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QSAR Study of New Compounds Based on 1,2,4-Triazole as Potential Anticancer Agents

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Pancreatic cancer is an aggressive cancer, usually with poor prognosis, as it is mostly discovered at an advanced stage of development where treatment is challenging. Using principal components analysis (PCA) of variable selection, multiple linear regression (MLR), multiple non-linear regression (MNLR) and the artificial neural network (ANN), 2D-QSAR models for the anti-pancreatic cancer activity are developed from a set of twenty three molecules of 1,2,4-triazole derivatives to build the QSAR models. The well generated MLR and MNLR models exhibit the cross validation coefficients Q^2 of 0.51 and 0.90, respectively. Moreover, the predictive ability of those models has been evaluated by the external validation using a test set of four compounds with predicted determination coefficients R^2 test of 0.936 and 0.852, respectively. The artificial neural network (ANN) method has shown a correlation coefficient of 0.896 with an architecture 3-2-1. The obtained results indicate the validation and the good quality of the 2D-QSAR models.

Keywords: QSAR, 1,2,4-Triazole, Multiple linear regression, Non-linear regression, Artificial neural network, Anticancer agents

INTRODUCTION

Currently, cancer is among the most dangerous life-threatening diseases [1]. More than 90% of cancer patients die due to chronic tumor metastases [2]. On the basis of recent findings, all cancer treatments are based on the drugs controlling the spread and growth of cancer cells, by interfering with specific molecules involved in the growth, progression, and spread of cancer. Hormone therapy, angiogenesis inhibitors, and apoptosis inducers constitute a target variety providing researchers with different options to concern with each of them [3].

In recent years, the use of technologies that make it possible to synthesize a large number of molecules simultaneously and to test their actions on therapeutic targets has given attractive results. This is the main focus of both quantitative structure-activity relation (QSAR) and quantitative structure property relationship (QSPR) studies.

These studies are essentially based on the search for similarities between molecules in a large database of existing molecules whose activities or properties are known. The objective of the QSAR study is to find a relationship between the physicochemical parameters (descriptors) of all the compounds studied and their anticancer activity [4,5]. The discovery of such a relationship can predict the activities and the properties of the new compounds, and consequently, guide the syntheses of new molecules without realizing them.

Much attention has been devoted to 1,2,4-triazole derivatives due to their wide spectrum of biological activities such as anticonvulsant [6], anticancer, antidepressant [7], antibacterial [8], antifungal [9], anti-inflammatory, analgesic [10] and antiviral activities [11]. The objective of the present work is to carry out a descriptive and predictive study of the anticancer activity of a series of twenty three (23) compounds of 1,2,4-triazole derivatives to find a correlation between the biological

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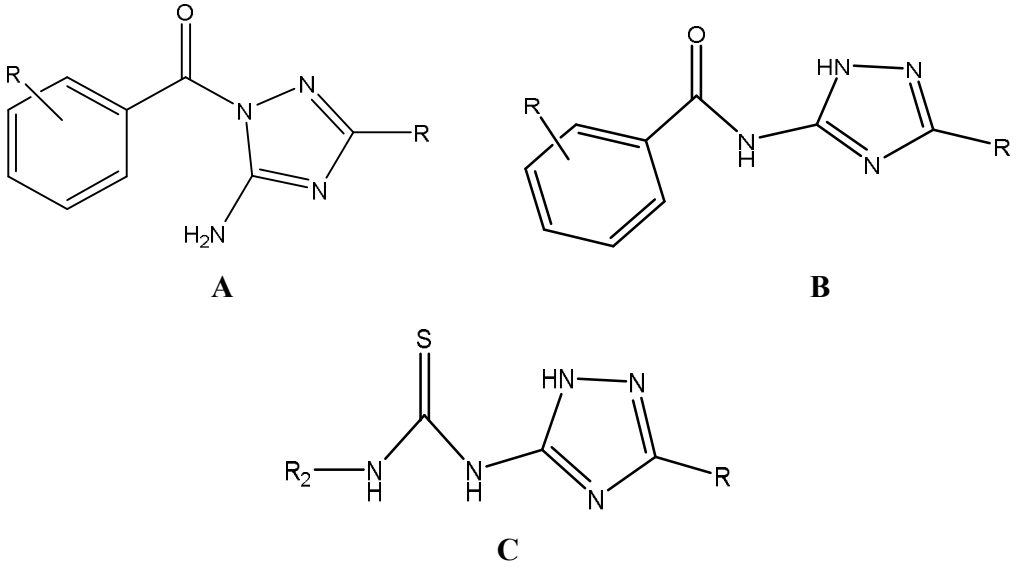

Fig. 1. General structures of 1,2,4-triazole derivatives**.**

activity and the various descriptors.

