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Biological study of several Alectinib as Cancer Cells Inhibitor using QSAR and Monte Carlo methods

R. Sayyadi kord Abadi[1,], R. Rajabi Nezhad[2], K. Akhavan[3]*

[1, 3] *Department of Chemistry and Chemical Engineering, Rasht Branch, Islamic Azad University, Rasht, Iran*

[2] *Department of Fisheries, Bandar Anzali Branch, Islamic Azad University, Bandar Anzali, Iran*

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ABSTRACT: QSAR investigations were conducted using multiple linear regression (MLR) and artificial neural network (ANN) as modeling tools, along with simulated annealing (SA), genetic algorithm (GA) and Imperialist Competitive Algorithm (ICA) optimization algorithms. In addition CORAL software was used to correlate the biological activity to the structural parameters of the drugs. Comparing the examined non-linear methods revealed that ANN-GA and MLR-ICA were the best approach. According to the results, in GA-ANN method minimum value in BLTA96 (Verhaar model of Algae based-line toxicity from MLOGP (mmol/l)/ Molecular properties) descriptor and maximum value in Mor 02u (indicates that the size of the inhibitor molecule has certain effect on the extent of the interaction between the drug and molecule) descriptor and in ICA-MLR method minimum value in atomic Sanderson electronegativities descriptors and maximum value in polarizibility, weighted by atomic masses, descriptors and in Monte Carlo method the number of Nitrogen atom, presence of double bond and cyclic ring with branching can be used for designing new drugs because reducing the half maximal inhibitory concentration (IC50) value.

Keywords: *Alectinib, Antitumor Drugs, Monte Carlo method, QSAR.*

INTRODUCTION

The Anaplastic lymphoma kinase (ALK) inhibitor [1, 2] Alectinib is used for the treatment of ALK positive non-small-cell lung cancer (NSCLC) [3, 4]. Alectinib is at least in part effective by triggering suicidal death or apoptosis of tumor cells [5, 6]. Modeling and optimization approaches that relate the descriptors (constitutional, geometrical, topological, quantum chemical, etc.) to the biological activity of drugs are named QSAR [7, 8]. Multiple Linear Regression (MLR), Artificial Neural Networks (ANN), Simulated Annealing algorithm (SA) [9], Genetic Algorithm (GA) [10], and Partial Least Squares (PLS), are the most common mathematical methods that utilized to describe the quantitative relationship between the molecular descriptors of the drugs and their properties [11, 12]. CORAL has been proposed as competent software for the QSAR studies. It uses Monte Carlo method to find the most important simplified molecular input-line entry system (SMILES)-based descriptors and calculate their correlation weights to predict an endpoint (e.g., -log(IC_{50})).

(*) Corresponding Author - e-mail: sayyadi_04@yahoo.com
sayyadi@iaurasht.ac.ir

SMILES are lines of symbols, representing the molecular structure [13]. Imperialist Competitive Algorithm (ICA) is a new population-based optimization algorithm that was proposed by Atashpaz-Gargari and Lucas in 2007 [14] and since then it was employed in solving a variety of optimization problems [15]. The algorithm starts with an initial population. The individuals (countries) are two types: imperialists and colonies. The most powerful countries are selected as imperialists and the rest as the colonies of these imperialists. The total power of an empire depends on both power of the imperialist country and power of its colonies [16]. In the current study, MLR and ANN modeling tools coupled with SA, GA and ICA optimization techniques and Monte Carlo method were used to find the best set of descriptors that correlate the biological activity (half maximal inhibitory concentration (IC50)) [17] of 21 Alectinib Drugs.

