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QSAR Studies of Inhibitory Properties of 2-Substituant -1H-Benzimidazole-4-Carboxamide Derivatives against Enteroviruses

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ABSTRACT: A series of benzimidazole derivatives evaluated for their activities against four types of enteroviruses, coxsackievirus A16, B3, B6 and enterovirus 71 in Vero cells have been built and subjected to 3D-QSAR analysis to derive a correlation between TC_{50} and IC_{50} activities, and various physic-chemical descriptors. Both QSAR models were performed using multiple linear regression (MLR) and neural network (NN). Best correlations are obtained for both IC_{50} (r_{RLM} = 0.90, r_{NN} = 0.93), and TC_{50} (r_{RLM} = 0.88, r_{NN} = 0.95). To test the performance of these models, we used cross-validation method with LOO procedure

KEY WORDS: quantitative structure activity relationship (QSAR), Entrovirus, Multiple linear Regression (MLR), Neural network (NN), Cross validation (CV).

I. INTRODUCTION

Compounds with the benzimidazole nucleus are commonly encountered in drugs having a broad diversity of pharmacological activities: anthelmintic, gastroprotective, antitumoral, antiviral, antifungical, and antibacterial [1]. The fact that 2, 5-dimethylbenzimidazole was a component of natural vitamin B_{12} had triggered the interest of researchers to ward benzimidazole derivatives, it's had proven abilities to suppress bacterial growth and proton pump function [2]. Due to the ability to interact with DNA, benzimidazole unit become an effective precursor for a wide array of drugs targeting DNA and DNA associated processes. The benzimidazole unit could interact with DNA in the minor groove to interfere with DNA processing enzymes, such as DNA polymerase, RNA polymerase, and to poisomerases I and II.

The enteroviruses can cause a variety of illnesses ranging from gastroenteritis to myocarditis and aseptic meningitis [3]. Human enteroviruses are prevalent worldwide, excreted at high concentrations in human wastes of infected individuals and persistent in the environment [4], conventionally, enteroviruses were classified into polioviruses, coxsackie A viruses, coxsackie B viruses, echoviruses, and enteroviruses 68-71 (EV 68-71). Coxsackie virus B_3 (CVB_3) is an important human pathogen inducing acute and chronic viral mycraditis in children and young adults, precarditis, and hepatitis.

After the host cell infected, the genome of enterovirus was translated in a cap independent manner into a single polyprotein, and processed by virus encoded proteases into structural capsid proteins were mainly involved in the replication of virus [5].

Quantitative structure-activity/ property relationship are tools to estimate physico-chemical and biochemical parameters and reduce the coast, time and efforts. QSAR/QSPR study is an important section in computational chemistry and is used frequently for predicting physico-chemical and biological activity of organic compounds. To establish the relation between structural characteristics of molecule and its activity the mathematical methods can be used [6]. At present, there are a large number of molecular descriptors that can be used in QSAR studies.

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In this work we attempt to establish a quantitative structure-activity relationship for Activity of benzimidazole derivatives against Coxsackie virus B3 in VERO cells, by studying a series of 40 compounds of 2-substituted -1H-Benzimidazole-4- carboxamide derivatives (Figure 2) [7,8]

We accordingly propose a quantitative model, and we try to interpret the activity of the compounds relying on the statistical analyses. The multiple linear regression (MLR) has served to select the descriptors used as the input parameters for the artificial neural network (ANN), these results are valued by Cross validation method with LOO procedure

II. MATERIALS AND METHODS

2-1 Experimental data

The structure of the 2- substituted-1H-benzimidazole-4-carboxamide is represented in Figure1.

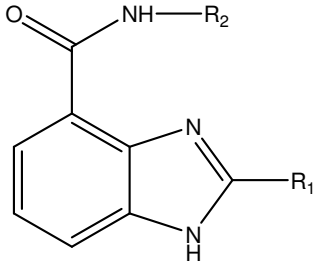
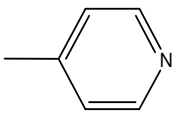
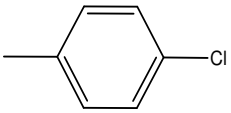
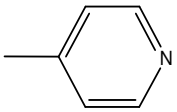
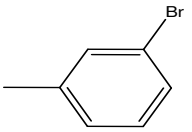
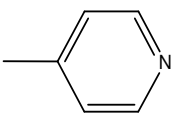
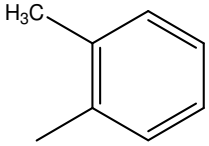
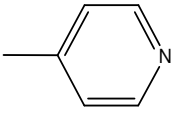
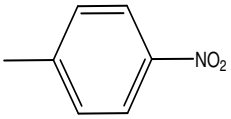