MATERIAL AND METHODS

Experimental Data

In the present study, twenty three (23) of 1,2,4-triazole have been chosen for their anticancer activities against the human pancreatic cancer cell line (Panc-1). Experimentally, those novel hybrids of 1,2,4-triazole have been prepared by gathering the two bioactive entities 1,2,4-triazole and isothiocyanates in one compact structure for the purpose of synergism. For their experimental activity, GraphPad Prism software (GraphPad Software, San Diego, CA, USA) has been used to calculate the median inhibition concentration (IC50) for all compounds [12]. Figure 1 represents the basic structure of the 1,2,4-triazole and Table 1 shows the studied substitutions of the compounds and corresponding experimental activities of pIC50 with ($pIC_{50} = \log_{10} IC_{50}$).

Calculation of the Molecular Descriptors

The different descriptors used in this work are calculated by ACD/ChemSketch program [13,14]. Steric descriptors and thermodynamic ones are calculated using ACD/ChemSketch and ChemBioOffice 14.0 [15], after the energy optimization for each compound using the MM2 method (force field method with gradient setting root mean square (RMS) 0.1 kcal mol^{-1}) [16]. In this work, as shown in Table 2, 11 descriptors have been chosen to describe the target molecular structures.

Statistical Analysis

The 11 descriptors calculated for this series are used to find the relation linking the molecular structures by the biological activity (Table 2). To explain the structure-activity relationship, the 11 quantitative descriptors of the 1,2,4-triazole (1 to 23) compounds are studied using different statistical methods:-The principal component analysis (PCA) has been performed using the XLSTAT software, version 2015 [17], to predict anticancer activities pIC_{50}. PCA is a statistical method based on minimizing all the information encoded in the structures of the compounds. In most cases of QSAR studies, the researchers confront problems such as the elimination of irrelevant information in the original descriptors matrix involved, the unfavorable ratio of the number of descriptors to that of molecules of interest, and collinearity among the descriptors used. PCA is a useful method in dealing with the problems of the unfavorable more descriptor/molecule ratio and collinearity. This method aims to select descriptors that are directly related to biological activity [18]. The information contained in the data is listed in Tables 1 and 2.

Table 1. Compounds and Radicals under Study

	Compounds	R	R_1	R_2	pIC_{50}
A	1	C_6H_5	4-OCH_3	-	5.60
	2	Pyridine-3-yl	4-OCH_3	-	5.82
	3	Pyridine-4-yl	4-OCH_3	-	5.72
	4	C_6H_5	3,4-di(OCH_3)	-	5.13
	5	3,4,5-Tri(OCH_3)C_6H_2	3,4-di(OCH_3)	-	5.10
	6	Pyridine-3-yl	3,4-di(OCH_3)	-	5.14
	7	Pyridine-4-yl	3,4-di(OCH_3)	-	5.38
	8	C_6H_5	3,4,5-tri(OCH_3)	-	5.25
	9	3,4,5-Tri(OCH_3)C_6H_2	3,4,5-tri(OCH_3)	-	5.23
	10	Pyridine-3-yl	3,4,5-tri(OCH_3)	-	5.02
	11	Pyridine-4-yl	3,4,5-tri(OCH_3)	-	4.92
	12	4-Cl-C_6H_4-	3,4,5-tri(OCH_3)	-	5.34
B	13	4-OCH_3-C_6H_4-	4-OCH_3	-	5.88
	14	3-Cl-C_6H_4-	4-OCH_3	-	5.45
	15	4-OCH_3-C_6H_4-	3,4-di(OCH_3)	-	5.49
	16	3-Cl-C_6H_4-	3,4-di(OCH_3)	-	6.00
	17	4-OCH_3-C_6H_4-	3,4,5-tri(OCH_3)	-	5.14
C	18	3,4,5-Tri(OCH_3)-C_6H_2-	-	C_6H_5	5.37
	19	3,4,5-Tri(OCH_3)-C_6H_2-	-	C_2H_5	5.25
	20	4-OCH_3-C_6H_4-	-	C_6H_5	5.49
	21	4-OCH_3-C_6H_4-	-	C_2H_5	5.31
	22	3-Cl-C_6H_4-	-	C_6H_5	5.22
	23	3-Cl-C_6H_4-	-	C_2H_5	5.13

pIC50 = -log(IC50).

