Estimation of the volume of distribution of some pharmacologically important compounds from their structural descriptors

MOHAMMAD H. FATEMI* and ZAHRA GHORBANNEZHAD

Chemometrics Laboratory, Faculty of Chemistry, University of Mazandaran, Babolsar, Iran

Abstract: Quantitative structure–activity relationship (QSAR) approaches were used to estimate the volume of distribution (V_d) using an artificial neural network (ANN). The data set consisted of the volume of distribution of 129 pharmacologically important compounds, *i.e.*, benzodiazepines, barbiturates, nonsteroidal anti-inflammatory drugs (NSAIDs), tricyclic anti-depressants and some antibiotics, such as betalactams, tetracyclines and quinolones. The descriptors, which were selected by stepwise variable selection methods, were: the Moriguchi octanol–water partition coefficient; the 3D-MoRSE-signal 30, weighted by atomic van der Waals volumes; the fragment-based polar surface area; the d COMMA2 value, weighted by atomic masses; the Geary autocorrelation, weighted by the atomic Sanderson electronegativities; the 3D-MoRSE – signal 02, weighted by atomic masses, and the Geary autocorrelation – lag 5, weighted by the atomic van der Waals volumes. These descriptors were used as inputs for developing multiple linear regressions (MLR) and artificial neural network models as linear and non-linear feature mapping techniques, respectively. The standard errors in the estimation of V_d by the MLR model were: 0.104, 0.103 and 0.076 and for the ANN model: 0.029, 0.087 and 0.082 for the training, internal and external validation test, respectively. The robustness of these models were also evaluated by the leave-5-out cross validation procedure, that gives the statistics $Q^2 = 0.72$ for the MLR model and $Q^2 = 0.82$ for the ANN model. Moreover, the results of the *Y*-randomization test revealed that there were no chance correlations among the data matrix. In conclusion, the results of this study indicate the applicability of the estimation of the V_d value of drugs from their structural molecular descriptors. Furthermore, the statistics of the developed models indicate the superiority of the ANN over the MLR model.

Keywords: quantitative structure–activity relationship; molecular descriptor; volume of distribution; artificial neural network.

INTRODUCTION

The volume of distribution (V_d) of a drug is a major pharmacokinetic property that determines the drug half life and affects the dosing regimen. This parameter is simply a proportionality constant which relates to the amount of drug in the body and/or compartment of the body to its plasma concentration and can represent a measure of the relative partitioning of drug between plasma (the central compartment) and the tissues.[1] The concentration of drug in the plasma or tissues depends on the amount of systemically absorbed drug and the volume in which the drug is distributed as well as the clearance (Cl). The clearance of a drug is the volume of plasma from which the drug is completely removed per unit time. The amount of eliminated drug depends on the concentration of the drug in the blood. The fraction of the drug in the body eliminated per unit time is showed by the elimination constant (k_{el}). The volume of distribution is calculated from these two parameters using the following equation:

$$V_d = Cl / k_{el} \tag{1}$$

The volume of distribution in humans is traditionally estimated from *in vivo* data from preclinical animals with appropriate scaling to man, which is a slow, labor intensive and costly process.[2] Moreover, low rates of throughput provide detailed and informative data at the expense of animal usage.[3] Therefore *in silico* estimation methods, such as quantitative structure–activity relationships (QSAR) can be used as an alternative to animal scaling to predict V_d.[4,5] A quantitative structure activity relationship model describes a mathematical relationship between a structural attribute (*s*) and the activity of a set of chemicals. The use of such mathematical relationships to predict the target property of interest for a variety of chemicals prior to or *in lieu* of expensive and labor-intensive experimental measurements has naturally been very enticing. The potential promise of using QSAR models for the screening of chemical databases or virtual libraries before their synthesis appears equally attractive to chemical manufacturers, pharmaceutical companies and government agencies, particularly in times of shrinking resources.[6] There are some reports concerning the prediction of the volume of distribution of chemicals.[7,8] For example, Hirono and coworkers studied the correlation of chemical structures with the volume of distribution of some aromatic, non-aromatic and hetero-aromatics medicines, to construct an expert system for predicting the pharmacokinetic properties of organic chemicals using fuzzy adaptive least-squares.[7] Artificial neural networks for the prediction of the human pharmacokinetic parameters of some drugs using a combination of physico-chemical properties and animal pharmacokinetic parameters were used by Ritschel *et al.*[9] Protein binding, partition coefficients, dissociation constants, total clearance (Cl_{tot}) and volume of distribution (V_d) in rat and dog species of 41 drugs were evaluated for the prediction of human total clearance and volume of