COMPUTATIONAL METHODS

Selection of descriptors using linear regression

Geometrical optimizations of the 21 Alectinib Drugs were carried out with B3lyp/6-311g at the Gaussian 03W [18, 19]. Dragon program [20] was used for calculation of 3226 molecular descriptors for each of the 25 Doxazolidine compounds [14] that were categorized in topological, geometrical, MoRSE [21], RDF [22], GETAWAY [23], auto-correlations [24] and WHIM [25]. Three refining steps were performed to reduce the number of descriptors using SPSS [26]. Ddescriptors that had the same value for at least 70% of the Alectinib compounds in the dataset and then the descriptors with correlation coefficient of less than 0.25 with the dependent variable logarithm half maximal inhibitory concentration (–logIC50) were considered redundant and subsequently removed [27] that the number of descriptors was reduced 1276. The selected descriptors were further screened using the following coupled methods. A stepwise multiple linear regression procedure based on the forward-selection and backward-elimination techniques was used for the rejection of descriptors in the linear models. The Multiple Linear Regression (MLR) model maps independent variables X to a dependent variable (response) Y using the following equation (1):

$$Y = W_1X_1 + W_2X_2 + ... + X_pX_p \quad (1)$$

Where W_i is the coefficient of the regression [28]. An ideal method is a method that has low standard deviation, high correlation coefficient [29].

Combination methods

QSAR methods including GA-ANN, SA-ANN, MLR-GA 1276 descriptors were considered as possible input of the ANN and fed into the input layer of the ANNs that they were all three-layer and Levenberg-Marquart algorithm [29] was applied for training on the TSET members. Modeling and optimization calculations were carried out using Matlab 7.12. The 1276 SPSS [20] screened descriptors were used as the feed to a MLR- ICA approach as the population matrix in order to find the best descriptors for the gas phase. The numbers of the most effective descriptors (8 for the gas phase) had chosen by a stepwise multiple linear regression procedure in this work. The developed algorithm of this work is depicted in Fig. 1. The procedure begins from random points (matrix indices of descriptors) called the initial countries that are the counterpart of chromosomes in GA and it is a set of values of a candidate solution for the optimization problem. The empires are sub-populations of the countries. Assimilation, which can be considered as a primitive form of Particle Swarm Optimization [14, 30, 31] moves all non-best countries (called colonies) in an empire toward the best country (called imperialist) in the same empire to find the colonies with the lowest error (RMSE of MLR-predicted XLOGP versus the empirical values). Different number of decision variables (nDes) and different number of empires (nEmp) were investigated to obtain the least RMSE and highest R^2. The number of decision variables (nDes)) and number of empires/ imperialists (nEmp) were considered 5 and 10, 20, 30, respectively.

Monte Carlo method

CORAL [32] software was used for calculation of descriptor correlation weight (DCW) of the 25 Doxazolidine compounds with a hybrid optimization scheme including hydrogen-suppressed molecular graph

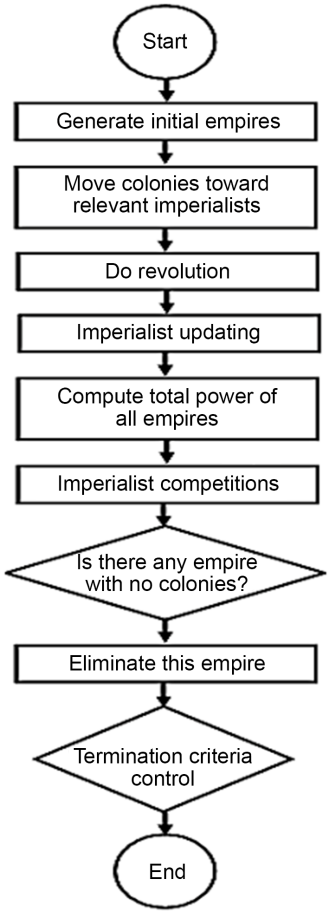

Fig. 1. Flowchart of the employed MLR-ICA algorithm

(HSG), hydrogen-filled graphs (HFG) and SMILES representation of molecular structures. Modeling using CORAL software was carried out for thresholds of 1 up to 3 and 100 epochs (i.e., an overall number of 900 runs were performed) [33, 34]. The SMILES-based and Graph -based optimal descriptors were using from the other work [35, 36]. The hybrid objective function for finding the optimal descriptors is defined as:

$$DCW(T,Nepoch)^{Hybrid} = DCW(T,Nepoch)^{SMILES} + DCW(T,Nepoch)^{Graph} \quad (2)$$