- The multiple linear regression statistic techniques (MLR) are used to study the relationship between one dependent variable and several independent variables. It is a mathematical technique to minimize the difference between the actual and predicted values;

- The nonlinear multiple regression statistic (NMRS) technique is a nonlinear method in which the descriptors proposed by MLR are applied in accordance to the data set (training set). In the previous works, the preprogrammed function has been used:

Table 2. Dataset Used for the QSAR Analysis of the 1,2,4-Triazole Derivatives

Compounds	MW	MR	MV	Pc	n	γ	D	αe	logP	HBA	HBD
A1	82.67	244.5	294.30	605.8	1.657	52.9	1.31	32.77	3.47	5	1
A2	81.11	213.1	295.29	587.0	1.686	57.4	1.38	32.15	2.22	6	1
A3	81.11	213.1	295.29	587.0	1.686	57.4	1.38	32.15	2.22	6	1
A4	89.39	246.3	324.33	681.4	1.645	58.5	1.31	35.43	3.78	6	2
A5	87.60	234.3	328.75	660.6	1.670	63.2	1.40	34.73	4.47	5	2
A6	88.48	246.2	324.33	656.1	1.637	50.4	1.31	35.07	3.12	6	1
A7	105.92	311.1	414.41	806.8	1.596	45.1	1.33	41.99	2.57	9	1
A8	86.92	234.8	325.32	637.2	1.662	54.2	1.38	34.46	1.87	7	1
A9	86.92	234.8	325.32	637.2	1.662	54.3	1.38	34.46	1.87	7	1
A10	96.07	270.3	354.35	738.1	1.628	55.5	1.31	38.08	3.66	7	2
A11	94.28	258.3	358.77	717.3	1.650	59.4	1.38	37.37	4.34	6	2
A12	94.29	267.9	354.35	706.3	1.621	48.3	1.31	37.38	3.02	7	1
B1	92.74	256.5	355.34	687.5	1.642	51.6	1.38	36.76	1.77	8	1
B2	111.73	332.8	444.43	857.1	1.586	43.9	1.33	44.29	2.47	10	1
B3	92.74	256.5	355.34	687.5	1.642	51.6	1.38	36.76	1.77	8	1
B4	92.74	256.5	355.34	687.5	1.642	51.6	1.38	36.76	1.77	8	1
B5	98.89	277.1	388.80	735.2	1.632	49.5	1.40	39.20	3.64	7	1
B6	92.74	256.5	355.34	687.5	1.642	51.6	1.38	36.76	1.77	8	1
C1	102.75	294.3	384.38	794.8	1.615	53.1	1.30	40.73	3.534	8	2
C2	107.75	279.7	385.44	798.1	1.695	66.2	1.37	42.64	4.480	6	3
C3	91.25	257.7	337.39	711.5	1.626	58.0	1.30	36.17	3.154	6	3
C4	77.89	209.7	277.34	598.1	1.664	66.1	1.32	30.88	3.407	4	3
C5	76.11	197.7	281.76	577.3	1.696	72.7	1.42	30.17	4.092	3	3

$$Y = a + (bX1 + cX2 + dX3 + eX4 \ldots) + (fX12 + gX21 + hX32 + iX42 \ldots) \quad (1)$$

where a, b, c, d ….represent the parameters and X1, X2, X3, X4…represent the variables.

- The ANN analysis has been performed using the MATLAB R2016a software [19]. A neural fitting tool (nftool) on a data set of the 1,2,4-triazole compounds [20].

