

Predictive Activity Modeling of 2-Substituent-1H-Benzimidazole-4-Carboxamide Derivatives against Enteroviruses using QSAR Approach

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Abstract

The present study was focused on development of the potential compound containing 2-substituent-1H-benzimidazole-4-carboxamide derivatives against enteroviruses using QSAR studies. We discussed the two-dimensional QSAR studies of 2-substituent-1H-benzimidazole-4-carboxamide analogues to elucidate the structural properties required for enteroviruses activity. The 2D-QSAR studies were performed using multiple linear regressions, giving square of correlation coefficient (r^2)=0.7458, cross validated squared correlation coefficient (q^2)=0.7128 and predictable ability (pred_r^2)=0.7092. The present study reveals that presence of less bulky group at R1 position of benzimidazole scaffold increase the enteroviruses activity. We hope that the current study provides better insight into the designing and development of more potent benzimidazole-4-carboxamide inhibitors as enteroviruses drug in the future.

Keywords: Benzimidazole; Enteroviruses; 2D-QSAR; Multiple linear regressions

Introduction

Antiviral drugs are urgently needed for the treatment of acute and chronic diseases caused by enteroviruses such as coxsackievirus B3 (CVB3). Enteroviruses are members of the picornavirus family, a large and diverse group of small RNA viruses characterized by a single positive-strand genomic RNA. Enteroviruses affect millions of people worldwide each year, and cause many serious diseases as poliomyelitis, nonspecific febrile illness, aseptic meningitis, pleurodynia, myocarditis [1]. Enteroviruses were a genus of (+) ssRNA viruses are those belonging to the picornaviridae family [2]. This family includes nine genera, some of which comprise major human pathogens, namely, *Enterovirus* (including *Poliovirus*, *Coxsackievirus*, *Echovirus*), *Rhinovirus* (approximately 105 serotypes), and *Hepatovirus* (Hepatitis A virus [HAV]). It is estimated that enteroviruses cause each year 10–15 million (or more) symptomatic infections [3]. The viruses in the Picornaviridae family cause an extraordinarily wide range of illnesses [4-7]. The syndromes associated with these agents include asymptomatic infection, aseptic meningitis syndrome (the most common acute viral disease of the CNS), colds, febrile illness with rash, conjunctivitis, herpangina, muscle infection, heart infection, and hepatitis. Human enterovirus 71 (EV71), a single-stranded, positive-sense RNA virus, belongs to the *Enterovirus* genus of the Picornaviridae family. *Picornavirus* infections are among the most common viral infections in man [8]. *Coxsackievirus* B3 (CVB3) is an important human pathogen inducing acute and chronic viral myocarditis in children and young adults [9]. Quantitative structure activity relationship (QSAR) methods have been applied in numerous scientific disciplines such as computational drug design, predictive toxicology models, and high-throughput screening [10]. QSAR studies have been a major tool in drug optimization [11] and successful QSARs have been developed for ligands of uniform mode of action and congeneric chemical frameworks. A 2D QSAR technique is of particular interest since it eliminates the need for determining 3D structure, putative binding conformation, and molecular alignment [12]. A great number of structural molecular descriptors were explored using the stepwise multiple linear regression, replacement method and recently proposed enhanced replacement method to select the best subset of variables for

2D QSAR study. This approach is available in VLife Molecular Design Suite and takes advantage of interaction descriptors [13].

The present work was undertaken to find a correlation between physicochemical parameters and the biological activity from a series of 2-substituent-1H-benzimidazole-4-carboxamide derivatives against enteroviruses analogs. These correlations will be helpful in the development of benzimidazole-4-carboxamide as anti-enterovirus activities with increased therapeutic efficacy.

Materials and Method

A data set of thirty two compounds of 2-substituent-1H-benzimidazole-4-carboxamide for against enteroviruses activity was used for the present QSAR study [14]. The IC_{50} (μM) values reported in the literature were converted to negative logarithmic values to get pIC_{50} which were used for QSAR study. The structures of these inhibitors and their pIC_{50} values are given in Table 1. It insists as to select these series of compounds for our QSAR studies.

The structures of the compounds under study have been drawn in molecular design suite (MDS) 3.5. The drawn structures were then converted into 3D modules using the default conversion procedure implemented in the MDS. Energy minimizations were performed using Merck molecular force field (MMFF) and MMFF charge [15] followed by considering distance dependent dielectric constant of 1.0 and the convergence criterion of 0.01 kcal/mol.