RESULTS AND DISCUSSION

All the optimized Alectinib compounds are illustrated in Fig. 2. The half maximal inhibitory concentration (IC50) for these compounds was obtained from pubchem [17]. The RMSE and the correlation coefficient (R^2) in MLR–PCR, MLR–PLS1 and MLR–MLR for the predicted biological activity were found to be [0.3058-0.7381], [0.2444-0.8550] and [0.2301-0.8617], respectively. Furthermore, the calculated parameters indicated that MLR–MLR method were better than all other employed linear methods (MLR–PLS1 and MLR–PCR). The 1276 descriptors were fed to the SA-ANN, GA-ANN and MLR-GA models and then the best descriptors were selected and then statistical parameters were calculated. Table 1 show that RMSE and R^2 for predicted activity in GA-ANN were found to be 0.1443 and 0.9701, respectively. Therefore GA-ANN model were better than the other nonlinear models and therefore, the selected descriptors using GA–ANN are discussed in the Table 2. GETAWAY (Geometry, Topology, and Atom Weights Assembly) descriptors in compounds encode the geometrical information obtained from the molecular matrix, the topological information obtained from the molecular graph and the information obtained from atomic weights which are specially designed with the aim of matching the 3D-molecular geometry [37]. The radial distribution function (RDF) descriptors, which are based on the distance of distribution in the molecule and ensemble of n atoms, can be interpreted as the probability distribution of finding an atom in a spherical volume of radius R [37]. The molecular transformation employed in electron diffraction studies created the 3D-MoRSE descriptors [38]. The BLTA96 (Verhaar model of Algae based-line toxicity from MLOGP (mmol/l) is Molecular properties descriptor. The MLOGP2 (Squared Moriguchi Octanol-Water partition coeff. (logP^2) is Molecular properties descriptor that is a method for the calculation of the n-octanol/water partition coefficient based on similarities in the structure or properties of chemical compounds [39].

Optimum value/range descriptors in GA-ANN method are depicted in Table 3 in gas phase. According to this table, for designing new drugs, BALTA96 and Mor12u descriptors are recommended to be at their minimum value. Adversely, Mor02u and RDF085m descriptors should have the maximum value and H6u in the range of 0.8 to 2.2.

In MLR-ICA approach as a first trial, 200 numbers of iterations were done to find the most powerful empires and, subsequently, the best descriptors. A plot of the best cost values versus the number of iterations is