distribution by these researchers. Their results indicated that drugs with partition (log P) < 1.17 showed predictability of 63.41 % for Cl_{tot} and 48.78 % for V_d, while drugs with low protein binding (approximately 20 %) showed a predictability of 19.51 % for Cl_{tot} and 41.46 % for V_d. Comparison of these results with an *in vitro* estimation showed no bias in the prediction of either clearance (p < 0.2) or volume of distribution (p < 0.5). In another study, a quantitative structure–pharmacokinetic relationship model to predict some pharmacokinetic properties of a cephalosporins series was developed by J. V Turner *et al.*[10] Moreover, F. Lombardo and co-workers published some reports about the prediction of human volume of distribution values for neutral and basic drugs using physico–chemical measurements and protein binding data.[11] Finally, Ghafourian and co-workers reported a QSAR model for the prediction of V_d of some acidic and basic drugs using a universal 7-parameter MLR model.[4] In their model, the obtained correlation coefficient between the observed and predicted V_d values for the test set was $R^2_{pred} = 0.699$. They concluded that this QSAR model was able to predict the volume of distribution of drugs belonging to different chemical classes with a prediction error similar to that of other more complicated prediction methods, including the commonly practiced interspecies scaling. In the present work, this model was improved by using an ANN as a nonlinear feature mapping technique.

METHODOLOGY

Data set

The experimental values of distribution for 129 drugs were extracted from the literature,[4] and reported as log V_d, they are listed in Table I-S (Supplementary material). These drugs are benzodiazepines, barbiturates, NSAIDs, tricyclic anti-depressants and some antibiotics, such as betalactams, tetracyclines and quinolones. The distribution of the experimental log V_d values of data set is shown in Fig. 1.

The data set was randomly divided into training, internal and external test sets that had 103, 13 and 13 members, respectively. The training set was used to develop the model, the internal test set was used to prevent over training and the external test set was used to evaluate the predictive ability of the obtained model.

Descriptor generation and screening

One important step in obtaining a QSAR model is the numerical representation of the structural features of molecules (molecular descriptors). The molecular descriptors used to search for the best model of log V_d were calculated by the Dragon program[12] based on the minimum energy molecular geometries that were optimized by the Hyperchem package (version 7.0) (HyperChem 2002, release 7.0) based on the AM1 semi-empirical method.[13] After calculation of the molecular descriptors, those that were constant or near constant for all molecules were eliminated and pairs of variables with a correlation coefficient greater than 0.90 were classified as inter-correlated and one of each correlated pair was deleted. Then, the stepwise multiple linear regression variable subset selection method[14] was used for the selection of the most relevant descriptors from the pool of the remaining descriptors. These descriptors were used as inputs for the construction of the ANN and MLR models.
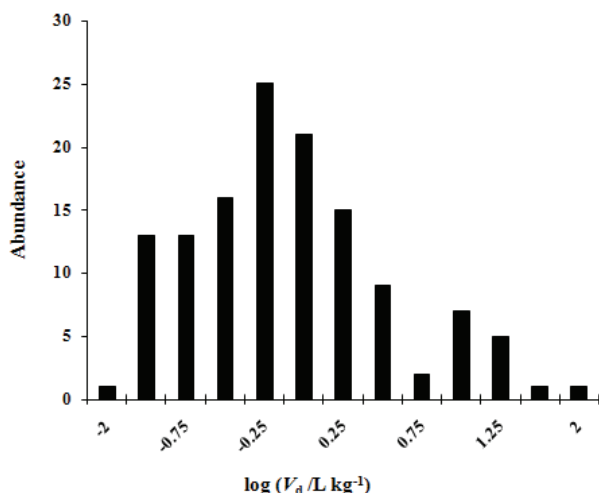
Fig. 1. The distribution of the experimental log V_d values.