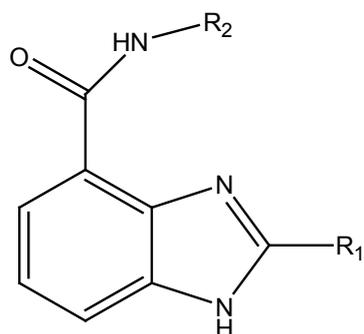
The sphere exclusion method [16] was adopted for division of training and test data set comprising of 26 and 6 molecules, respectively,

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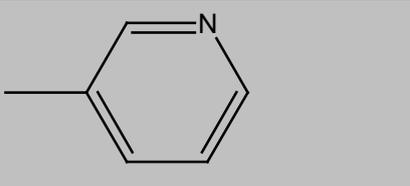
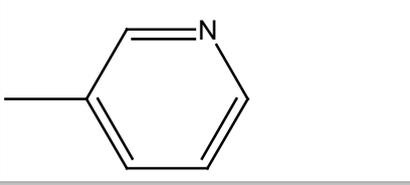
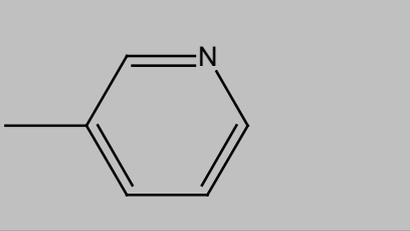
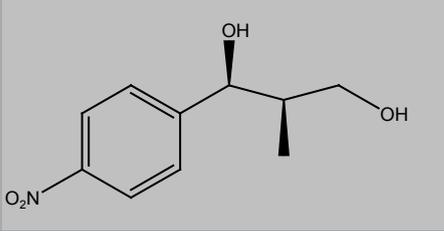
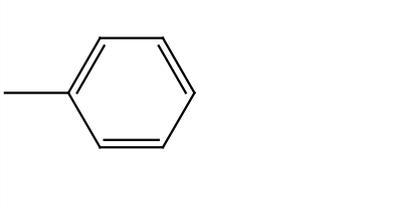
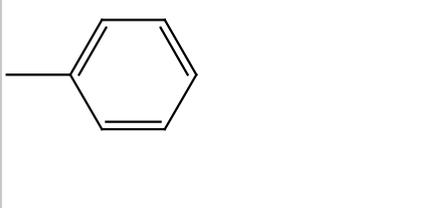
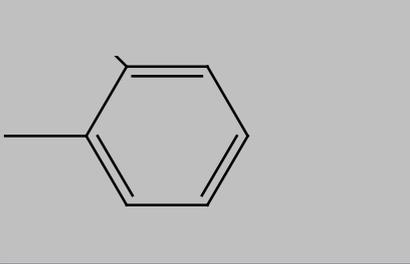
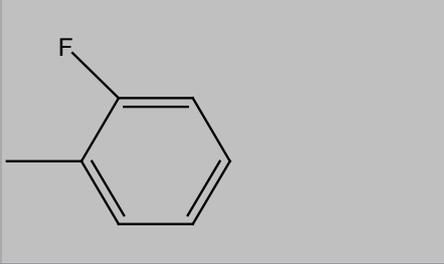
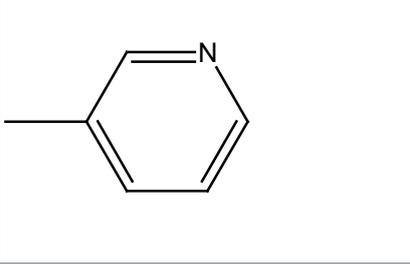
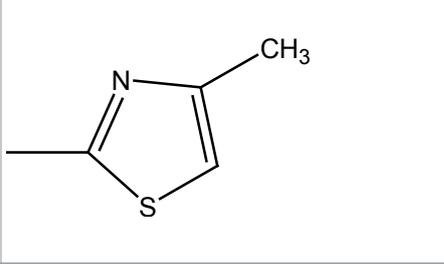
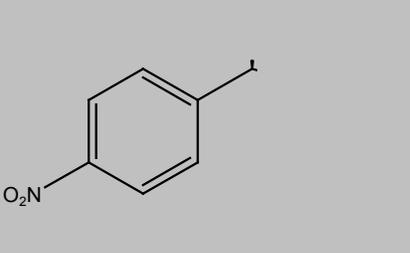
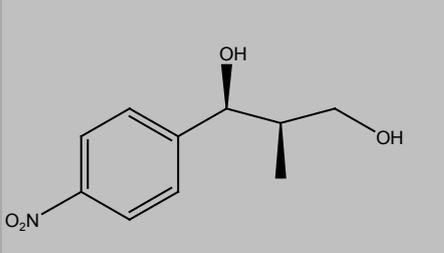
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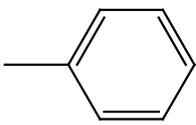