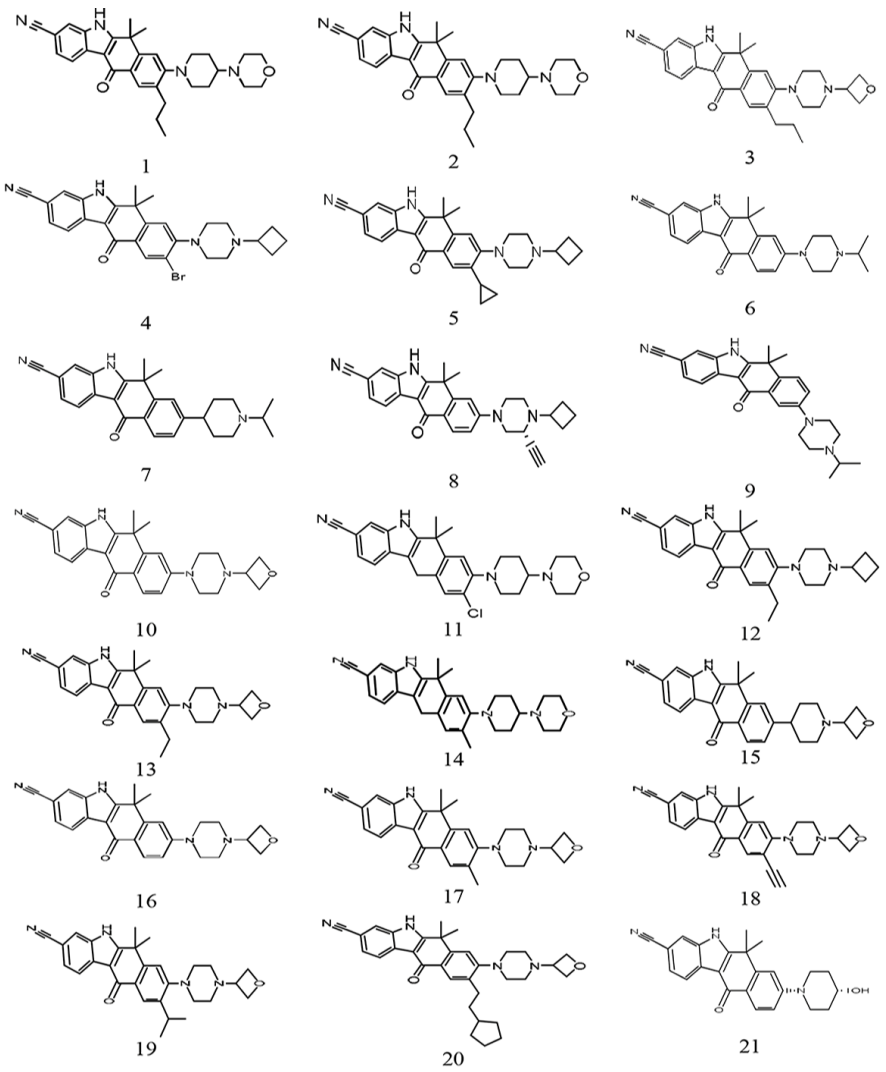

Fig. 2. Optimized structure of the Alectinib derivatives used to build QSAR models with B3lyp/6-31g in gas phase.

Table 1. Statistical parameters of QSAR models

QSAR Models*	Predicted	
	R^2	RMSE
SA-ANN	0.9389	0.1510
MLR-GA	0.9	0.1890
GA-ANN	0.9701	0.1443

[a] The naming is according to Fig. 2.

represented in Fig. 3. It implies that there is no variation in the best cost (MSE) after about 200 iterations. Therefore the number of iterations for the rest of computations was set to 200.

The effects of number of selected descriptors on the chosen descriptors and the prediction quality (according to R^2 and RMSE) was investigated and it is ex-

Table 2. Definition of the selected descriptors using GA-ANN Method

Descriptor	Definition	Type
RDF085m	Radial Distribution Function -8.5 /weighted by atomic masses	RDF descriptors
BLTA96	Verhaar model of Algae base / toxicity from MLOGP(mmol)	Molecular properties descriptor
Mor12u	3D-MoRSE- signal 12/ unweighted	3D-MoRSE descriptors
Mor02u	3D-MoRSE- signal 02/ unweighted	3D-MoRSE descriptors
H6u	H autocorrelation of leg 6/ unweighted	GETAWAY descriptors

Table 3. Optimum value/range descriptors in GA-ANN method

Descriptor	range	Optimum value/range
RDF085m	8-20	13
BLTA96	-5-0	-5
Mor12u	-5—1.5	-1.5
Mor02u	35-65	35
H6u	0.8-2.2	2.2

pected, the model's accuracy regarding to R^2 and RMS increases by increasing the number of model parameters (descriptors in this case). In order to choose the most suitable number of empires, the model was run using different number of empires and the results are demonstrated in Table 4. According to this table the optimum number of empires was chosen as 20. The predicted values of –logIC50 using the MLR-ICA are plotted against the observed values in Fig. 4, which indicates a very strong agreement. The best selected descriptors using MLR-ICA Method with nDes= 5 and nEmp= 20 are RDF 020u, HATs2u, Mor28m, R7e and H5p discussed in the Table 5.

