Orbital: The Electronic Journal of Chemistry
journal homepage: www.orbital.ufms.br
ISSN 1984-6428

| Vol 7 | | No. 2 | | April-June 2015 |

Full Paper

QSAR Studies of Toxicity Towards Monocytes with (1,3-benzothiazol-2-yl) amino-9-(10H)-acridinone Derivatives Using Electronic Descriptors

Samir Chtita[a], Majdouline Larif[b], Mounir Ghamali[a], Mohammed Bouachrine[c], and Tahar Lakhlifi[a*]

[a]*MCNSL, Faculty of Science, University Moulay Ismail, Meknes, Morocco.*
[b]*Separation Process Laboratory, Faculty of Science, University Ibn Tofail, Kenitra, Morocco.*
[c]*ESTM, University Moulay Ismail, Meknes, Morocco.*

Article history: Received: 24 November 2014; revised: 17 March 2015; accepted: 09 April 2015. Available online: 29 June 2015. DOI: http://dx.doi.org/10.17807/orbital.v7i2.677

Abstract: DFT-B3LYP method, with the basis set 6-31G (d), was employed to calculate nine quantum chemical descriptors of 16 acridin-9-(10H)-ones substituted with amino or (1,3-benzothiazol-2-yl)-amino groups compounds. The above descriptors were used to establish a Quantitative Structure Activity Relationship (QSAR) of the Anti-proliferative towards human monocytes activity of these compounds by Multiple Linear Regression (MLR), Multiple Non Linear Regression (MNLR) and Artificial Neural Network (ANN). The statistical results indicate that the correlation coefficients R were 0.864, 0.908 and 0.844 respectively. Results showed that the three modeling methods can provide a good prediction of the studied activity and may be useful for predicting the bioactivity of new compounds of similar class, and showed that the Multiple Non Linear Regression (MNLR) results have substantially better predictive capability than the MLR and ANN. The statistical results indicate that the models are statistically significant and show very good stability towards data variation in leave one out cross validation.

Keywords: acridinone; anti-proliferative; QSAR; DFT; MLR

1. INTRODUCTION

Acridines family includes a wide range of tricyclic molecules with various biological properties and consists of a nitrogen atom (N-atom) in its heterocyclic nucleus. Natural and synthetic compounds of the acridine family have shown a broad spectrum of biological activities including anti-leishmanial, anti-microbial [1, 2], anti-oxidant [3], anti-malarial [4], anti-inflammatory [5], analgesic [6], anti-parasitic [7], anti-tumoral [8], anti-bacterial or anti-cancer chemotherapy [9-12] and so forth.

First employed as anti-bacterial agents during the beginning of the twentieth century [13], they have rapidly revealed interesting anti-proliferative activities against both protozoa and tumor cells [7-8]. As a consequence, they have been extensively used in anti-parasitic chemotherapy and a wide range of new numerous acridines derivatives have been synthesized and successfully assessed for their anti-leishmanial properties [1, 14].

In order to assess the specificity of chemical compounds for leishmanial parasites, Florence Delmas et al. have previously reported the anti-proliferative towards human monocytes activity of sixteen acridin-9-(10H)-ones substituted with amino or (1,3-benzothiazol-2-yl)-amino groups compounds [15].

Quantitative structure–activity relationship (QSAR) methodology is an essential tool in medicinal chemistry [16]. It's based on the hypothesis that the activity (or effect or property) can be put in relationship with the chemical parameters (descriptors). It's also utilized to predict the same activities of the compounds not involved in the training set from their structural descriptors. Whether the activities can be predicted with satisfactory accuracy depends to a great extent on the performance of the applied multivariate data analysis method, provided the property being predicted is related to the

*Corresponding author. E-mail: tahar.lakhlifi@yahoo.fr

descriptors. Many multivariate data analysis methods such as multiple linear regression (MLR), multiple non-linear regressions (MNLR) and artificial neural network (ANN) have been used in QSAR studies.

In the current study, we develop QSARs linear and non-linear models able to correlate the structural features of acridin-9-(10H)-ones derivatives with their toxicity towards monocytes activity.

Leave-one-out is an approach particularly well adapted to the estimation of that ability. In this procedure, one compound is removed from the data set; the model is trained with the remaining compounds and used to predict the discarded compound. The process is repeated in turn for each compound in the data set. In this paper the leave-one-out cross validation procedure was used to evaluate the predictive ability of the proposed models.