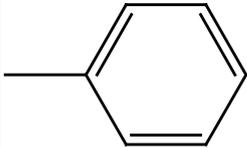
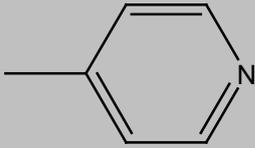
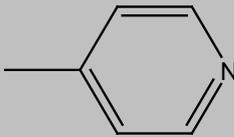
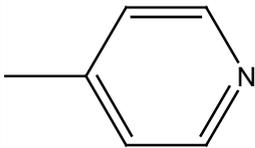
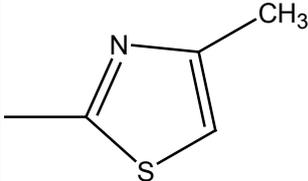
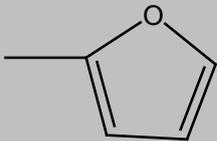
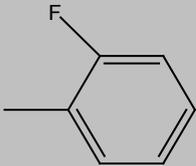
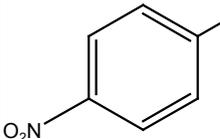
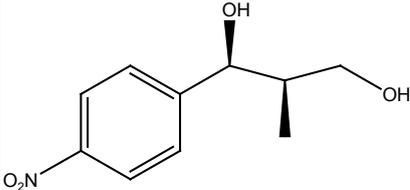
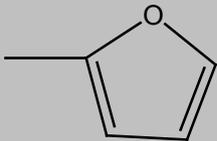
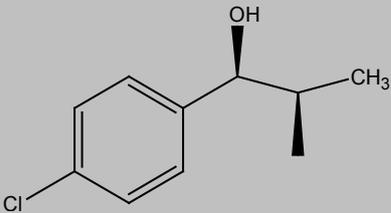
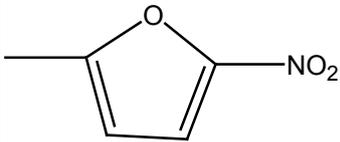
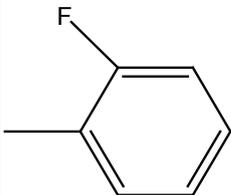
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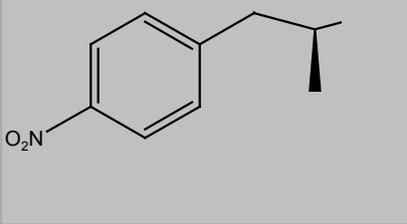
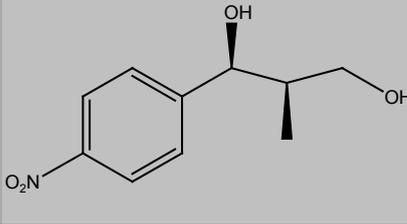
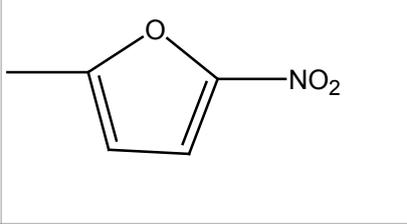
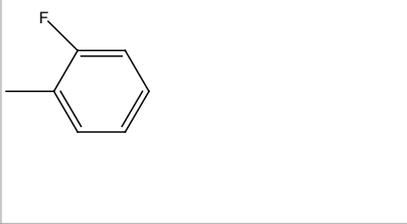