The graphs of RDF 020u, HATs2u, Mor28m, R7e and H5p descriptors versus –logIC50 were plotted using Matlab program (Fig. 5). The charts showed that with increase in RDF020u, HATs2u and R7e descriptors the response (-logIC50) was reduced. Also, as

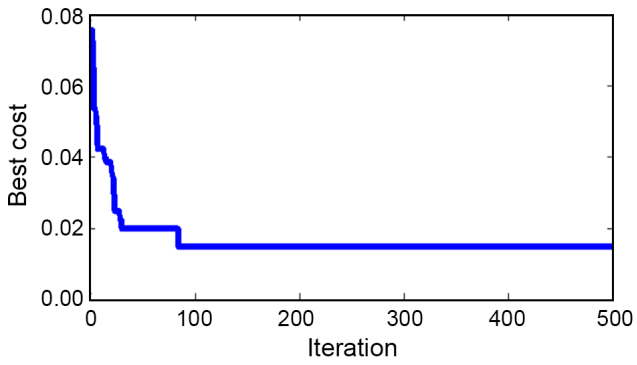

Fig. 3. Plot between Best Cost values versus the variation of Iteration.

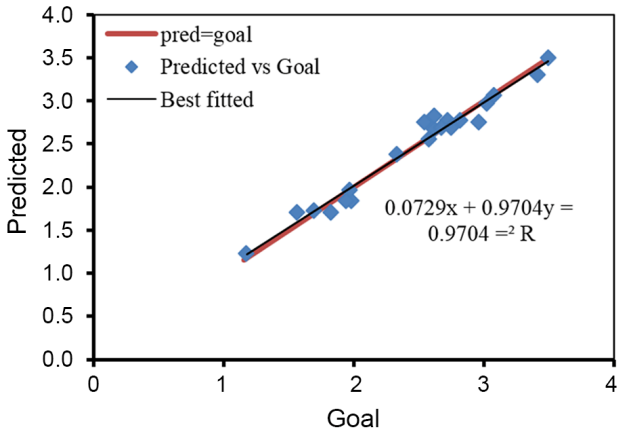

Fig. 4. Plot between predicted values versus Goal with nVar= 5 and nEmp= 20.

Mor28m descriptor increased, response (-logIC50) increased as well. As the H5p descriptor increased from 0.5 to 0.9, no changes in response were observed. Thus during this period, a bar was seen in the response. Therefore descriptors that increased response the amount of -logIC50 are more effective because the half maximal inhibitory concentration (IC50) value is reduced.

Result of the Monte Carlo Method

The statistical parameters of the models obtained using molecular graphs (HSG) and SMILES are shown in Table 6. Performance of the models were compared with each other by the criterion of the predictability in test set (Rm^2) which should be larger than 0.5 [34], correlation coefficient (R^2) in each set and standard error of estimation (s). The difference between R^2m

Table 4. Statistical parameters of ICA-MLR models in gas phase with different nEmp (Max.It= 200).

nVar- nEmp	Predicted (Gas phase)	
	R^2	RMSE
5-10	0.9691	0.1051
5-20	0.9704	0.1028
5-30	0.9691	0.1051

Table 5. Definition of the selected descriptors using ICA-MLR Method

Descriptor	Definition	Type
RDF 020u	Radial Distribution Function-2.0/ unweighted	RDF descriptors
HATs2u	Leverage –weighted autocorrelation of lag 2/ unweighted	GETAWAY descriptors
Mor28m	Radial Distribution Function -2.8 /weighted by atomic masses	3D-MoRSE descriptor
R7e	R autocorrelation of leg 7/ weighted by atomic Sanderson electronegativities	GETAWAY descriptors
H5p	H autocorrelation of leg 5/ weighted by atomic polarizabilities	GETAWAY descriptors

Table 6. The best split model in Monte Carlo Method

Split 1: (T= 2, prob= 2)
-logIC50 = -2.4831394 (± 0.5130138) + 0.0661489 (± 0.0067268) * DCW(2,100)
n= 6, R^2= 0.9694, s= 0.107 (training set)
n= 5, R^2= 0.9792, s= 0.624 (calibration set)
n= 5, R^2= 0.8025, s= 0.531 (test set), R^2m TEST= 0. 0.5100