Figure1 : The general structure of the 2 - substituted-1H-benzimidazole -4 – carboxamide

The experimental activities observed TC_{50} (Cytotoxic concentration required to inhibit VERO cell growth by 50 %.) And IC50 (Concentration required to inhibit Coxsackie virus B3 growth by 50 %.) are collected from recent publications [7, 8]. Observations are converted into logarithmic scale $logIC_{50}$ and log TC_{50}, and are included in the table 1

Table 1 : Structure and Activity of benzimidazole derivatives against Coxsackie virus B3 in VERO cells

Compounds	R_1	R_2	$logIC^{a}_{50EXP}$ (µM)	$logTC^{b}_{50EXP}$ (µM)
1			0,9405	1,3107
2			0,6149	0,9159
3			0,3483	1,0310
4			1,2676	1,7443

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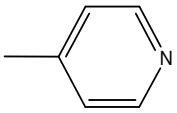
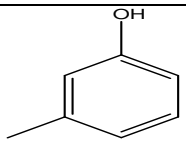
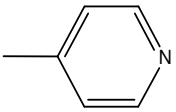
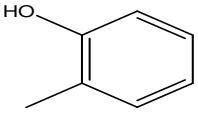
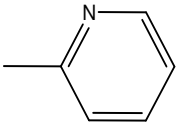
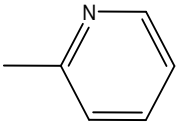
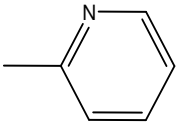
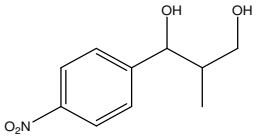
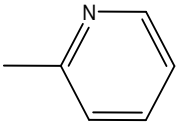
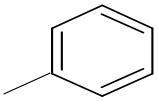
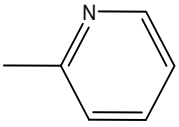
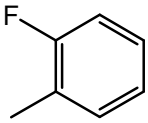
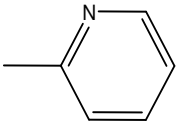
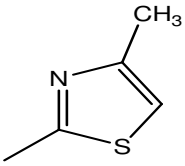
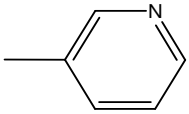
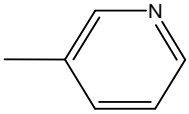
5			NT [c]	0,7709
6			0,6075	1,2672
7		H	1,4857	2,3502
8			2,1173	2,7543
9			0,6085	3,1245
10			-0,3382	1,2529
11			0,2122	1,7380
12			0,2455	1,2480
13		H	1,4150	1,8904
14			1,9576	2,8338

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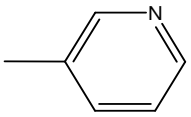
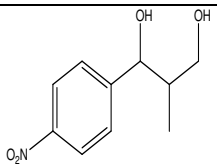
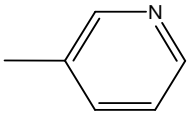
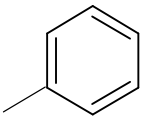
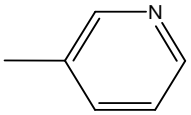
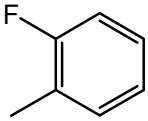
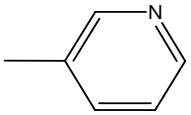
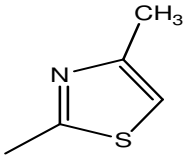
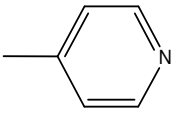
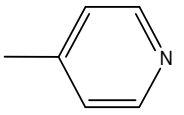
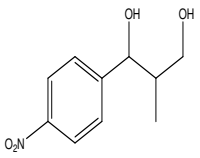
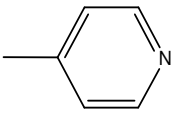
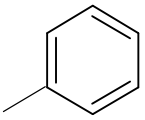
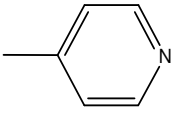
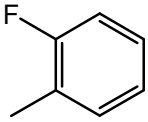
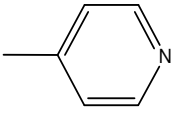
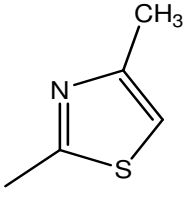
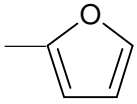
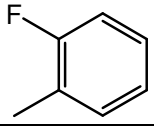
15			1,4564	2,1703
16			0,5705	1,5340
17			0,9881	1,7380
18			1,2095	2,0453
19			NT [c]	2,6972
20			1,4800	2,0899
21			1,0899	1,6972
22			1,5705	2,0453
23			1,3284	2,0453
24			0,5185	1,3979