2. MATERIAL AND METHODS

Experimental data set

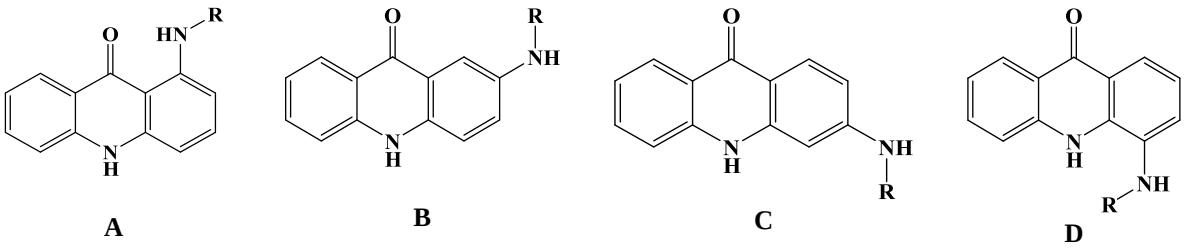
The purpose of the present study was to perform quantitative structure-activity relationship (QSAR) determinations of a series of sixteen compounds based on (1,3-benzothiazol-2-yl) amino-9-(10H)-acridinone (shown Figure 1) that have been synthesized and evaluated for their toxicity towards monocytes IC_{50} (concentration of acridine compounds responsible for a 50% decrease of monocyte growth), as demonstrated by Florence Delmas et al. [15], using density functional theory (DFT) and time-dependent density functional theory (TD/DFT) methods. All experimental IC_{50} values (µM) were converted to Log (IC_{50})). The studied activities are presented in Table 1.

Figure 2 depicts the optimized geometries obtained by B3LYP functional employing 6–31G (d) basis set of the studied molecules.

The findings of the optimized structures show that they have similar conformations (quasi-planar conformation). It's also found that the modification of several groups attached to the acridinone does not change the geometric parameters.

Molecular descriptor generation

In this work, all calculation of the studied compounds were carried out with the Gaussian 09 program package [17] on an Acer i5 3.3 GHz PC running Windows 7 supported by Gauss View 5.0.8 [18]. These methods are widely used because they can lead to similar precision to other methods and because they are also less demanding and time-saving from the computational point of view. Using the B3LYP functional [Becke's three-parameter functional (B3) and includes a mixture of HF with DFT exchange terms associated with the gradient corrected correlation functional of Lee, Yang and Parr (LYP)] exchange correlation functional [19, 20]. The 6-31G (d) basis set was chosen as a compromise between the quality of the theoretical approach and the high computational cost associated with the high number of dimensions to the problem for all atoms [21, 22].



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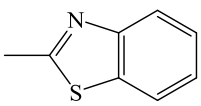
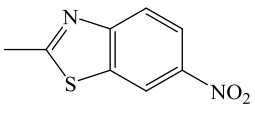
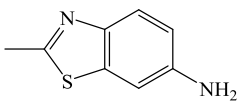
R	H			

Figure 1. Chemical structure of studied compounds A (1-4), B (1-4), C (1-4) and D (1-4).