Table 7. SMILES attribute with positive correlation weights for split 1

SMILES attributes	CWs	SMILES attributes	CWs
3...(.....	4.12658	C6....H.4...	4.74797
3.....	3.00231	C5.....0...	4.18360
5.....	3.93714	1...(.....	3.74544
C...#.....	3.24927	2...(.....	3.93426
C...3.....	4.75234	N...3.....	3.62419
C...C.....	4.12234	[...1.....	4.99970
C3.....0...	3.99523	[...3.....	3.62199
BOND11000000	5.49567	N...(.....	4.37442
EC0-C...2...	3.68794	-	-

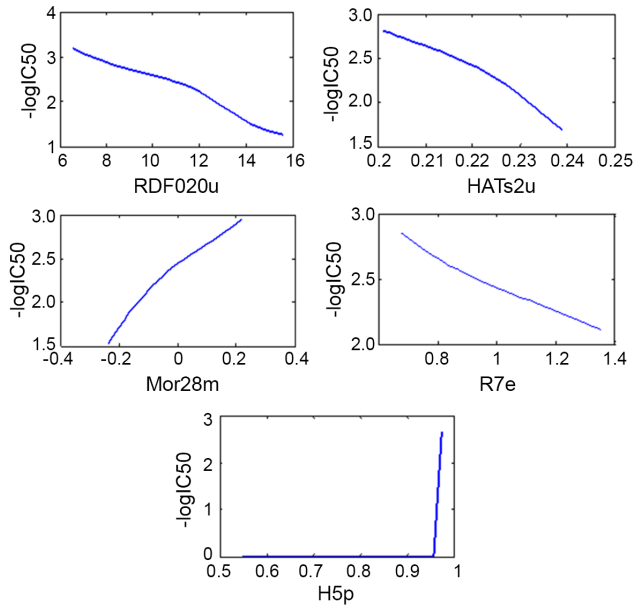

Fig. 5. Plot between biological activity (-logIC50) versus of the RDF020u, HATs2u, Mor28m, R7e, H5p descriptors.

and R'^{2}m values (ΔRmTEST) was used as another criterion in this issue. The best split model in Monte Carlo Method is presented in Table 6. As shown in this table, the predictions for probe 2 and threshold of 2 are better than the others. The variation of correlation coefficient (test set) with respect to threshold and the number of epochs are plotted in Fig. 6. This Fig. confirms that 2 and 10 are the most appropriate values for threshold and number of epochs, respectively.

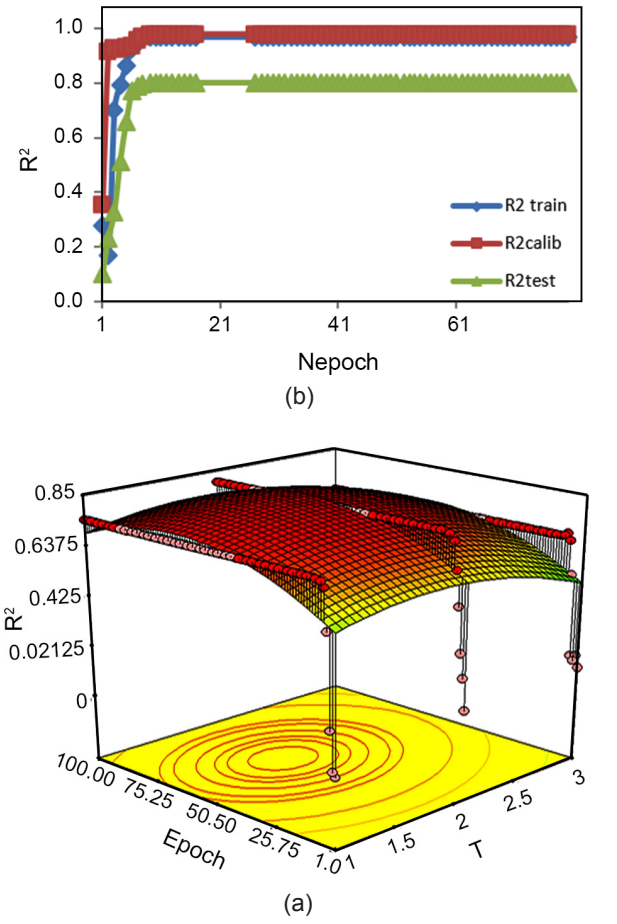

Fig. 6. The variation of correlation coefficient for test set by threshold and number of epochs. (A) Effects of the number of epochs. (B) 3-D surface plot of R2 according to the threshold and the number of epochs.