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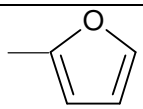
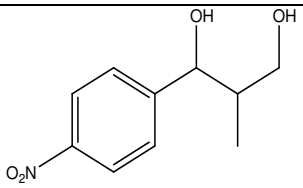
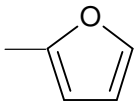
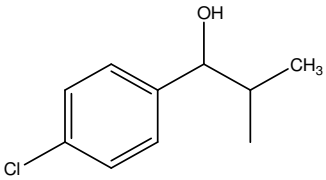
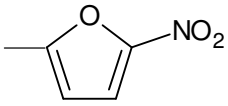
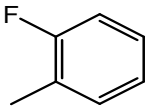
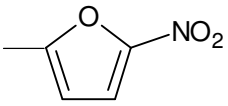
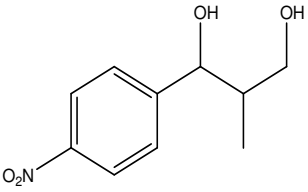
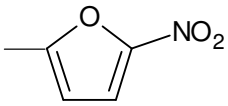
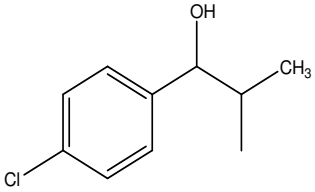
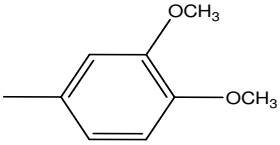
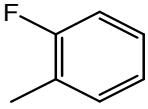
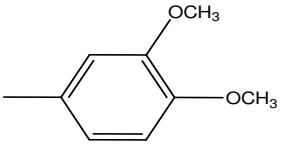
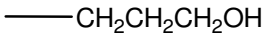
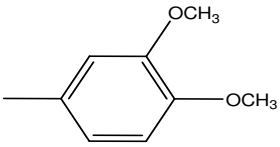
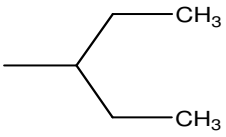
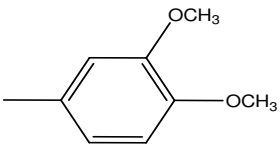
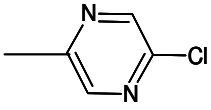
25			1,5763	2,1818
26			1,1271	2,2095
27			1,4031	1,8802
28			1,3598	1,8370
29			1,2095	1,6866
30			0,5441	1,3892
31			1,2355	1,6628
32			-0,1549	0,3483
33			1,2648	1,8938

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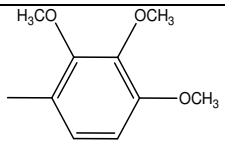
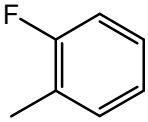
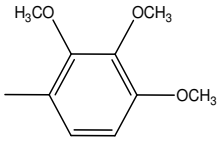
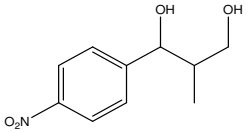
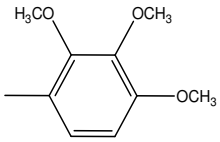
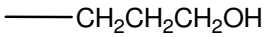
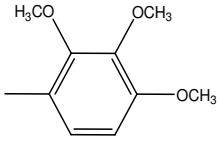
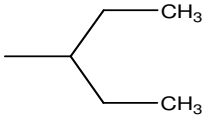
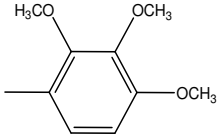
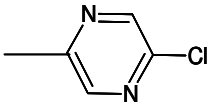
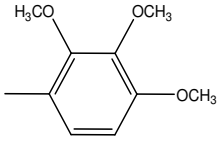
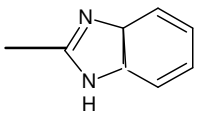
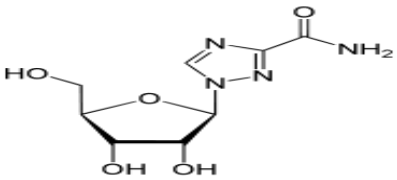
34			0,9912	1,5775
35			0,6749	0,9934
36			1,2900	1,6021
37			1,2718	1,5092
38			1,2405	1,8142
39			1,2279	1,4624
40 [d]			3,2279	3,9133

a : Cytotoxic concentration required to inhibit VERO cell growth by 50%.
b : Concentration required to inhibit Coxsackie virus B3 growth by 50%.
c: Not tested.
d :RVB (Ribavirine)