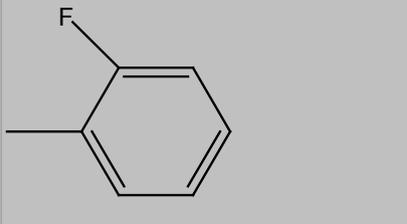
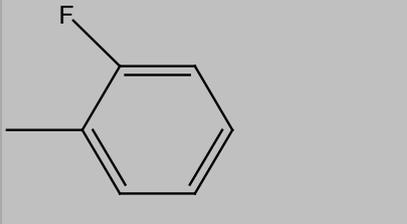
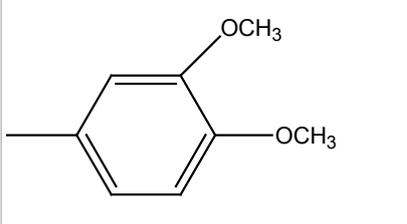
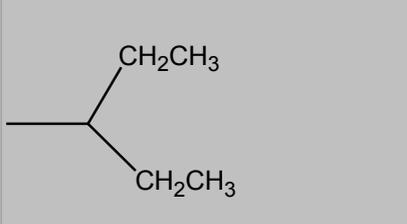
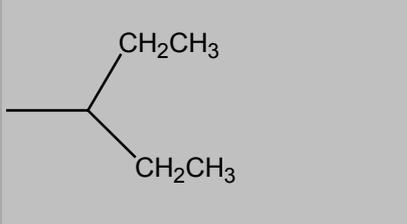
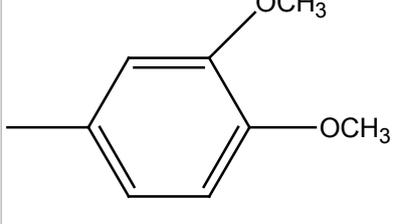
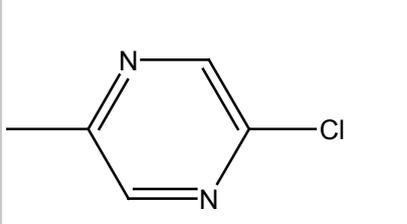
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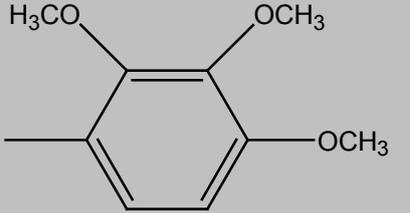
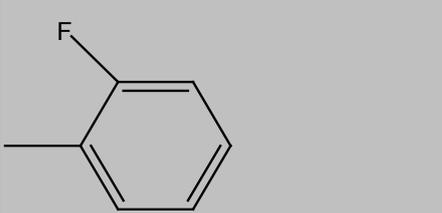
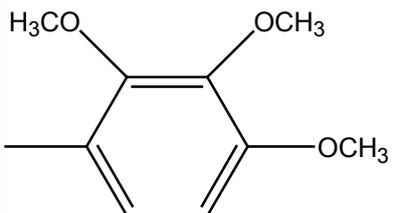
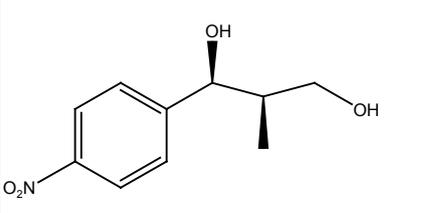
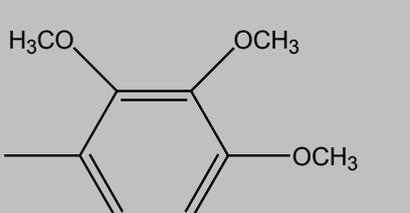
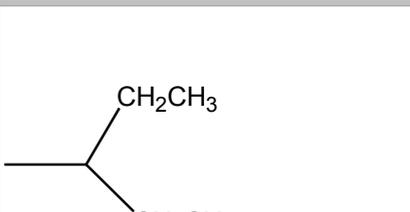
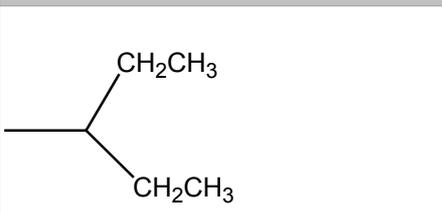
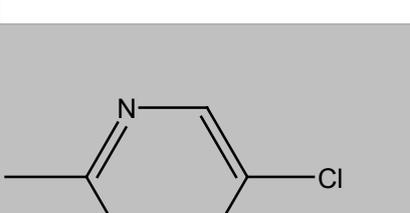
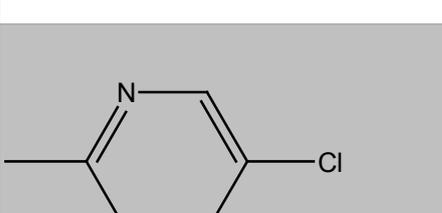
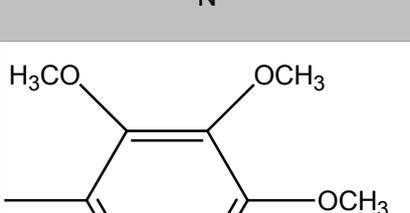
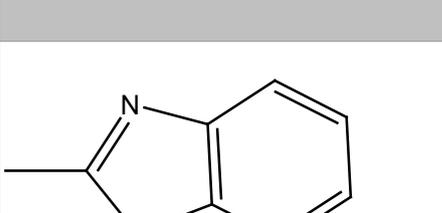