Table 3. The Correlation Matrix (Pearson (n)) between Different Obtained Descriptors

Variable	PIC_{50}	MR	MV	MW	Pc	n	ϒ	D	αe	logP	HBA	HBD
PIC50	1											
MR	0.134	1										
MV	0.135	0.933	1									
MW	0.188	0.963	0.967	1								
Pc	0.046	0.979	0.962	0.959	1							
n	-0.035	-0.393	-0.693	-0.544	-0.507	1						
ϒ	-0.266	-0.337	-0.610	-0.493	-0.377	0.904	1					
αe	0.105	-0.164	-0.413	-0.173	-0.279	0.764	0.653	1				
D	0.134	1.000	0.933	0.963	0.979	-0.395	-0.338	-0.164	1			
logP	-0.328	0.086	-0.136	-0.070	0.086	0.520	0.713	0.331	0.085	1		
HBA	0.262	0.646	0.817	0.764	0.662	-0.804	-0.869	-0.465	0.647	-0.654	1	
HBD	-0.413	-0.071	-0.262	-0.231	-0.021	0.5263	0.819	0.253	-0.072	0.747	-0.669	1

The nodes, the topology of the connections between the nodes, and the learning rule are the three components of neural network. However, the most frequent type of ANN in QSAR is the three-layered feed-forward network [21].

- The validation is a crucial aspect of QSAR modeling, two basic principles (internal and external validation) are available [22]. The cross validation is one of the most popular methods for internal validation. A good Q^2 often indicates a good robustness and high internal predictive power of a QSAR model. Indeed, the external predictive ability is evaluated by R^2 test. For this reason, the statistical external validation has been applied to the models as described by Globarikh and Tropsha [23].

RESULTS AND DISCUSSION

In this QSAR study, the collected data are first randomly divided into two parts: a learning set consisting of 19 molecules, and a test set consisting of 4 molecules used to validate the models formed; both parts are presented in Table 2. However, the test set does not undergo any processing during the construction of the models and it is reserved only for testing the reliability of the models. Also, the values of the descriptor's bivariate linear correlation coefficients R are presented in Table 3. The calculated linear correlation coefficients R of the series of descriptors are less than 0.95 ($R < 0.95$). This demonstrates the non-dependence of the descriptors used to develop the models.

3.1. Principal Components Analysis (PCA)

In this paper, PCA has been used to determine the descriptors that are straightly linked to the anticancer activity. All the 11 descriptors of the 23 molecules are submitted to PCA. The three main axes are enough to describe the information provided by the data-matrix. Indeed, the variance percentages are 55.85%, 24.87% and 11.27% for axes F1, F2 and F3, respectively (Fig. 2). The estimation of the total information is 91.90%.

PCA has been conducted to identify the relationship between the different descriptors. Bold values are different from 0 to a significance level of $P = 0.05$. The correlations between the 11 descriptors are presented in Table 3 as a correlation matrix, and in Fig. 3 these descriptors are represented in a correlation circle.

The correlation circle was made to detect the connection

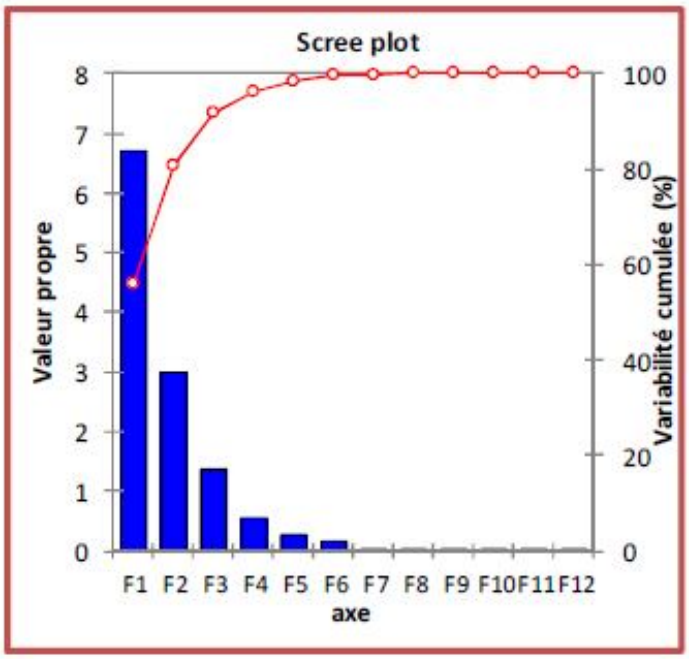

Fig. 2. The principal components and there variances.