Molecular diversity analysis

Diversity analysis was performed on the data set to ensure that the structures of the training or test sets can represent those of the whole ones.[15] A database of n compounds generated from m highly correlated chemical descriptors $\{x_j\}_{j=1}^{m}$ was considered. Each compound, X_i, is represented as a vector of:

$$X_i = (x_{i1}, x_{i2}, x_{i3}, ..., x_{im}) \quad \text{for} \quad i = 1, 2, L, n \tag{2}$$

In the above equation, $x_{i,j}$ denotes the value of descriptor j of compound X_i. The collective database $\left(X = \{X_i\}_{i=1}^{N}\right)$ is represented by an $n \times m$ matrix (X) as follows:

$$X = (x_1, x_2, L, X_N)^T = \begin{bmatrix} x_{11} & x_{12} & \cdots & x_{1m} \\ x_{21} & x_{22} & \ddots & x_{2m} \\ \vdots & \vdots & \ddots & \cdots \\ x_{m1} & x_{m2} & \cdots & x_{nm} \end{bmatrix} \tag{3}$$

Here the superscript T denotes the vector/matrix transpose. A distance score for two different compounds X_i and X_j can be measured by the Euclidean distance norm d_{ij}, based on the compound descriptors:

$$d_{ij} = \|X_i - X_j\| = \sqrt{\sum_{k=1}^{m} (x_{ik} - x_{jk})^2} \tag{4}$$

The relative mean distances $\left(\bar{d}_i\right)$ of one sample to the remaining ones were computed as follow:

$$\bar{d}_i = \frac{\sum_{j=1}^{n} d_{ij}}{n-1} \quad i = 1, 2, ..., n \tag{5}$$

Then the relative mean distances were normalized within the interval (0,1). The values of the relative mean distances of samples *versus* the experimental log V_d are plotted in Fig. 2. The results of this test illustrate the good distribution of the test sets among the whole data set. The training set with a broad representation of the chemistry space was adequate to ensure models stability and the diversity of the test set can prove the predictive capability of the model.
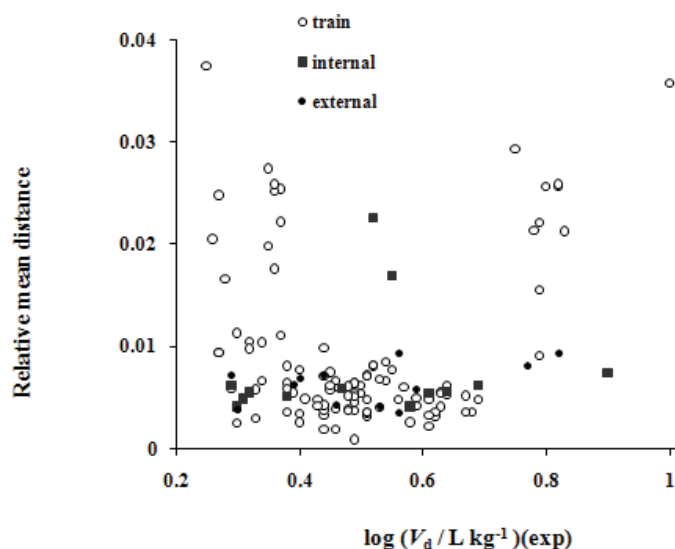
Fig. 2. The results of the diversity analysis (the relative mean distance
was calculated from Eq. (5)).

