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Journal of Chemical and Pharmaceutical Research

J. Chem. Pharm. Res., 2011, 3(1):108-114

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

Physico-chemical parameter prediction from drug structure using multiple linear regression and artificial neural networks

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ABSTRACT

*A set of adamantane derivatives (AD) as drug were tested for their chromatographic behavior and Kovats retention index (RI) were determined for all the compounds. Quantitative structure Property relationship (QSPR) analysis was applied to 32 of the AD.Molecular descriptors derived solely from 3D structures of the molecular compounds. Modeling of RI of AD as a function of the theoretically derived descriptors was established by multiple linear regression (MLR) And artificial neural networks (ANNs) for the prediction of Kovats retention index . The models were constructed using 25 molecules as training set, and predictive ability tested using 7 compounds. The usefulness of the quantum chemical descriptors, calculated at the level of the Density Functional Theory(DFT) theories using 6-31+G** basis set for QSPR study of AD was examined. A multi-parametric equation containing maximum five descriptors at B3LYP/6-31+G** method with good statistical qualities (R^2_{train}=0.914, F_{train}=97.674, R^2_{test}=0.770, F_{test}=3.214, Q2LOO=0.895, R2adj=0.904,Q^2_{LGO}=0.84451) was obtained by Multiple Linear Regression using stepwise method.*

Keywords: Adamantane derivatives, Kovats retention index (RI), MLR, QSPR, ANNs

INTRODUCTION

Adamantane is simplest diamondoid molecule and originally isolated from oil in 1933, is a hydrocarbon ($C_{10}H_{16}$) possessing a rigid but unstressed structure comprising four condensed cyclohexane rings in a chair conformation, in which the carbon atoms have the same spatial arrangement as in the cell of the diamond crystal structure (this structural resemblance explains the name of adamantane, from Greek adamas (adamantos) for diamond).The spatial

configuration of the adamantane molecules has a nearly perfect spherical shape [1]. For this reason, the surface of these molecules is relatively very small. Rigid ring structure prevents liquefaction of the crystalline form, which explains the very high melting point (268°C). Various methods for constructing QSAR/QSPR models have been used including multilinear regression (MLR) and artificial neural networks (ANNs) have become popular due to their success where complex nonlinear relationships exist amongst data, as is often the case when dealing with drug data sets (Turner et al., 2003b). Moreover, the generalization ability of ANNs makes them useful for construction of predictive models. ANNs represent learning tools which are distinctly different from standard statistical methods, and as such are not necessarily bound by the same constraints that linear methods are[2]. A number of theoretical descriptors were generated from the drug structures were used to derive optimal subsets of descriptors for quantitative structure-pharmacokinetic relationship models. Models were trained on one set of compounds and validated with another. Absolute predicted ability was evaluated using a further independent test set of compounds.Correlations between physicochemical properties and chromatographic retention parameters of AD. were studied. Correlations for test compounds ranged from 0.855 to 0.992. Predicted values agreed closely with experimental values for AD. [3-10]

EXPERIMENTAL SECTION

2.1. Experimental data

The ANN technique develops data-driven models, such that known information about drugs from empirical methods does not influence the system. The data set of 32 compounds was divided randomly into a working data set for model construction and a testing set to evaluate the predictive performance of each model[11]. The working set was further divided into a training subset of 25 compounds and a validation subset of 7 compounds used to monitor network performance during training. Final predictive ability was determined using the 7 independent compounds in the testing set. Subsets were all examined statistically to ensure that validation and testing data did not lie outside the limits of the training set . The properties data for the complete set of compounds are presented in Table 1 and 2.To derive QSPR 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 RI for AD training set

Name	EXP.	Pred	Ref.
Adamantane	1118	1131	11
1 3 dimethyl adamantine	1151	1198	11
1-fluoro adamantine	1159	1259	11
2-methylene adamantine	1160	1172	11
1,3,5 -trimethyl adamantine	1163	1226	11
2-methyl adamantine	1196	1219	11
1 2-dimethyl adamantine	1236	1231	11
1-ethyl adamantine	1260	1221	11
2 2-dimethyl adamantine	1269	1274	11
1-ethyl-3,5 di methyl adamantine	1279	1291	11
1-chloroadamantane	1298	1295	11
2-adamantanon	1320	1322	11
2-chloro adamantine	1342	1342	11
1-propyl adamantine	1347	1298	11
2-isopropyl adamantine	1349	1391	11