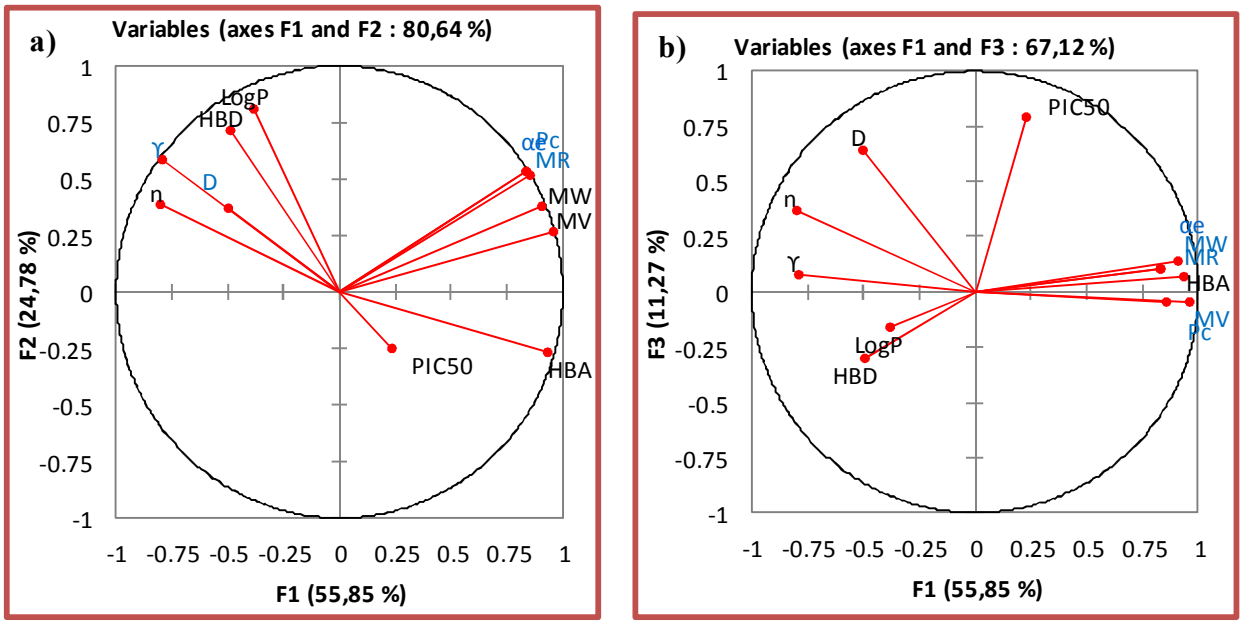

Fig. 3. Correlation circle for axes F1, F2 (a) and F1, F3 (b).

between the different descriptors. Every single variable (descriptor) was represented by a vector. The direction and length of each vector provide information about the impact of descriptors on the individual axe. As seen in Fig. 3, the majority of variables were located near the circle, indicating that the information "coded" in the variable was explained

by the three main axes, F1, F2 and F3. The vicinity of the descriptors indicates the positive correlations between them, (See αe, PC, and MR in Fig. 3a; αe, MW and MR; Pc and MV in Fig. 3b). Vectors located vertically indicated no correlations between the attributes (see MW and HBD; logP and MW in Fig. 3a). Negative correlations between the attributes are represented by vectors located opposite to each other, like HBD and ϒ.

The obtained matrix provides information on the high or low interrelationship between the descriptors and identifies their potential collinearity. In general, good collinearity (R > 0.5) was observed between most of the variables. A high interrelationship was observed between D and MR (R = 1.00), and a low interrelationship was observed between Pc and HBD (R = -0.021). Additionally, to decrease the redundancy existing in our data matrix, the descriptors that are highly correlated (R ≥ 0.9) were excluded.

In order to reduce the number of non significant parameters and form the results obtained by the matrix and the circle of correlations, the following correlations are observed:

- αe is perfectly correlated with MR and Pc (r (αe, MR) = 1; r (αe, Pc) = 0.97.
- MW is highly correlated with MR and MV (r (MW, MR) = 0.963; r (MW, MV) = 0.992).
- γ and n are highly correlated (r (Pc, MW) = 0.968).

We have also tried to eliminate the descriptors Pc or MR, (because they are also correlated) but we could not find adequate models. We therefore retained the descriptors MR and Pc and eliminated only αe, MW, γ, n and D.

Multiple Linear Regressions (MLR)

Based on the topological descriptors selected by the PCA method, the objective is to predict quantitatively the effects of the substituents on the activity of the twenty three molecules against the human pancreatic cancer cell line, using multiple linear regression.