Nonlinear modeling

In order to examine any non-linear relationships between selected molecular descriptors and the volume of distribution, an artificial neural network was used. A detailed description of theory behind artificial neural networks has been adequately described elsewhere.[16–19] In addition, some relevant principles of ANNs were reported in previous papers.[20–22] ANNs are parallel computational devices consisting of groups of highly inter-connected processing elements called neurons. Neurons in traditional neural networks are arranged in a series of layers. The first layer is termed the input layer; each neuron in this layer receives information from the exterior, corresponding to the independent variables (molecular descriptors). The last layer is the output layer, and its neurons handle the output from the network, which is log V_d in this study. The layers of neurons between the input and output layers are called hidden layers. The number of neurons in these layers is optimized during model development.[23] In the first step of developing an ANN model, the program of a feed-forward neural network, which was trained by a back-propagation algorithm, was written in Matlab (ver. 7.4.0). This network had seven nodes in the input layer and one node in the output layer. The initial weights were selected from a uniform distribution of numbers that ranged between –0.3 and 0.3. The initial bias values were set to be one. These values were optimized during the network training. The value of each input was divided into its mean value to bring them into the dynamic range of the sigmoid transfer function of an ANN. Before training, the network parameters were optimized. These parameters were: number of nodes in the hidden layer, weights and biases learning rates and the momentum. Then the optimized network was trained using a training set for adjustment of the values of the weights and biases.

RESULTS AND DISCUSSION

The descriptors which were selected by the stepwise variable selection method are: the Moriguchi octanol–water partition coefficient (*M*log *P*); the 3D-

-MoRSE – signal 30, weighted by atomic van der Waals volumes (Mor30v); the fragment-based polar surface area (PSA); the d COMMA2 value, weighted by atomic masses (DISPm); the Geary autocorrelation, weighted by the atomic Sanderson electronegativities (GATS2e); the 3D-MoRSE – signal 02, weighted by atomic masses (Mor02m) and the Geary autocorrelation – lag 5, weighted by atomic van der Waals volumes (GATS5v). These descriptors encode different aspects of the molecular structure and were applied to construct the MLR and ANN models. Detailed explanations about these descriptors can be found in the Hand–book of Molecular Descriptors.[12] Table I represents the correlation between these descriptors. As can be seen from this table, there were no high correlations between these descriptors.

TABLE I. Correlation matrix between the selected descriptors

	Mlog P	Mor30v	PSA	DISPm	GATS2e	GATS5v	Mor02m
Mlog P	1	0.174	–0.558	0.25	0.232	0.222	–0.306
Mor30v		1	–0.216	0.026	0.264	0.131	0.182
PSA			1	–0.248	–0.387	–0.087	–0.145
DISPm				1	0.038	–0.039	–0.145
GATS2e					1	0.088	0.037
GATS5v						1	–0.123
Mor02m							1

In the case of the MLR models, good correlations with the experimental volume of distribution were selected based on the correlation coefficient (R), the Fisher criterion (F) and the standard error of regression (SE) of the models. The specifications of the selected MLR model are shown in Table II. The standard error (SE), average error (AE) and average absolute error (AAE) in the calculation of log V_d by this model for the training set are: $SE = 0.420$, $AE = 0.003$ and $AAE = 0.310$; for internal test set, they are: $SE = 0.430$, $AE = 0.066$ $AAE = 0.342$ and for external test set, are: $SE = 0.085$, $AE = 0.00$, $AAE = 0.082$.

Moreover, an artificial neural network was applied to further examine any non-linear relations between selected molecular descriptors and the volume of distribution. Before training the network, the parameters of the number of nodes in the hidden layer, weights and biases learning rates and momentum values were optimized. The architecture and the specification of the optimized neural network are given in Table III. After optimization, the network was trained by using the training set for the adjustment of the values of the weights and biases. To maintain the predictive power of the network at a desirable level, training was stopped when the value of error for the internal test set started to increase. Since the test error is not a good estimate of the generation error, the prediction potential of the model was evaluated on a third set of data, named the external test set. Then the trained network was applied to calculate the values of V_d for the

internal and external test sets. The statistics of this model in the estimation of V_d were: $SE = 0.119$, $AE = 0.00$ and $AAE = 0.082$ for the training set; $SE = 0.439$, $AE = 0.100$ and $AAE = 0.363$ for the internal test set and $SE = 0.078$, $AE = 0.005$ and $AAE = 0.060$, for the external test set.