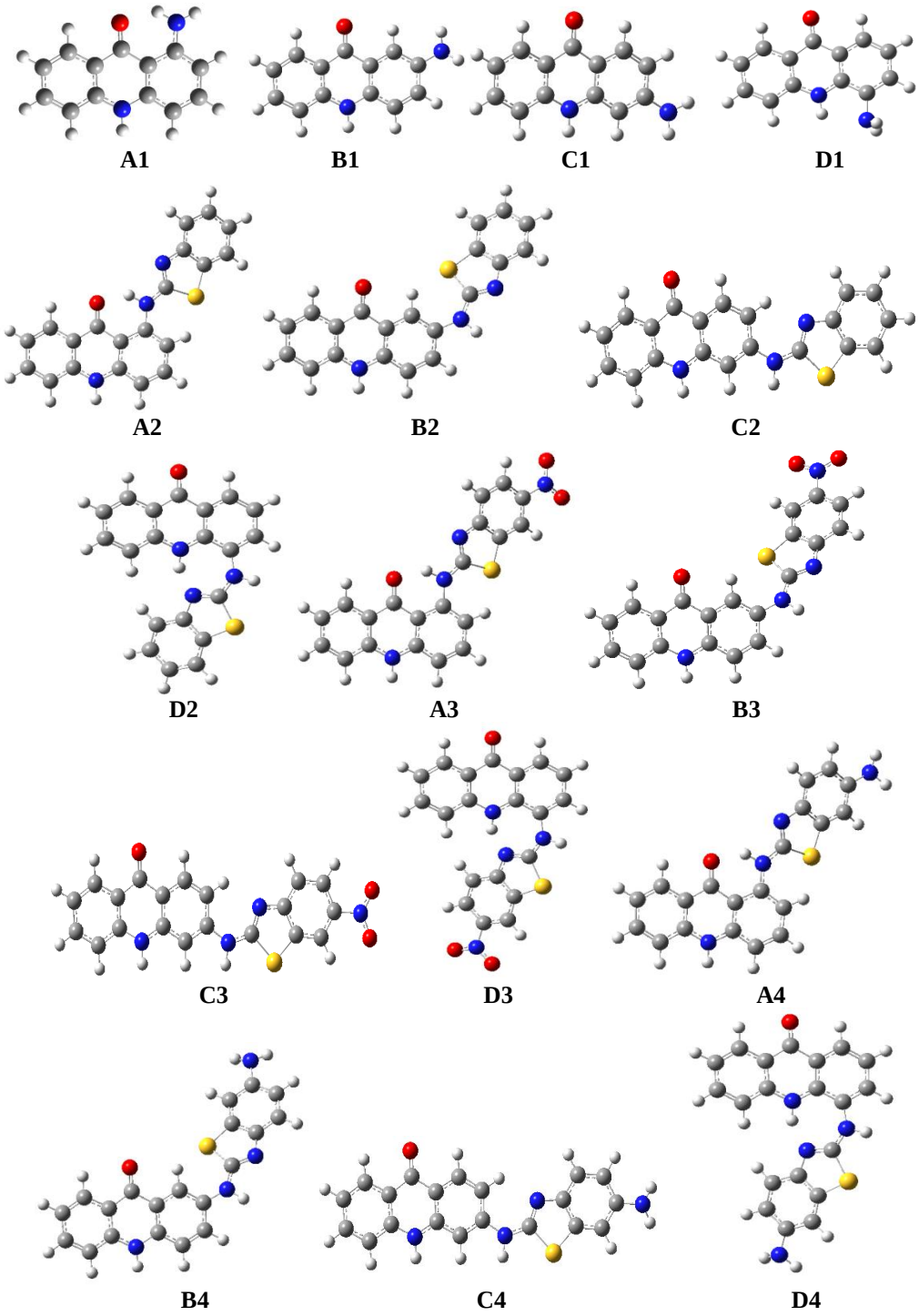


Figure 2. Optimized geometries obtained by B3LYP/6-31G (d) of the studied molecules.

Gauss View software program (version 5.0.8) was used to generate the 3D structures of the molecules. The total energy (E), the highest occupied molecular orbital energy (E_{HOMO}), the lowest unoccupied molecular orbital energy (E_{LUMO}) and their difference in absolute value (E_{gap}), the dipole moment (μ) and the sum of negative charges on molecule (TNC), were also deduced from the stable structure of the neutral form. The transition energies were calculated at the ground-state and excite-state geometries using TD-DFT calculations on the fully optimized geometries, the results obtained gave us the values of the absorption maximum (λ_{max}), their corresponding activation energy (Ea) and the factor oscillation strengths (f).

In order to predict the correlation between

these nine electronic descriptors of the sixteen studied molecules with their toxicity towards monocytes pIC_{50} (Table 2), we evolved a quantitative models by the multiple linear regression (MLR), the Multiple Non Linear Regression (MNLR) and the artificial neural network (ANN).

Statistical analysis

XLSTAT 9 statistical software was employed to realize the MLR, MNLR analysis and the ANN is done on Matlab 9 software using a program written in C language.

A QSAR MLR, MNLR and ANN models were developed, compared and evaluated to predict new compounds activity.

3. RESULTS AND DISCUSSION

Data set for analysis

The QSAR analysis was performed using the pIC_{50} of the sixteen compounds toxicity towards monocytes (experimental values) as reported by Florence Delmas et al. [15], the values of the nine calculated descriptors as shown in Table 2.