2-2 Descriptors:

Advanced chemistry development's ACD/ChemSketch program [9, 10] was used to calculate, Molar Volume (MV (cm3)), Molecular Weight (MW), Molar Refractivity (MR (cm3)),

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Parachor (Pc (cm3)), Density (D (g/cm3)), Refractive Index (n), Surface Tension (ST (dyne/cm) and Polarizability (Pol (cm3)).
Steric, electronic and thermodynamic descriptors (Table 1) are calculated using ChemDraw Ultra 8.0 [11] after optimization of the energy for each compound using the MM2 method (force field method with Gradient setting Root Mean Square (RMS) 0.1 kcal mol-1) [12]

Table 2: various Descriptors chosen for QSAR model.

Category of descriptors	**Elrctronic**	**Steric**	**Thermodynamic**
Name of the descriptors	Electronic energy (ElcE), Highest occupied molecular orbital energy (HOMO), Lowest unoccupied molecular orbital energy (LUMO), Repulsion energy (NRE), Total energy (E) Dipole length (μ)	Dipole moment (DIP) Molecular Refraction(RM) Radus (R) Exact mass (EM) Cluster Count (Cls) Wiener Index (Windx)	Henry's law constant (H), Bend energy (Eb), Heat of formation (Hf), logP

2-3Methods

2-3-1 Multiple Linear Regression

The QSAR model is developed using the standard method for multivariate data analysis, the multiple linear regression (MLR). It's also called as ordinary least squares regression (OLS). So, MLR estimates the values of the regression coefficients by applying least squares curve fitting method [13]. The regression equation takes the form:

$$Y_{MLR} = a_0 + \sum_{i=1}^{n} a_i \times C_i \quad Y_{MLR} = a_0 + \sum_{i=1}^{n} a_i \times C_i$$

Or, Y_{MLR}: dependent variable; a_0: regression constant or intercept; a_i: regression coefficient;C_i: independent variable;

The Multiple Linear Regression model (MLR) has served also to select the descriptors used as the input parameters for a back propagation network (NN).

2-3-2 Neural Network (NN):

Neural network (NN) is able to create internal models for complex input-output relationships, based on learning from examples and therefore is useful in prediction.
The NN techniques are also suited for quantitative structure activity relationship (QSAR) applications, so a set of compounds with known activities is available for training, in contrast to simple QSAR methods based on regression analysis, where one has to assume in priority an input-output relation [14].

The first step in designing a NN is data pre-processing, which mainly consists in encoding the input information into an object representation so that this could be processed by the NN. This is a crucial step as the NN performance critically depends on how information is presented to the NN. An ideal encoding scheme should extract maximal information from the input data and satisfy the basic coding assumption that similar item is represented by close vectors. In QSAR-like NN methods, the compounds are usually encoded by molecular descriptors physico-chemical parameters that may be either experimental (e.g. refractive index, octanol/water partition coefficient or spectral data) or theoretical (e.g. molecular volume, weight, charge, electronic, lipophilic and steric properties) [15].
To establish the best NN architecture, precisely to determine the number of hidden layer neurons we defined the parameter ρ, as follows :

$$\rho = \frac{nb.of\ .data.in.the.training.set}{sum.of\ .the.nb.of\ .connection.in.the.NN}$$

In order to avoid over fitting or under-fitting it's recommended that $1.8 \leq \rho \leq 2.3$ [16].

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2-3-3 Cross Validation:

One of the most popular methods for the selection of regression models is based on minimizing the cross-validation (CV) criterion of Stone among [17] an appropriate class of model candidates. This may be particularly motivated when prediction (or, similarly, estimation of the unknown regression function) is the aim of the statistical analysis. [18].

Cross validation was carried out by the Leave-One-Out (LOO) procedure. [19-21] , and the correlation coefficient r_{cv} (q^2) was calculated with equation (3),

$$r_{cv} = q^2 = 1 - \frac{\sum (Y_{pred} - Y_{exp})^2}{\sum (Y_{exp} - Y_{mean})^2}$$

Where Y_{pred}, Y_{exp} and Y_{mean} are the values for the predicted activity, experimental activity and mean activity, respectively.