TABLE II. Specification of the MLR model

Descriptors	Notation	Coefficient	SE	t-value	p-value
Moriguchi octanol–water partition coefficient	Mlog P	0.298	0.072	4.131	0.000
3D-MoRSE- signal 30, weighted by atomic van der Waals volumes	$Mor30v$	–0.273	0.069	–3.982	0.000
Fragment-based polar surface area	PSA	–0.212	0.067	–3.161	0.002
d COMMA2 value, weighted by atomic masses	$DISPm$	0.154	0.057	2.718	0.008
Geary autocorrelation, weighted by atomic Sanderson electronegativities	GATS2e	0.260	0.067	3.884	0.000
Geary autocorrelation – lag 5, weighted by atomic van der Waals volumes	$GATS5v$	0.169	0.081	2.095	0.039
3D-MoRSE - signal 02, weighted by atomic masses	$Mor02m$	0.150	0.066	2.260	0.026
Constant	–	0.190	0.087	2.186	0.031

TABLE III. Architecture and specifications of the ANN model

Transfer function	Sigmoid
No. of hidden layer nodes	8
Weight learning rate	0.8
Bias learning rate	0.7
Momentum	0.2
No. of input layer nodes	7
No. of output layer nodes	1

In order to evaluate the robustness of the developed models, cross-validation was employed.[24] The obtained statistical parameters of the leave-5-out cross-validation test were: $Q^2 = 0.72$ for the MLR model and $Q^2 = 0.82$ for the ANN model. In addition, the Y-scrambling procedure was performed to investigate any chance correlations between V_d and selected molecular descriptors.[25] The obtained mean value of R^2 after a 30-time scrambling of the data set and modeling was 0.09, which indicates that there were no chance correlations in the data matrix.

Plots of the ANN calculated *versus* the experimental values of log V_d for the training, internal and external test sets are shown in Fig. 3, which represent good correlations between these parameter. In addition, the residuals of the calculated V_d values are plotted against their experimental values in Fig. 4. Random propagation of the residuals on both sides of the zero line indicates that no systematic error exists in the developed ANN model. In order to compute the relative importance of each input variable on the output of the neural network,[26] sensitivity

analysis was used. This test was performed based on the sequential removal of variables by zeroing the specific connection weights for an input variable in the first layer of the established ANN model. According to this method, the differences between the root-mean-square error (*RMSE*) of the complete prediction of the network and the *RMSE* obtained when the ith variable was excluded from the trained network ($RMSE_i$) were calculated and are shown as $Rmdiff_i$ (Eq. (6)).
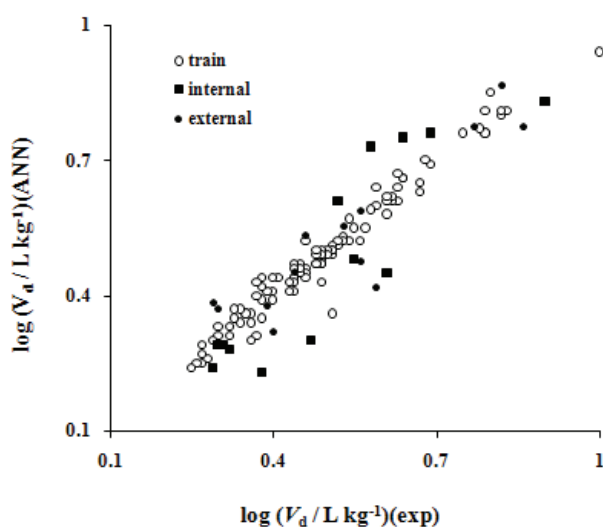
$$Rmdiff_i = RMSE_i - RMS \tag{6}$$

