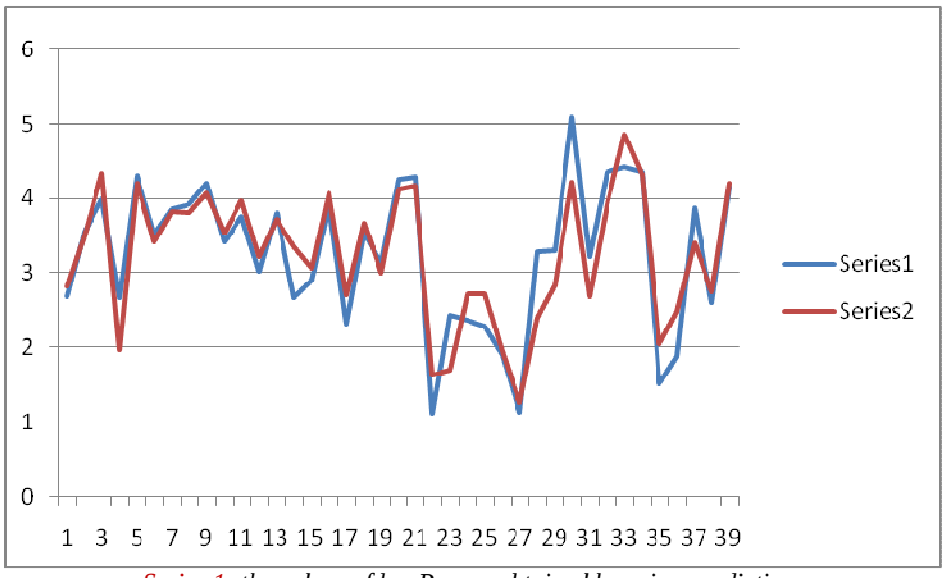
Table 3. The R^2_{train} and R values after several chance correlation tests

N	R	R2
1	0.619	0.384
2	0.467	0.218
3	0.478	0.229
4	0.508	0.258
5	0.525	0.275
6	0.516	0.266
7	0.365	0.113
8	0.663	0.439
9	0.373	0.139
10	0.437	0.191

The MLR analysis was employed to derive the QSAR models for different anti-cancer drugs. MLR and correlation analyses were carried out by the statistics software SPSS (Table 4).

Table 4. The correlation coefficient existing between the variables used in different MLR and equations with B3LYP/6-31+G method.**

	PC	MC_4	LogP	M	σ_5
PC	1	0	0	0	0
MC_4	0.335	1	0	0	0
LogP	0.875	0.163	1	0	0
M	0.322	0.326	0.282	1	0
σ_5	0.292	0.47	0.2	0.159	1



Series 1: the values of log P were obtained by using prediction.
Series 2: the values of log P were obtained by using Experimental methods

Figure 3. The comparison between properties ($LogP_{o/w}$) using experimental and prediction

Interpretation of descriptors

The QSAR developed indicated that Nuclear magnetic Resonance (σ_5), mass (M), Mullikan charge (MC_4) and Partition coefficient (LogP) compound $LogP_{o/w}$. negative values in the regression coefficients indicate that the indicated descriptor contributes positively to the value of $LogP_{o/w}$, whereas positive values indicate that the greater the value of the descriptor the lower the value of $LogP_{o/w}$. In other words, increasingthe σ_5, MandMC_4 will decrease $LogP_{o/w}$and increasing the LogPincreases extent of $LogP_{o/w}$ of the adamantine derivatives. The standardized regression coefficient reveals the significance of an individual descriptor presented in the regression model.

CONCLUSION

In this article, a QSAR study of 38adamantine derivatives. was performed based on the theoretical molecular descriptors calculated by the GAUSSIAN software and selected. The built model was assessed comprehensively (internal and external validation) and all the validations indicated that the QSPR model built was robust and satisfactory, and that the selected descriptors could account for the structural features responsible for the adamantine derivatives properties of the compounds. The QSPR model developed in this study can provide a useful tool to predict the $LogP_{o/w}$ of new compounds and also to design new compounds with high $LogP_{o/w}$.

REFERENCES

[1] Huuskonen J., Salo M., Taskinen J., *J. Pharm. Sci.*, 86, 450—454 (**1997**).
[2] Huuskonen J., Salo M., Taskinen J., *J. Chem. Inf. Comput. Sci.*, 38, 450—456 (**1998**).
[3] Hansch, C.; Fujita, T. *J. Am. Chem. Soc.* **1964**, *86* (8), 1616–1626.
[4] Sammes PG, Taylor JB. Comprehensive Medicinal Chemistry. Oxford: Pergamon Press, **1990**:766.
[5] Riahi S, Pourbasheer E, Dinarvand R, Ganjali MR, Norouzi P. *ChemBiol Drug Des* **2008**;74:165–172.
[6] Riahi S, Pourbasheer E, Ganjali MR, Norouzi P. *J Hazard Mater* **2009**;166:853–859.
[7] Riahi S, Pourbasheer E, Ganjali MR, Norouzi P. *ChemBiol Drug Des* **2009**;73:558–571
[8] Tropsha A, Gramatica P, Gombar VK. *QSAR Comb Sci* **2003**;22:69–77.
[9] Riahi S, Ganjali MR, Norouzi P, Jafari F. *Sens. Actuators* B **2008**; 132: 13–19.
[10] Eriksson L, Johansson E, Muller M, Wold S. *J Chemometr* **2000**; 14: 599–616.
[11] Golbraikh A, Shen M, Xiao Z, Xiao Y-D, Lee K-H, Tropsha A. *J Comput Aided Mol Des* **2003**;17:241–253.
[12] Gramatica P, Pilutti P, Papa E. Validated QSAR prediction of OH tropospheric degradability: splitting into training-test set and consensus modeling. **2004**; 44: 1794–1802
[13] Riahi S, Pourbasheer E, Dinarvand R, Ganjali MR, Norouzi P. *ChemBiol Drug Des* **2008**;74:165–172.
[14] Riahi S, Ganjali MR, E Pourbasheer, Divsar F, Norouzi P, Chaloosi M. *Curr Pharm Anal* **2008**;4:231–237.
[15] Riahi S, Pourbasheer E, Ganjali MR, Norouzi P, ZeraatkarMoghaddam A. *J Chin ChemSoc* **2008**;55:1086–1093.
[16] Riahi S, Pourbasheer E, Dinarvand R, Ganjali MR, Norouzi P. *ChemBiol Drug Des* **2008**;72:205–216.

[17] Riahi S, Pourbasheer E, Dinarvand R, Ganjali MR, Norouzi P. *ChemBiol Drug Des* **2008**;72:575–584
[18] S. V. Kurbatova and S. N. Yashkin, *Journal of Structural Chemistry*, Vol. 41, No. 4, **2000**
[19] K. K. Konstantinova and S. V. Kurbatova, *Russian Journal of Applied Chemistry*, 2006, 79, 8, 1251-1259, **2006**.