4-Results and Discussion:

QSAR study was carried for a series of 40 benzimidazole derivatives, in order to determine a quantitative relationship between structure and potential anti-enterovirus activities. The results obtained for 3D-QSAR using MLR, NN and CV method are represented in Table 3

Table 3: Comparative observed and predicted activities of statistically significant models obtained by 3D models

compounds	log IC_{50EXP}	$LogIC_{50\ MLR}$	$LogIC_{50NN}$	$LogIC_{50VC}$	$logTC_{50EXP}$	$logTC_{50MLR}$	$logTC_{50NN}$	$logTC_{50VC}$
1	0,9405	0,6606	0,8255	0,9986	1,3107	1,2949	1,2056	1,4444
2	0,6149	0,9096	0,8009	0,9362	0,9159	1,2355	0,7563	0,9561
3	0,3483	0,0104	0,4234	0,3736	1,0310	1,1336	1,1808	1,1806
4	1,2676	0,8801	0,9450	1,0798	1,7443	1,7980	1,8542	1,7832
5	NT	NT	NT	NT	0,7709	0,7476	0,5705	0,7668
6	0,6075	0,5565	0,8697	0,8719	1,2672	1,6089	1,5758	1,3406
7	1,4857	1,4745	1,6251	1,5473	2,3502	2,0903	2,3564	2,5018
8	2,1173	2,2038	2,2020	2,3132	2,7543	2,2143	2,4162	2,3823
9	0,6085	0,2707	0,5775	0,9245	3,1245	2,3284	2,7939	2,1822
10	-0,3382	0,3340	-0,0393	-0,2244	1,2529	1,5982	1,5381	1,5302
11	0,2122	0,6389	0,3394	0,4501	1,7380	1,6617	1,7014	1,6342
12	0,2455	0,6321	0,2529	0,1215	1,2480	1,7862	1,2850	1,7473
13	1,4150	1,3178	1,3548	1,3456	1,8904	2,0099	2,0406	2,2091
14	1,9576	1,5509	1,6788	1,5768	2,8338	2,5126	3,0431	2,2527

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15	1,4564	1,6779	1,7474	1,4325	2,1703	2,2238	2,3841	2,2086
16	0,5705	0,6678	0,6579	1,3734	1,5340	1,6584	1,5616	1,5831
17	0,9881	0,7816	0,7260	0,7784	1,7380	1,5794	1,5550	1,7361
18	1,2095	1,1843	1,2242	1,2683	2,0453	1,7075	1,6322	1,6970
19	NT	NT	NT	NT	2,6972	2,4169	2,6058	2,6135
20	1,4800	1,4746	1,6112	1,4571	2,0899	2,0217	1,9981	2,0822
21	1,0899	0,9308	0,7189	1,0271	1,6972	1,7843	1,6873	1,6907
22	1,5705	1,4259	1,4429	1,9767	2,0453	1,5991	1,5833	1,9418
23	1,3284	1,5070	1,3580	1,5021	2,0453	2,3751	2,1644	2,1723
24	0,5185	0,6406	0,6212	0,4111	1,3979	1,3234	1,4604	1,0049
25	1,5763	2,0838	1,4890	1,7795	2,1818	2,1337	2,3265	2,2391
26	1,1271	1,1322	1,0728	1,1439	2,2095	2,1822	2,2376	2,2225
27	1,4031	1,7626	1,6198	1,8219	1,8802	2,0897	2,0020	1,8792
28	1,3598	1,6296	1,4039	1,3555	1,8370	1,9250	1,6482	2,0081
29	1,2095	0,9661	1,0568	0,9645	1,6866	1,9155	1,6618	1,8239
30	0,5441	0,4676	0,4626	0,4792	1,3892	1,2583	1,4624	1,4187
31	1,2355	0,9539	0,9757	1,1981	1,6628	1,8260	1,6812	1,5970
32	-0,1549	-0,2027	-0,0398	-0,1252	0,3483	1,0844	0,6236	1,3724
33	1,2648	1,2872	1,2534	1,1799	1,8938	1,9459	1,7930	1,8739
34	0,9912	0,7504	0,8886	0,9289	1,5775	1,3428	1,4858	1,3636
35	0,6749	0,8458	0,7070	0,9224	0,9934	1,2266	1,4383	1,6459
36	1,2900	1,1793	1,2830	1,1671	1,6021	1,8182	1,6906	1,8005
37	1,2718	0,9128	1,4745	1,4532	1,5092	1,0961	1,3806	1,2377
38	1,2405	1,3033	1,3190	1,2147	1,8142	1,9052	1,9213	1,8364
39	1,2279	1,0684	1,0758	1,1535	1,4624	1,3508	1,4318	1,3590
40	3,2279	2,6890	3,2137	2,0825	3,9133	4,2569	3,9191	3,2884