The following equation represents the best linear QSAR model obtained using the regression linear multiple (MLR) method:

$$pIC_{50} = 5.42 + 0.74 \times MR + 0.26 \times MV - 0.23 \times Pc + 1.95 \times logP + 2.134 \times HBA + 3.80 \times HBD \quad (1)$$

$N = 23$; $R = 0.89$; $R^2 = 0.80$; $Q^2 = 0.51$; $MSE = 0.028$; $F = 8.03$; $P = 0.0012$

The established models are judged by the statistical keys; precisely, R^2 is the coefficient of determination, F is the Fisher statistic and MSE is the mean squared error. Higher coefficient of determination and lower mean squared error indicates that the model is more reliable.

P value (smaller than 0.05) means that the obtained equation is statistically significant at the 95% level. The leave-one-out cross-validated correlation coefficient LOO (Q^2 = 0.51) illustrates the reliability of the model by emphasizing its sensitivity to the elimination of any data point. When the value of Q^2 is greater than 0.5, the model is valid. The correlations of observed activity (pIC_{50}) and predicted values calculated by MLR are illustrated in Fig. 4.

The proposed descriptors by MLR in Eq. (1) (MR, MV, PC, logP, HBD and HBA) could be used as the input parameters in the multiple non-linear regression method (MNLR) and the artificial neural network (ANN).

Multiple Nonlinear Regressions (MNLR)

The statistical nonlinear regression method has been used to improve the predicted activity (pIC_{50}) quantitatively. It has taken into account the 6 chosen descriptors.

The resulting equation is:

$$pIC_{50} = 17.00557 + 0.47943 \times MR + 0.11951 \times MV + 0.17840 \times Pc + 2.74684 \times logP + 3.38813 \times HBA - 2.96510 \times HBD - 0.00056 \times MR^2 + 0.00002 \times MV^2 + 0.00002 \times Pc^2 + 0.03587 \times logP^2 - 0.02738 \times HBA^2 + 1.44924 \times HBD^2$$

$N = 23$; $R = 0.995$; $R^2 = 0.992$; $Q^2 = 0.90$; $MSE = 0.002$

The performance parameters obtained by the non-linear regression method indicates that this model is more reliable. The model obtained has been validated by the cross-validation technique. The value of Q^2 is greater than 0.5; this indicates the best predictive MNLR model.

The inhibitory activity values pIC_{50} predicted by this model are almost similar to those observed. Correlations between the observed and predicted pIC_{50} values are shown in Fig. 5.

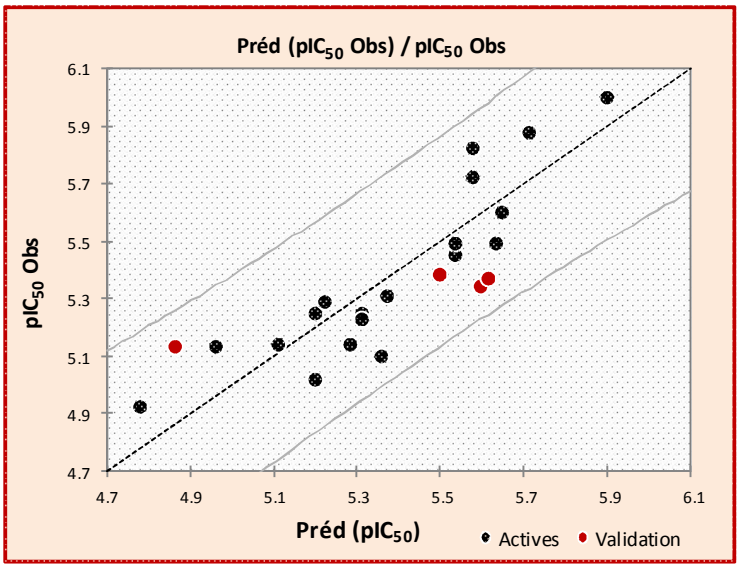

Fig. 4. Graphical representation of observed activity (pIC_{50}) and predicted values calculated by MLR.