Table 1. Values of the 9 chemical descriptors calculated for the 16 compounds.

	E (eV)	E_{HOMO} (eV)	E_{LUMO} (eV)	μ (Debye)	E_{gap} (eV)	f	λ_{max} (nm)	E_a (eV)	TNC	pIC_{50} (*)
A1	-18670.812	-5.074	-1.276	3.062	3.798	0.149	287.500	4.313	-4.107	1.097
B1	-18670.511	-5.040	-1.390	4.833	3.649	0.206	271.690	4.563	-3.924	1.467
C1	-18670.635	-5.439	-1.192	6.189	4.247	0.104	299.890	4.134	-4.034	1.584
D1	-18670.493	-5.439	-1.411	5.741	4.028	0.629	241.170	5.141	-3.962	2.348
A2	-38303.017	-5.284	-1.773	5.988	3.511	0.321	408.970	3.032	-5.480	1.155
B2	-38302.766	-5.223	-1.704	6.133	3.519	0.808	313.270	3.958	-5.349	1.456
C2	-38302.881	-5.611	-1.520	6.212	4.092	0.583	329.410	3.764	-5.425	2.184
D2	-38302.824	-5.412	-1.524	5.868	3.889	0.174	363.670	3.409	-5.386	1.511
A3	-43867.574	-5.755	-2.286	11.938	3.469	0.596	404.590	3.065	-5.952	1.566
B3	-43867.320	-5.692	-2.149	12.229	3.543	0.269	386.740	3.206	-5.821	2.357
C3	-43867.388	-5.858	-2.443	8.544	3.414	0.721	360.490	3.439	-5.892	2.546
D3	-43867.305	-5.723	-2.573	3.517	3.150	0.140	357.490	3.468	-5.844	2.561
A4	-39809.127	-4.815	-1.657	4.763	3.158	0.293	450.130	2.754	-6.137	1.260
B4	-39808.868	-4.772	-1.612	5.152	3.160	0.712	333.430	3.718	-6.003	1.734
C4	-39809.002	-5.138	-1.412	6.743	3.726	0.418	367.890	3.370	-6.085	2.096
D4	-39808.949	-5.201	-1.417	7.588	3.784	0.179	373.190	3.322	-6.048	1.666

(*) **pIC_{50} = Log (IC_{50})**

Multiple Linear Regressions (MLR)

The linear relationship between the studied activity data of compounds and their structure parameters was fitted by multiple descendent regression (MLR) method in 95% confidence intervals. It is employed to model the structure activity relationships. It is a mathematic technique that minimizes differences between actual and predicted values. It has served also to select the descriptors used as the input parameters in the multiple non-linear regression method (MNLR), and artificial neural network (ANN).

In order to propose a mathematical model and to evaluate quantitatively the substituent's physicochemical effects on the activity of the totality of the set of these 16 molecules, we submitted the data matrix constituted obviously from the nine electronic variables corresponding to the studied molecules, to a progressive multiple regression analysis. This method used the coefficients R, R^2, MSE and F-value to select the best regression performance.

Where R is the correlation coefficient; R^2 is the coefficient of determination; MSE is the means of the squares of the errors and F is the Fisher F-statistic.

The QSAR models built using multiple linear regression (MLR) method is represented by the following equation:

$$pIC_{50} = - 9.779 + 0.890\ E_{Gap} + 0.880\ Ea - 0.650\ TNC - 0.956\ E_{LUMO} \quad \text{(Equation 1)}$$

$$n = 16;\quad R^2 = 0.746;\quad R = 0.864;\quad MSE = 0.083;\quad F = 8.096\ ;\quad F\text{-value} = 0.003$$

The values of predicted activities calculated from equation 1, the observed values and the residues are given in Table 2.

We investigated the best linear QSAR

regression equation established. The descriptors proposed by MLR in equation 1 (E_{Gap}, Ea, TNC and E_{LUMO}) could be used to evaluate the biological activity of newly synthesized compounds based on (1,3-benzothiazol-2-yl) amino or amino -9-(10H)-acridinone. Given the fact that the probability corresponding to the F-value is lower than 0.05, it means that we would be taking a lower than 0.03% risk in assuming that the null hypothesis is wrong and that the regression equation has statistically significance. Therefore, we can conclude, after validation, with confidence that the proposed model do bring a significant amount of information and that the selected descriptors are pertinent.