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A-Multiple Linear Regression (MLR)

The derived MLR QSAR models are represented by the following equations:

$\log IC_{50} = -3{,}750 + 2{,}684\mathbf{d} + 0{,}270\mathbf{E}_{LUMO}$

n=41; r=0,901; r^2 =0,811; sd= 0,291; F=48,633

$\log TC_{50RLM} = -1{,}392 - 0{,}007\ \mathbf{RM} + 0{,}024\ \mathbf{ST} + 0{,}614\ \mathbf{E}_{LUMO} - 0{,}218 \log \mathbf{P} + 0{,}086\ \mathbf{DIP} + 0{,}168\ \mathbf{CLS}$

n=40, r=0,89, r^2 =0,79 S= 0,334 F= 16,756

Where n is the number of compounds, r is the correlation coefficient, r^2 is the Squared Multiple, Sd is the standard deviation, F is the Fisher F-statistic.

The most important descriptors involved in the IC_{50} QSAR model are LUMO Energy (Lowest Unoccupied Molecular Orbital) and density, and Good correlation is obtained (r = 0,901). However, Cluster count, Dipole moment, Molecular Refraction and Surface tension LUMO Energy seem to be the relevant descriptors for TC_{50} activity with r = 0,89 . The linear fit between $\log IC_{50EXP}$,$\log IC_{50RLM}$ and $\log TC_{50RLM}$ is sketching in Figures(2;3).

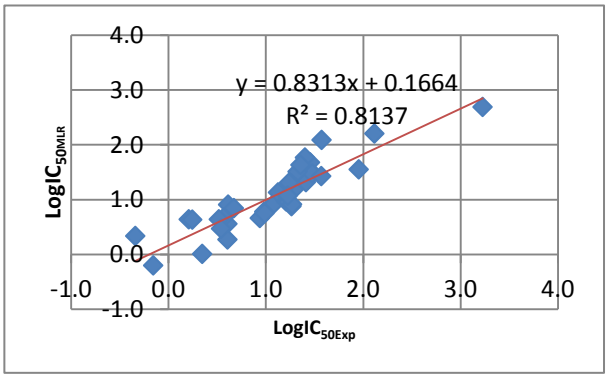

Figure 2: Predicted inhibitory enterovirus activities by MLR correlated to experimental Values of IC_{50}

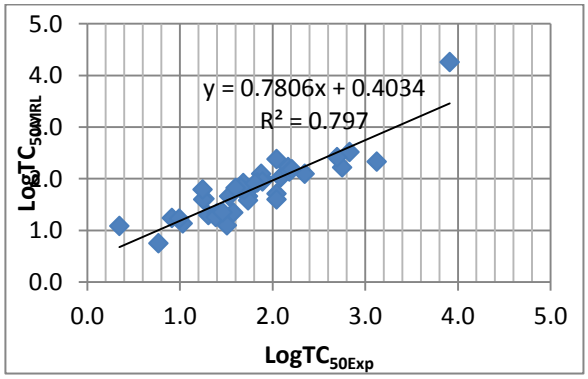

Figure 3: Predicted inhibitory enterovirus activities by MLR correlated to experimental Values of TC_{50}

B-Artificial Neural Network (ANN)

In order to increase the probability of good characterization of studied compounds, 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 activity.

NN models were generated using the descriptors appearing in the MLR models as their inputs. One neuron, which encoded the enterovirus activity, constituted the output layer, and the hidden layer contained a variable number of neurons. In this study, the selected variables by Multiple Linear Regression were used as input and the activity was used as output, the hidden layer and contains a variable number of neurons, the number of the hidden layer neurons are: one neuron for IC_{50}, three hidden neurons for TC_{50}. Interval learning rate was set at 0.1, and the number of times was 500.

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The correlation between ANN calculated and experimental activity values are very significant as illustrated in Figures (4; 5) and as indicated by R and R^2 values, Table 4.