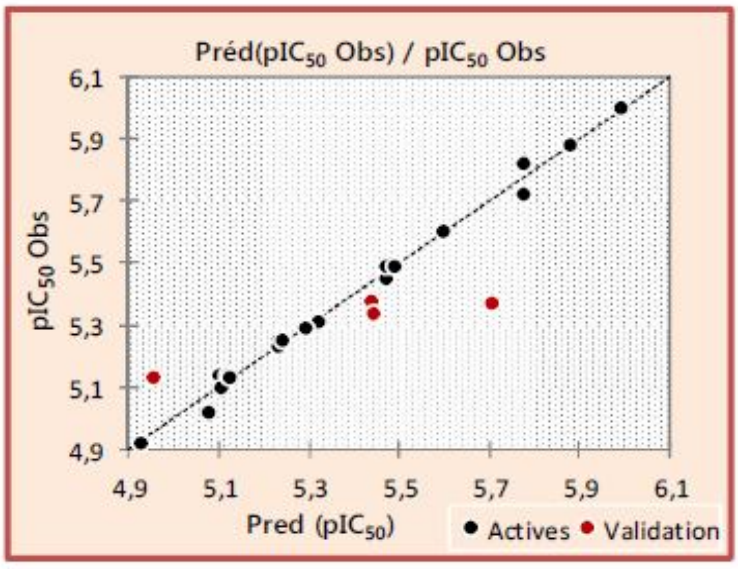

Fig. 5. Graphical representation of observed activity (pIC_{50}) and predicted values calculated by MNLR.

External Validation

To test the predictive ability of the models obtained, it is necessary to use a set of tests for external validation. Thus, the models generated on the training set using (23) 1,2,4-triazole have been used to predict the anticancer activity of the remaining molecules. The performance parameters of the generated models are presented in Table 4.

It can be clearly seen that the MNLR is statistically better than the MLR model in terms of coefficient of determination; however, the MLR has a better predictive ability and a good internal stability.

Among the models obtained for this series, the MNLR

Table 4. Performance Comparison between Models Obtained by MLR and RNLM

	Set of Learning				Set of Test		
	R	R^2	Q^2	MSE	R_{test}	R^2_{test}	MSE
RLM	0.89	0.80	0.51	0.0021	0.967	0.936	0.028
RNML	0.95	0.92	0.90	0.0022	0.923	0.852	0.002

Table 5. Observed and Calculated pIC_{50} Values for both MLR and MNLR Methods

Composés	pIC_{50} (Obs)	pIC_{50} (Pred)	
		$pIC_{50\ MLR}$	$pIC_{50\ MNLR}$
1	5.60	5.65	5.60
2	5.82	5.58	5.77
3	5.72	5.59	5.77
4	5.14	5.28	5.10
5*	5.13	4.86	4.95
6	5.10	5.35	5.10
7*	5.38	4.49	5.44
8	5.25	5.31	5.23
9	5.23	5.31	5.23
10	5.02	5.19	5.08
11	4.92	4.78	4.92
12[a]	5.34	5.59	5.44
13	5.88	5.71	5.88
14	5.45	5.53	5.47
15	5.49	5.53	5.47
16	6.00	5.89	5.99
17	5.14	5.11	5.11
18[a]	5.37	5.61	5.70
19	5.25	5.20	5.24
20	5.49	5.63	5.49
21	5.31	5.37	5.32
22	5.29	5.22	5.29
23	5.13	4.96	5.12

[a]Test.

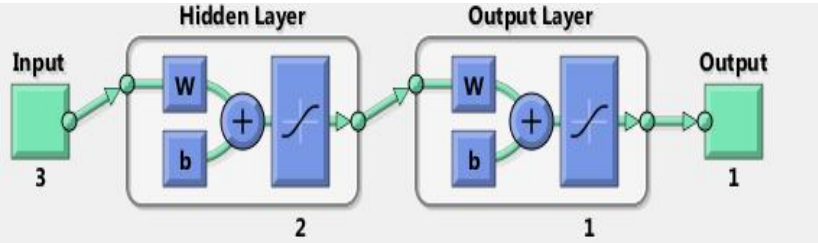

Fig. 6. Architecture of the artificial neural network used in our study.