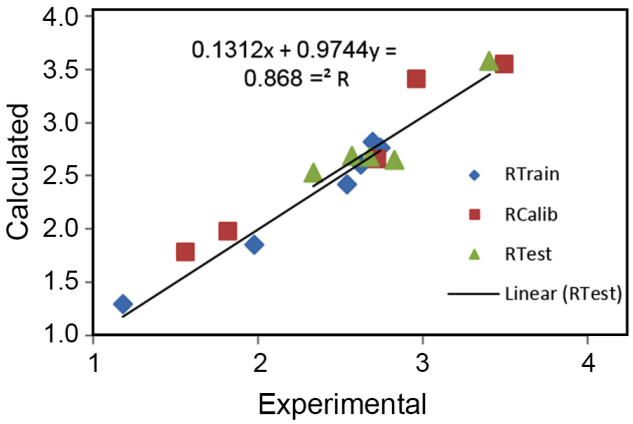

Fig. 7. Correlation between experimental and predicted –logIC50 calculated.

The experimental and calculated -logIC50 for the sequence of compounds are plotted against each other in Fig. 7. A good correlation between the calculated and empirical values of -logIC50 can be observed in this Figure that approves the appropriateness of the developed model.

Molecular features are sorted according to their correlation weights and are given in Table 7. Molecular feature with negative correlation weights are omitted due to their inverse effect on the -logIC50 value. The higher the correlation weigh of a molecular feature, the reduce value of IC50; therefore the feature is more significant. Definitions of the molecular features are given by Kumar and Chauhan [37]. According to Table 7, Presence of cyclic rings with branching, presence of carbon in sp^2 and triplet bond, sp^2 Carbon connected to ring, 6 six-member cycles with aromaticity and H atom in cycle, three and five-member cycles, Nitrogen connected to branch and ring, double and triple bonds, two sp^2 Carbon connected are the most important molecular features that might be considered in designing new drugs.

CONCLUSION

The GA-ANN and ICA-MLR show the best performance among the considered approaches. In ICA-MLR method the RDF 020u, HATs2u, Mor28m, R7e and H5p descriptors were found to have an important role in change in -logIC50. On the other hand, size of the inhibitor molecule, and atomic Sanderson electronegativities should be minimum and weighted by atomic masses and polarizibility should be maximum in new drug design. In Monte Carlo method the structural descriptors including presence of three and five-member cycles, presence of double triplet bonds and cyclic ring with branching are important. In GA-ANN method toxicity from MLOGP (mmol) descriptor is recommended to be at their minimum value. Adversely, atomic masses and Mor02u descriptors should have the maximum value. These Physico-Chemical and structural descriptors can be used for designing new drugs because decreasing the Biological activity (IC50).

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AUTHOR (S) BIOSKETCHES

Robabeh Sayyadi Kord Abadi, Assistant Professor, Department of Chemistry and Chemical Engineering, Rasht Branch, Islamic Azad University, Rasht, Iran, *Email: sayyadi_04@yahoo.com & sayyadi@iaurasht.ac.ir*

Reza Rajabei Nezhad, Assistant Professor, Department of Fisheries, Bandar Anzali Branch, Islamic Azad University, Bandar Anzali , Iran, *Email: reza_igl@yahoo.com*

Kobra Akhavan, Assistant professor, Department of Chemistry, Rasht Branch, Islamic Azad University, Rasht, Iran, *Email: kobra.akhavan@gmail.com*