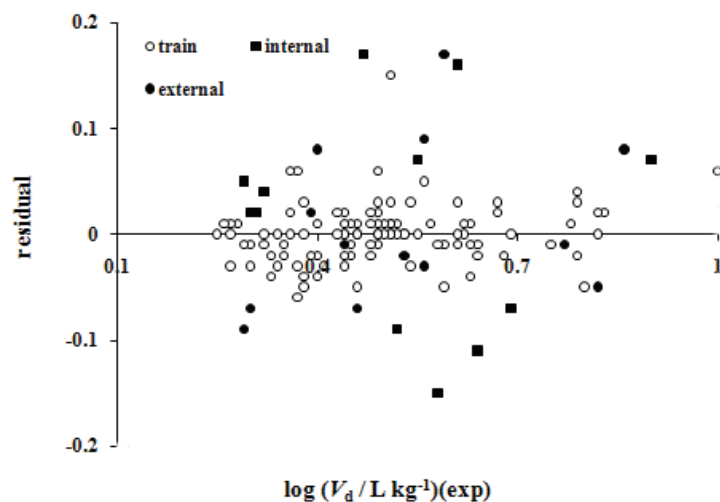Fig. 3. The plot of the ANN calculated *versus* the experimental values of log V_d.

Fig. 4. The plot of the residuals (log $V_{d,ANN}$ – log $V_{d,exp}$) *versus* the experimental values of log V_d.

It is obvious that the most important variable is the one that leads to the highest value of $Rmdiff_i$. The values of $Rmdiff_i$ for the ANN model were calculated and are plotted in Fig. 5. As can be seen in this figure, the order of importance of the selected molecular descriptors was; Mlog P > $Mor30v$ > GATS2e > $GATS5v$ > PSA ≈ $DISPm$ > $Mor02m$.
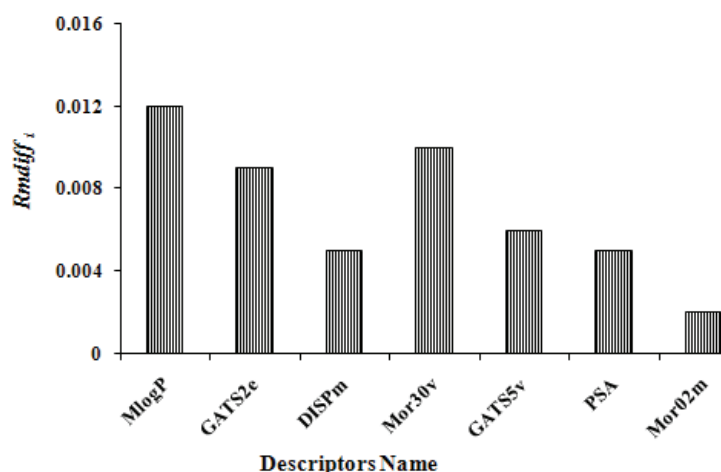

Fig. 5. The results of the sensitivity analysis ($Rmdiff_i$ was calculated from Eq. (6)).

According to this analysis, the most important descriptor in the model was Mlog P, which is a popular and traditional descriptor used in many QSAR models.[12] Mlog P describes the solute lipophilicity, which is one of the most important properties of any compound and indicates the ability of a solute to penetrate to lipid-rich zones from aqueous solutions. This is a very important feature of any drug that is administrated orally and is supposed to pass the gastrointestinal epithelium. Another variable is DISPm, which is a molecular geometry descriptor and was obtained using the Dragon software and describes the conformational features of the molecules. Low values of DISPm are expected for more rigid molecules that exhibit higher passivity due to the absence of long and flexible substituents and the presence of unsaturated bonds. The molecular polar surface area (PSA) encodes the sum of the surface belonging to polar atoms in a molecule; it is a descriptor that was affected on molecular transportation through membranes and therefore, allows an estimation of the apparent volume of distribution in the body. Another of the descriptors is the Geary autocorrelation-lag 2 weighted by atomic Sanderson electronegativities, which belongs to the GATSd family of 2D autocorrelation descriptors.[27,28] Generally, the 2D-autocorrelation descriptors explain how the values of certain functions, at intervals equal to the lag d, are correlated. In these descriptors, the lag is the topological distance and the atomic properties are the functions correlated. These descriptors can be ob-