The descriptors proposed by MLR in equation 1 (E_{Gap}, Ea, TNC and E_{LUMO}) could be used as the inputs parameters in the multiple non-linear regression method (MNLR) and the artificial neural network (ANN). Correlations of predicted and observed are illustrated in Figure 3.

Table 2. Experimental, predicted activities and residues values according to MLR method.

N°	pIC_{50}	Pred (pIC_{50})	Residue
A1	1.097	1.286	-0.189
B1	1.467	1.364	0.103
C1	1.584	1.401	0.184
D1	2.348	2.254	0.095
A2	1.155	1.272	-0.117
B2	1.456	1.942	-0.486
C2	2.184	2.154	0.030
D2	1.511	1.641	-0.130
A3	1.566	2.061	-0.495
B3	2.357	2.035	0.322
C3	2.546	2.454	0.092
D3	2.561	2.337	0.224
A4	1.260	1.031	0.229
B4	1.734	1.750	-0.016
C4	2.096	1.809	0.287
D4	1.666	1.799	-0.134

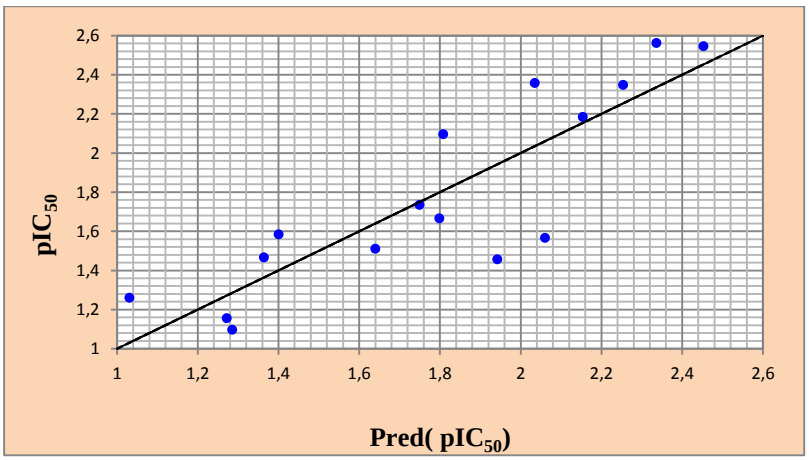


Figure 3. Correlations of observed and predicted activities calculated using MLR.

Multiple non-Linear Regression (MNLR)

The QSAR models built using multiple non-linear regression (MNLR) method is represented by the equation 2. The values of predicted activities calculated from equations 2 and the observed values are given in Table 3. The correlations of predicted and observed activities values are illustrated in Figure 4.

$$pIC_{50} = 5.079 - 3.752\ E_{Gap} + 0.02\ Ea + 1.883\ TNC - 0{,}683\ E_{LUMO} + 0.658\ E_{Gap}^2 + 2.859\ 10^{-5}\ Ea^2 + 0.254\ TNC^2 + 0.01\ E_{LUMO}^2 \quad \text{(Equation 2)}$$

$$n = 16;\quad R^2 = 0.825;\quad R = 0.908;\quad MSE = 0.090;\quad F = 8.096$$

Table 3. Experimental, predicted activities and residues values according to MNLR method.

N°	Obs. (pIC_{50})	Pred. (pIC_{50})	Residue
A1	1.097	1.200	-0.103
B1	1.467	1.322	0.145
C1	1.584	1.650	-0.066
D1	2.348	2.346	0.002
A2	1.155	1.082	0.073
B2	1.456	1.664	-0.208
C2	2.184	2.104	0.080
D2	1.511	1.478	0.033
A3	1.566	2.106	-0.540
B3	2.357	1.986	0.371
C3	2.546	2.478	0.068
D3	2.561	2.450	0.112
A4	1.260	1.224	0.036
B4	1.734	1.798	-0.064
C4	2.096	1.856	0.240
D4	1.666	1.846	-0.181