Table 6. The Obtained Results by the Model Established by the ANN for the Three Phases: Training, Validation, and Test

Pancreatic cancer				
	Samples	MSE	R	R^2
Modèle	23	0.0063	0.949	0.900
Apprentissage	17	0.0040	0.969	0.938
Validation	3	0.0066	0.843	0.710
Test	3	0.0014	0.994	0.988

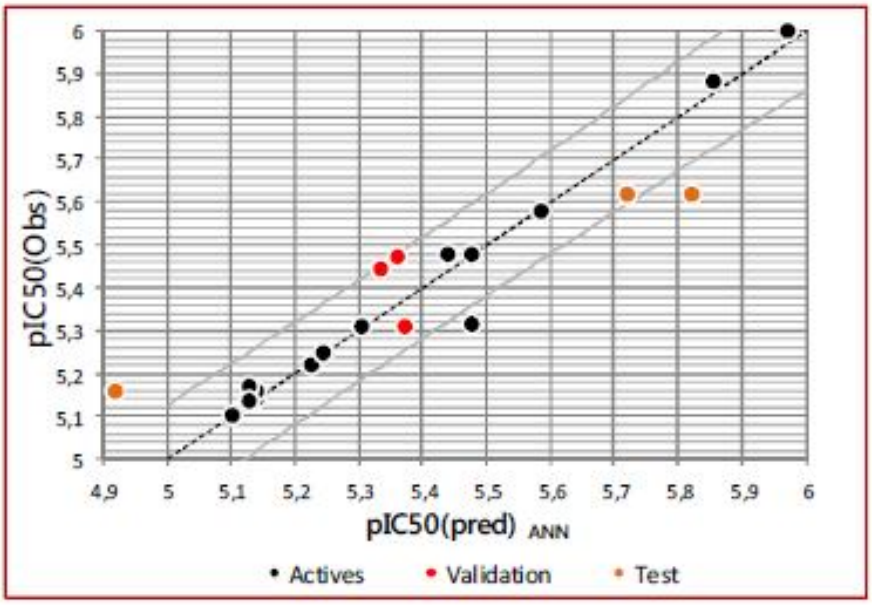

Fig. 7. Correlations between observed and predicted activities values calculated using ANN models (training set in black, validation set in red, and test set in brown).

Table 7. The Values of pIC_{50} According to ANN Method

Composés	pIC_{50} (Obs)	pIC_{50} (pred)$_{ANN}$
1	5.60	5.577
2[a]	5.82	5.621
3[a]	5.72	5.621
4	5.14	5.141
5	5.13	4.684
6	5.10	5.100
7	5.38	5.309
8[b]	5.25	5.221
9	5.23	5.221
10[b]	5.02	5.149
11[a]	4.92	5.161
12	5.34	5.442
13	5.88	5.882
14	5.45	5.481
15	5.49	5.481
16	6.00	6.000
17	5.14	5.157
18	5.37	5.474
19	5.25	5.247
20	5.49	5.313
21	5.31	5.312
22[b]	5.29	5.36
23	5.13	5.172

[a]Test. [b]Validation.

model has the highest cross-validation coefficient ($Q^2 = 0.90$), which supports the applicability of the proposed RNLM prediction model. The values of the activities (pIC_{50}) calculated from the two models, RLM and RNLM, and those obtained experimentally are shown in Table 5.

Artificial Neural Networks (ANN)

In this stage, a feed forward network with two layers has been used with a sigmoid transfer function in the hidden layer and a linear transfer function in the output layer. The architecture of the artificial neural network used in this

study is 3-2-1 (Fig. 6) and ρ = 1.35.

Total data are distributed randomly into three groups. The first group (70% of the total data) is used to drive the system. The second group (15% of the total data) will be used to validate the network, and the remaining 15% that did not participle in the learning models will be used as an independent test of network generalization.

The correlation between the experimental and calculated values obtained by artificial neural network is highly significant, as indicate by better R, R^2, and the small mean squared error value for all three phases: training, validation and test (Table 6).

The predicted activities calculated with the artificial neural network and the observed values are included in Table 7 and illustrated in Fig. 7.

CONCLUSIONS

In this work, the QSAR regression has been investigated to predict the anticancer biological activity against the human pancreatic cancer cell line (Panc-1) of several compounds, based on the 1,2,4-triazole derivatives. The key statistical terms like R or R^2 of different models obtained have been compared using different statistical tools and different descriptors, as it is shown in Table 2.

A good stability and prediction ability have been exhibited by MLR, MNLR and ANN models, on the same set of descriptor. Furthermore, the obtained results from each model on this series of compounds are quite similar. None of the established models is considered better than the other. The predictive power of the model obtained has been confirmed by LOO cross-validation. A strong correlation is observed between the experimental and predicted values of the biological activities, indicating the validity and quality of the QSAR model developed in this work.

Finally, based on the results obtained, the chosen descriptors are rich in information and have a great influence on the activity of the 23 studied molecules may be used with other descriptors for the development of predictive QSAR models.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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