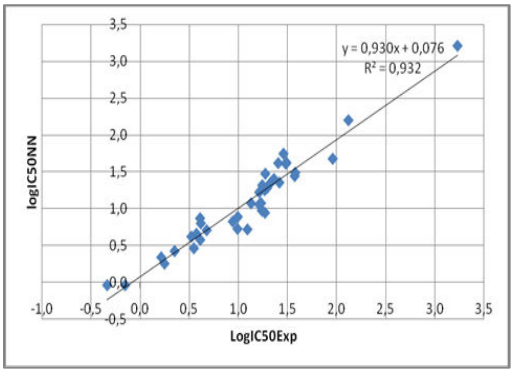

Figure. 4: Predicted inhibitory enterovirus activities by (ANN) correlated to experimental Values of IC_{50}

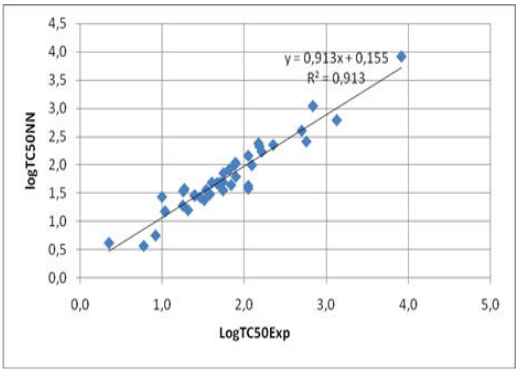

Figure. 5: Predicted inhibitory enterovirus activities by (ANN) correlated to experimental Values of TC_{50}

Table 4 : Correlation coefficient (R), Coefficient of determination (R^2), Standard Error (SD) And Model Architecture (M A)

Activity	R	R2	SE	M A
IC_{50}	0,93	0,86	0,07	2 1 1
TC_{50}	0,95	0,90	0,05	6 3 1

C- Cross Validation:

The consistency and reliability of the MLR and ANN model is validated using the cross-validation technique with leave-one-out (LOO) procedure. Indeed The consistency of the r_{cv} values (r_{IC50} = 0, 89; r_{TC50} = 0, 87) obtained with modified data sets reveals the high stability of the proposed models

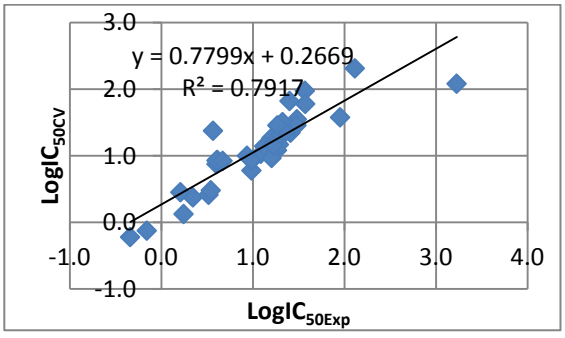

Figure. 6: Predicted inhibitory enterovirus activities by (CV) correlated to experimental Values

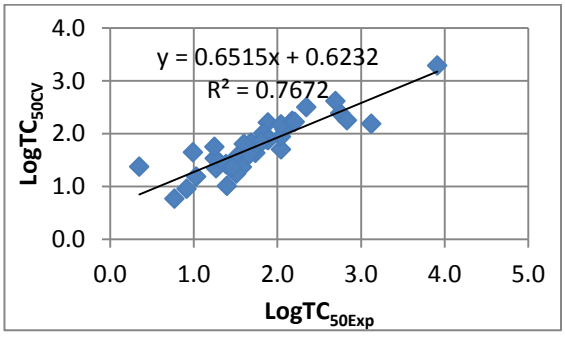

Figure. 7: Predicted inhibitory enterovirus activities by CV) correlated to experimental Values

The results obtained in this study, showed that both models are validated, which means that the prediction of the new compounds is feasible

- The correlation between SI experimental and SI calculated by RLM and R

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The bioactivity of each compound was evaluated by the combination of its IC_{50} and SI, The selectivity index that is defined as the ratio of TC_{50} to IC_{50}. Therefore, the most active compound is that has a minimum IC_{50}value and a maximum SI value. The results of $SI_{EXP,}$ SI_{MLR}, and SI_{NN} are summarized in Tables 4 and Figure 8

Table 4: Comparative observed and predicted selectivity index of each compounds, used statistical methods MLR and NN