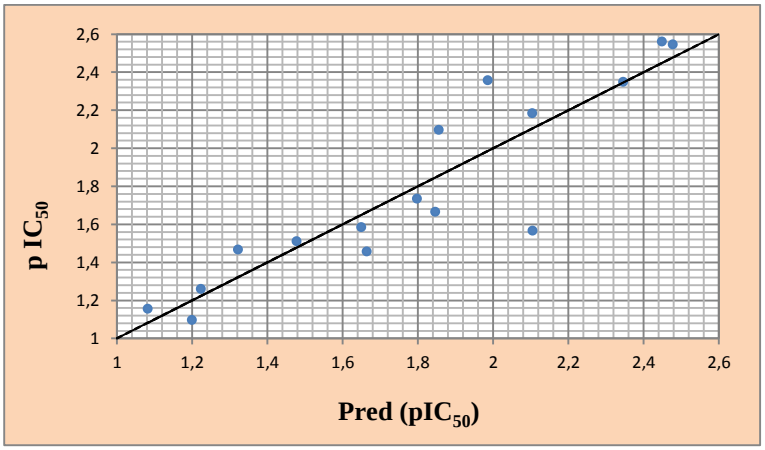


Figure 4. Correlations of observed and predicted activities calculated using MNLR.

Artificial Neural Networks (ANN)

So as to increase the probability of good characterization of studied compounds, artificial neural networks (ANN) can be used to generate predictive models of quantitative structure-activity relationships (QSAR) between a set of molecular descriptors obtained from the MLR, and observed activities. The ANN calculated activities model were developed using the properties of several studied compounds. Some authors [23, 24] have proposed a parameter ρ, leading to determine the number of hidden neurons, which plays a major role in determining the best ANN architecture defined as follows:

ρ = (Number of data points in the training set/Sum of the number of connections in the ANN).

In order to avoid over fitting or under fitting, it is recommended that $1.8<\rho< 2.3$ [25]. The output layer represents the calculated activity values pIC_{50}. The architecture of the ANN used in the current work (4-1-1), ρ = 2.

The correlation between ANN calculated and experimental activities and the residues values are very significant as illustrated in figure 5 and as indicated by R and R^2 values.

$$n = 16;\quad R^2 = 0.782;\quad R = 0.884$$

The values of predicted activities calculated using ANN and the observed values are given in Table 4.

The conclusion we came up with after drawing a comparison between the quality of the MLR, MNLR and ANN models shows that the MNLR models have substantially better predictive capability because the MNLR approach gives better results than MLR and ANN. MNLR was able to establish a satisfactory relationship between the molecular descriptor)s and the activity of the studied compounds.

The obtained squared correlation coefficient (R^2) value confirms that the multiple non-linear regression result were the best to build the quantitative structure activity relationship models. It is important to be able to use MNLR to predict the activity of new compounds.

Table 4. Experimental, predicted activities and residues values according to ANN method.

N°	Obs. (pIC_{50})	Pred (pIC_{50})	Residue
A1	1.097	1.300	0.203
B1	1.467	1.325	-0.142
C1	1.584	1.354	-0.230
D1	2.348	2.308	-0.041
A2	1.155	1.296	0.141
B2	1.456	1.862	0.406
C2	2.184	2.234	0.049
D2	1.511	1.543	0.033
A3	1.566	1.957	0.391
B3	2.357	1.935	-0.422
C3	2.546	2.631	0.085
D3	2.561	2.364	-0.198
A4	1.260	1.233	-0.027
B4	1.734	1.690	-0.044
C4	2.096	1.787	-0.309
D4	1.666	1.769	0.104

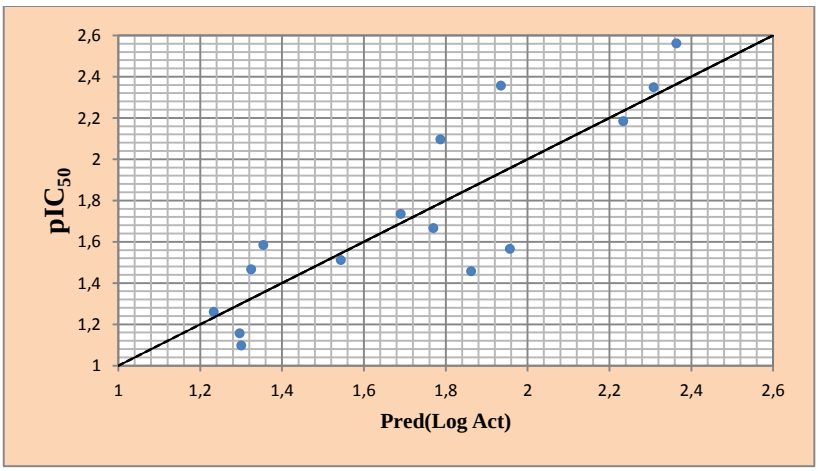


Figure 5. Correlations of observed and predicted activities calculated using ANN.