tained by summing the products of certain properties of two atoms, which are located at a given topological distance or spatial lag. In general, they describe how the considered property is distributed along the topological structure. The value of GATS2e shows the dispersion of electronegative atoms at a topological distance equal to 2 bonds in a molecule and also the value of GATS5v shows the dispersion of volume atoms at a topological distance equal to 5 bonds in a molecule. The remaining descriptors are *Mor02m* and Mor30v. These descriptors are defined based on the idea of obtaining information from the 3D atomic coordinates by the transform used in electron diffraction studies for preparing theoretical scattering curves.[29] A generalized scattering function, called the molecular transform, can be used as the functional basis for deriving from a known molecular structure, the specific analytic relationship of both X-ray and electron diffraction. These descriptors can encode the mass-distribution around the center of a molecule. In general, the descriptors that appeared in these QSAR models can encode different electronic, steric and lipophilic aspects of the molecules, which can affect the volume of distribution of drugs.

The fold errors (*FE*) in the prediction for the obtained QSAR models were calculated from the following equation:

$$FE = \text{antilog} \left(|\log V_{d,obs} - \log V_{d,pred}| \right) \qquad (7)$$

The calculated mean fold errors (*MFE*) for the training, internal and external test sets were 1.23, 2.5 and 1.92, respectively for the ANN model. In addition, as mentioned earlier, Ghafourian *et al*. used QSAR approaches on the same data set and obtained the statistics $MFE = 2.11$ and $R^2 = 0.699$ in a leave-32-out cross validation test for their best 7-parameter model (on elimination of 4 molecules as outlier). The results of the same test on the herein presented ANN model gives the statistics of $MFE = 1.17$ and $R^2 = 0.850$, without any elimination of outlier molecules. Comparisons between these results indicate the superiority of the present model over their model.

CONCLUSIONS

The results of this study indicate that it was possible to estimate the volume of distribution of drugs from their theoretically derived molecular descriptors. Since these descriptors encode electronic and topological features of molecules, it was concluded that lipophilicity and steric interactions affect the V_d of drugs. Moreover, the superiority of the ANN over the MLR model revealed that there are some nonlinear relationships between the volume of distribution and selected molecular descriptors.

SUPPLEMENTARY MATERIAL

Data set and the corresponding observed values as well as MLR and ANN calculated values of V_d are available electronically at http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

И З В О Д

ПРОЦЕНА ЗАПРЕМИНСКЕ РАСПОДЕЛЕ НЕКИХ ФАРМАКОЛОШКИ ВАЖНИХ ЈЕДИЊЕЊА НА ОСНОВУ ЊИХОВИХ СТРУКТУРНИХ ДЕСКРИПТОРА

MOHAMMAD H. FATEMI и ZAHRA GHORBANNEZHAD

Faculty of Chemistry, University of Mazandaran, Babolsar, Iran

Применом вештачких неуралних мрежа (ANN) нађене су квантитативне релације између структуре и активности (QSAR) за процену запреминске расподеле (V_d). Подаци се састоје из запреминске расподеле за 129 фармаколошки важних једињења: бензодиазепина, барбитурата, NSAID-а, трицикличних антидепресива и неких антибиотика, као што су бета-лактами, тетрациклини и хинолони. Дескриптори су Moriguchi-јев коефицијент расподеле октанол–вода, 3D-MoRSE сигнал, величина поларне површине засноване на фрагментима, вредности d COMMA2, Geary-јева аутокорелација, 3D-MoRSE сигнал 02, и др. Ови дескриптори су употребљени као улазни подаци за добијање мултилинеарних регресија (MLR) и за моделе вештачких неуралних мрежа. Стандардне грешке код процене V_d помоћу MLR модела су: 0,104; 0,103 и 0,076, док су за ANN моделе: 0,029; 0,087 и 0,082 за тренинг, интерни и екстерни валидациони тест. Робустност ових модела је такође процењена, што даје $Q^2 = 0,72$ за MLR модел и $Q^2 = 0,82$ за ANN модел. Статистичка анализа указује на то да је ANN модел бољи од MLR модела.

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