compounds	SI^a_{EXP}	SI^b_{RLM}	SI^c_{NN}	compounds	SI^a_{EXP}	SI^b_{RLM}	SI^c_{NN}
1	2,35	4,3073	2,3994	**21**	4	7,1362	9,2982
2	2	2,1176	0,9024	**22**	3	1,4899	1,3817
3	11,48	13,2795	5,7201	**23**	5,2	7,3795	6,4032
4	2,99	8,2771	8,1133	**24**	7,5	4,8169	6,9056
5	NT	NT	NT	**25**	4	1,1217	6,8786
6	4,56	11,2812	5,0828	**26**	12,1	11,2214	14,615
7	7,3	4,1281	5,3864	**27**	3	2,1236	2,411
8	4,3	1,0246	1,6376	**28**	3	1,9744	1,7551
9	**328**	**114,1949**	**164,5887**	**29**	3	8,9005	4,0272
10	38,9	18,3735	37,792	**30**	7	6,1761	9,9954
11	28,4	10,538	23,0144	**31**	2,7	7,4492	5,0757
12	10	14,2605	10,7671	**32**	3	19,3729	4,6068
13	3	4,9212	4,8507	**33**	4,3	4,5571	3,4642
14	7,5	9,1559	23,1366	**34**	3,9	3,9121	3,9555
15	5,2	3,515	4,3321	**35**	2	2,4032	5,3864
16	9,2	9,7857	8,0112	**36**	2,1	4,3547	2,5562
17	3,2	6,2781	6,7453	**37**	1,7	1,525	0,8056
18	6,8	17,084	2,5586	**38**	3,8	3,9983	4,0022
19	NT	NT	NT	**39**	1,7	1,9161	2,2699
20	4,1	3,5243	2,4372	**40**	4,9	36,9787	5,0746

a: $SI^a_{EXP} = TC_{50EXP}/IC_{50EXP}$ b : $SI^b_{RLM} = TC_{50RLM}/IC_{50RLM}$ c: $SI^c_{NN} = TC_{50NN}/IC_{50NN}$

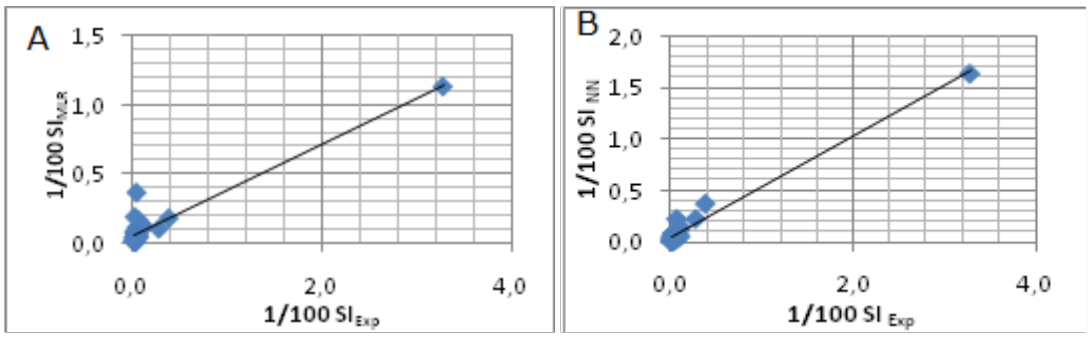

Figure 8: A/ Linear fit between SI_{EXP} and SI_{RLM} , B / Linear fit between SI_{EXP} and SI_{NN}

As shown in Table 2 and Table 4, compounds with 2-pyridyl, 3-pyridyl and 4-pyridyl at the R1 position generally showed good antiviral activity against CVB3, much better than RVB [18,22]. The most potent compound in this series, the compound 9 (IC50EXP = 4.06 µM and SI = 328) was 67 times more selective than RVB (SI = 4.9 µM). These Results are confirmed by MLR and NN models proposed in this work.

In addition, compounds with furyl and phenyl at the R1 position, exhibit excellent experimental IC50 and show best correlation with LMR and NN predicted IC50 values.

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Further, 2 - (3,4- Dimethoxyphenyl)-N- (pentan -3 -yl) -4-carboxamide 1Hbenzimidazole, the most toxic compound (TC50EXP = 2.23 µM) is also the most toxic compound theoretically (TC50MLR = 12.15 µM and TC50NN = 4.20 µM)

III. CONCLUSION

This study reveals how the enterovirus activities of various groups modified 2-substituted -1H-Benzimidazole-4-carboxamide may be treated statistically to uncover the molecular characteristics which are essential for high activity. The analysis methods, RLM, NN and VC applied to the series of 2-substituted-1H-benzimidazole-4-carboxamide Derivatives, allowed us to select the relevant descriptors that could have influence on the activity. In fact Density, LUMO energy showed high correlation to IC_{50} activities both for RLM (r_{IC50}= 0.90) and NN model (r_{IC50}= 0.93). In the other hand Cluster count, Dipole moment, Molecular Refraction Surface tension and LUMO Energy are the pertinent descriptors that form the MLR model (r_{TC50} = 0.89) and the NN model(r_{TC50} = 0.95). The performance of these models is tested by the cross-validation method (CV) (r_{IC50} = 0.89) and (r_{TC50}= 0, 87).

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