2-propyl adamantine	1371	1391	11
1-bromo adamantine	1382	1376	11
1-chloromethyladamantane	1404	1367	11
2-isobuthyl adamantine	1416	1383	11
1-buthyl adamantine	1443	1383	11
methyl-(1-adamanthyl) ketone	1443	1407	11
methyl-(2-adamanthyl)ketone	1445	1387	11
2-buthyl adamantine	1465	1416	11
1-bromomethyl adamantine	1488	1494	11
ethyl-(1-adamanthyl)ketone	1529	1491	11

Table 2. Experimental values of RI for AD test set

Name	Exp	Test	Ref.
1-methyladamantane	1137	1148	11
2-ethyl adamantine	1284	1269	11
1-isopropyl adamantine	1358	1284	11
3 5-dimethyl -1-bromo adamantine	1401	1433	11
2-bromoadamantane	1426	1464	11
3-(1-adamanthyl)pentane	1559	1430	11
propyl-(1-adamanthyl) ketone	1609	1538	11

2.2. Descriptors

Presentation of data containing adequately useful information to ANNs is the basis for construction of effective predictive models. 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 QSPR analysis are presented in Table 3.In this work, we used Gaussian 03 for ab initio calculations.DFT method at 6-31+G** were applied for optimization of AD and calculation of many of the descriptors. At first AD were built by Hyperchem software and some o 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.

Table 3. The calculated descriptors used in this study

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

2.3. ANN modeling

The ANN program used was Statistica Neural Networks (StatSoft Inc., 2000). All networks were of the three-layered feed-forward back-propagation (multilayer perceptron) type, containing a bias neuron in each layer and a single neuron in the output layer. Asigmoidal transfer function was employed in all neurons and weight adjustment was performed according to the generalised delta rule (Bourquin et al., 1997). Connection weights were initialised with random values.Models were constructed using the training set of compounds. The validation subset was then used to provide an indication of model performance. All generated descriptors were included in the initial model.Redundant descriptors were then pruned and the system was re-trained. Once optimum models were achieved true predictive ability was assessed using the testing subset of compounds. Both manual and automated methods were employed for descriptor selection. Sensitivity analysis of inputs was used to identify significance of individual molecular descriptors and to select descriptors that were considered the most important. Descriptors with sensitivities lower than one were deemed to be detrimental to the model. The higher the sensitivity above one the greater its influence on the model. Hence, those with lower sensitivities were able to be sequentially removed. The ANN program also utilized regularization and search algorithms for automated descriptor selection.[12-17]

RESULTS AND DISCUSSION

3.1. Data analysis and training

Molecules for this study were selected as follows. Our starting point was 32 AD For each of the selected molecules,geometry optimization was employed and then the descriptors were calculated through Density Functional Theory method at 6-31+G** basis set. MLR and ANN models were constructed in the present work using SPSS and MATLAB softwares. In order to build and test the model, a data set of 32 compounds was separated into a training set of 25 compounds, which were used to build the model and a test set of 7 compounds, which were applied to test the built model. Those descriptors that were too strongly correlated with the others were rejected. The first two QSAR models were derived from using all descriptors and molecules followed by these equations:

$$RI = -4.45754\ (\pm 1.161528)\ \sigma_9\ -80.1305\ (\pm 11.72555)\ \Delta G_{CYCLO+}\ 5.768715\ (\pm 0.292762)\ M - 121.607\ (\pm 42.44063)\ MC_{9+}\ 0.072961\ (\pm 0.015957)\ HF + 177.4361\ (\pm 112.5648)$$

(B3LYP/6-31+G**)

R^2_{train}=0.914 F_{train}=97.674 R^2_{test}=0.770 F_{test} = 3.214 R^2_{adj}=0.904

Q^2_{LOO}=0.895 Q^2_{LGO}= 0.84451 N_{train}= 25 N_{test} = 7

In this equation, N is the number of compounds, R^2 is the squared correlation coefficient, Q^2_{LOO} and Q^2_{LGO} are the squared cross-validation coefficients for leave one out, bootstrapping and external test set respectively, RMSE is the root mean square error and F is the Fisher F statistic. The predicted values for RI for the compounds in the training and test sets using equation RI were plotted against the experimental RI values in Figure 1.and the comparison between Retention Index 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 RI values are shown in Figure 2.