Validation

We use One Leave Out cross-validation as an internal test of the quality of the RLM and RNLM models. The model's performance was good and was characterized by Q (r_{CV}) value of 0.749 for the model proposed by the descendent RLM and 0.658 for the model proposed by the RNLM. The values of predicted activities calculated using One Leave Out cross-validation and the observed values are given in Table 5.

The good results obtained show that the model proposed in this paper is able to predict activity with a great performance, and that the selected descriptors are pertinent.

The developed equations can be used for the designing of new acridin-9-(10H)-ones derivatives with improved Anti-proliferative towards human monocytes activities (pIC_{50}). If we develop a new compound with high values than the existing compounds it may give the more active compound than the existing ones. In this way, we can designed news compounds by adding suitable substituents and calculated their activity using equations 1 and 2.

For example, Equation 1 for the descendent RLM indicated the negative correlation of the lowest unoccupied molecular orbital energy (E_{LUMO}) and the sum of negative charges on molecule (TNC), and the positive correlation of the energy Gap (E_{gap}) and the activation energy (Ea).

Table 5. The observed and the predicted activity according to Leave One Out cross validation.

		RLM		RNLM	
N°	**Obs. (pIC_{50})**	**Pred (pIC_{50})**	**Residue**	**Pred (pIC_{50})**	**Residue**
A1	1.097	1,354	-0,257	1,300	-0,203
B1	1.467	1,303	0,164	1,109	0,358
C1	1.584	1,278	0,306	1,946	-0,362
D1	2.348	2,164	0,185	2,275	0,073
A2	1.155	1,316	-0,160	1,009	0,147
B2	1.456	2,019	-0,562	1,838	-0,382
C2	2.184	2,141	0,044	2,023	0,161
D2	1.511	1,666	-0,156	1,462	0,048
A3	1.566	2,209	-0,643	2,426	-0,861
B3	2.357	1,970	0,387	1,733	0,624
C3	2.546	2,414	0,132	2,440	0,105
D3	2.561	2,194	0,367	2,015	0,546
A4	1.260	0,842	0,418	1,113	0,147
B4	1.734	1,765	-0,031	1,973	-0,239
C4	2.096	1,694	0,402	1,627	0,468
D4	1.666	1,850	-0,184	1,986	-0,321

4. CONCLUSION

In this study:

- Three different modeling methods, MLR, MNLR and ANN were used in the construction of a QSAR model for the Anti-proliferative towards human monocytes activities with acridin-9-(10H)-ones substituted with amino or (1,3-benzothiazol-2-yl)-amino groups compounds and the resulting models were compared.

- It was shown that the multiple regression non linear MNLR results have substantially better predictive capability than the MLR and ANN yields a regression model with improved predictive power.

- The accuracy and predictability of the proposed models were illustrated by the comparison of key statistical terms like R or R^2 of different models obtained by using different statistical tools and different electronics descriptors and the predictive powers of the equations were validated by an internal test (Cross validation).

- The descriptors proposed by MLR in equation 1 (E_{Gap}, Ea, TNC and E_{LUMO}) could be used to evaluate the biological activity of newly synthesized acridinones.

- These studies give an insight into electronic properties play the dominant role in modulating the toxicity towards monocytes activities values.

- The results obtained by MLR, and MNLR are very sufficient to conclude the performance of the model. So, this model could be applied to other (1,3-benzothiazol-2-yl) amino-9-(10H)-acridinone derivatives accordingly to table 1 and could add further knowledge in the improvement of new way in anti-proliferative drug research.

- Furthermore, we can conclude that studied descriptors (E_{Gap}, Ea, TNC and E_{LUMO}), which are sufficiently rich in chemical and electronic information to encode the structural feature may be used with other descriptors for the development of predictive QSAR models.

5. ACKNOWLEDMENTS

We are grateful to the “Association Marocaine des Chimistes Théoriciens” (AMCT) for its pertinent help concerning the programs.

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