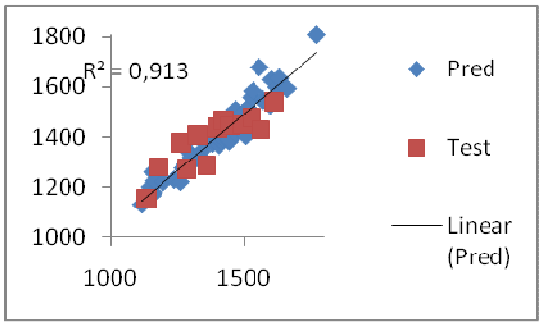


Figure1. The predicted versus the experimental RI by MLR.

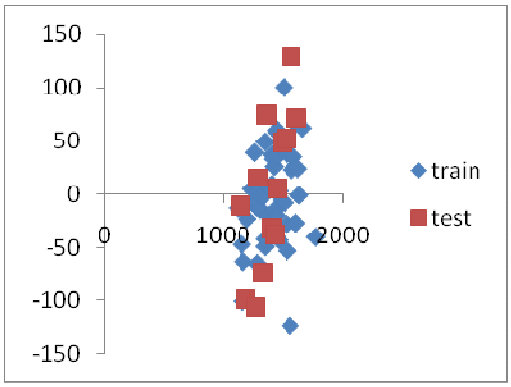


Figure 2. The residual versus the experimental RI by GA-MLR.
(See colour version of this figure online at www.informahealthcare.com/enz)

3.2. Training and validation

in this study to assess the robustness of the model, the Y-randomisation test was applied. The dependent variable vector (RI) was randomly shuffled and The new QSPR models (after several repetitions) would be expected to have low R^2 and Q^2_{LOO} values (Table 4). If the opposite happens then an acceptable QSPR model cannot be obtained for the specific modeling method and data.

Table 4. The R^2_{train} and Q^2_{LOO} values after several Y-randomisation tests

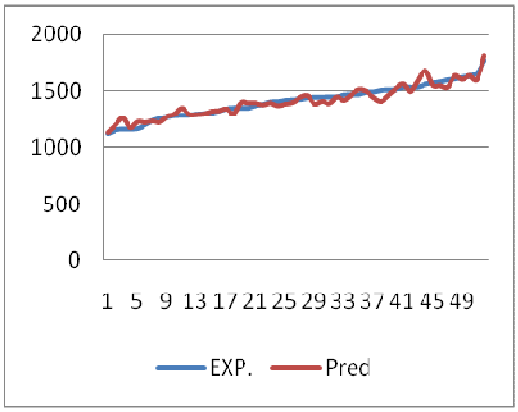
NO	Q^2	R^2
1	0.1045	0.0312
2	0.00002	0.0976
3	0.0939	0.0614
4	0.0042	0.1282
5	0.0457	0.0570
6	0.0340	0.1927
7	0.0060	0.1442
8	0.2991	0.0125
9	0.0175	0.1700
10	0.0251	0.0608

The MLR analysis was employed to derive the QSPR models for different AD. MLR and correlation analyses were carried out by the statistics software SPSS (Table 5).

Table5. The correlation coefficient existing between the variables used in different MLR and equations with b3lyp/6-31+G method**

	HF	MC_9	M	ΔG_{CYCLO}	σ_9
HF	1	0	0	0	0
MC_9	0.048869	1	0	0	0
M	0.39506	0.245901	1	0	0
ΔG_{CYCLO}	0.099875	0.22142	0.226936	1	0
σ_9	0.17506	0.485565	0.070032	0.04617	1

Figure 3 has showed that results were obtained from equation B3LYP/6-31+G** to the experimental values.



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

Figure 3. The comparison between properties (RI) using experimental and prediction.

CONCLUSION

The QSPR developed indicated that *Nuclear magnetic Resonance* (σ_9), free energy solvation (ΔG_{CYCLO}), Mulliken atomic charges (MC_9) and Hartee-fuck energy (HF)compound Kovats retention index. Positive values in the regression coefficients indicate that the indicated descriptor contributes positively to the value of RI, whereas negative values indicate that the greater the value of the descriptor the lower the value of RI. In other words, increasing the σ_9, ΔG_{CYCLO} and MC_9 will decrease RI and increasing the HF and M increases extent of RI of the AD. The standardized regression coefficient reveals the significance of an individual descriptor presented in the regression model.The results showed that b3ly /6-31+G** method provides results close to experimental values . The QSPR model developed in this study can provide a useful tool to predict the RI of new compounds and also to design new compounds with high RI.

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