S.No	R1	R2	IC ₅₀ (μM)	pIC ₅₀
1		H	30.6	4.5142
2		-CH ₂ CH ₂ OH	131	3.8827
3			4.06	5.3914
4			0.459	6.3381
5			1.63	5.7878
6			1.76	5.7544

7		H	26	4.5850
8*		-CH ₂ CH ₂ OH	90.7	4.0423
9			28.6	4.5436
10			3.72	5.4294
11			9.73	5.0118
12			16.2	4.7904
13*			30.2	4.5199

14			12.3	4.9100
15			37.2	4.4294
16			21.3	4.6716
17			3.3	5.4814
18			37.7	4.4236
19*			13.4	4.8728
20			25.3	4.5968

21			22.9	4.6401
22*			16.2	4.7904
23			3.5	5.4559
24		-CH ₂ CH ₂ CH ₂ OH	17.2	4.7644
25*			0.7	6.1549
26			18.4	4.7351

27			9.8	5.0087
28*			4.73	5.3251
29		-CH ₂ CH ₂ CH ₂ OH	19.5	4.7099
30			18.7	4.7281
31			17.4	4.7594
32			16.9	4.7721

*Test compounds

Table 1: Structure, and biological activity of 2-substituent-1H-benzimidazole-4-carboxamide.

with dissimilarity value of 2.9 where the dissimilarity value gives the sphere exclusion radius.

Calculation of 2D descriptors

The present study is an attempt to formulate QSAR modeling of 2-substituent-1H-benzimidazole-4-carboxamide compounds utilizing theoretical molecular descriptors such as 2D individual descriptors such as Mol. Wt., Volume, XlogP, smr; Estate Numbers, Estate contributions, Polar Surface Area Individual, Path count, Chain path count, Cluster, Path cluster, Kappa, Element Count, Estate number and Polar surface area electrostatic, constitutional, and geometrical, and topological indices calculated solely from the structures of these compounds. All the calculated 2D descriptors were considered as independent variable and biological activity as dependent variable.

A total of 230 descriptors were calculated by QSAR Plus module within VLife Sciences Molecular Design Suite. The descriptors having the same value or almost same value or highly correlated with other descriptors were removed initially, as they do not contribute to the QSAR.

Results and Discussion

In this study, QSAR equations are generated by multiple linear regression (MLR), and evaluated on the basis of various statistical terms like r^2 (correlation coefficient), q^2 (cross-validated correlation coefficient). 2D-QSAR equations were selected by optimizing the statistical results generated along with variation of the descriptors in

these models.

$$pIC_{50} = 0.6302(\pm 0.1722) T_C_N_4 - 0.8790(\pm 0.2915) \text{Hydrogen count} + 0.3705(\pm 0.0530) \text{SaasN (Noxide) E-index} + 0.5646(\pm 0.1618) \text{SssOE-index}$$

$$N_{\text{training}} = 26, N_{\text{test}} = 6, r^2 = 0.7458, q^2 = 0.7128, \text{pred}_r^2 = 0.7092$$

The model 1 with a coefficient of determination (r^2)=0.7458 was considered, as the model showed an internal predictive power (q^2 =0.7128) of 70% and a predictivity for the external test set (pred_r^2 =0.7092) of about 70%. The model indicates H-count descriptor increased number of hydrogen molecule will result in increased anti-enteroviruses drug potency of benzimidazole-4-carboxamide derivatives. SaasN(Noxide)E- indices for number of nitro-oxide group connected with two aromatic and one single bond, contributed positively and is detrimental to biologic activity in the aforementioned model at the R1, and R2 position. T_C_N_4 (count of number of carbon atoms separated from any nitrogen atom by 4 bonds) descriptor influencing activity variation. SssOE-index showed positive contribution indicated that the anti-enteroviruses drug was increased with the presence of methoxy groups of fragment R1 may lead to an increase in the activity. The correlation matrix between the physico-chemical parameters and the biological activity is presented in Table 2. The observed activity and predicted activity pIC_{50} along with residual values are shown in Table 3. The contribution chart and plots of observed vs. predicted values of pIC_{50} are shown in Figures 1a and 1b respectively.

$$pIC_{50} = -0.482(\pm 0.125) \text{Polarizability AHC} + 0.217(\pm 0.062)$$

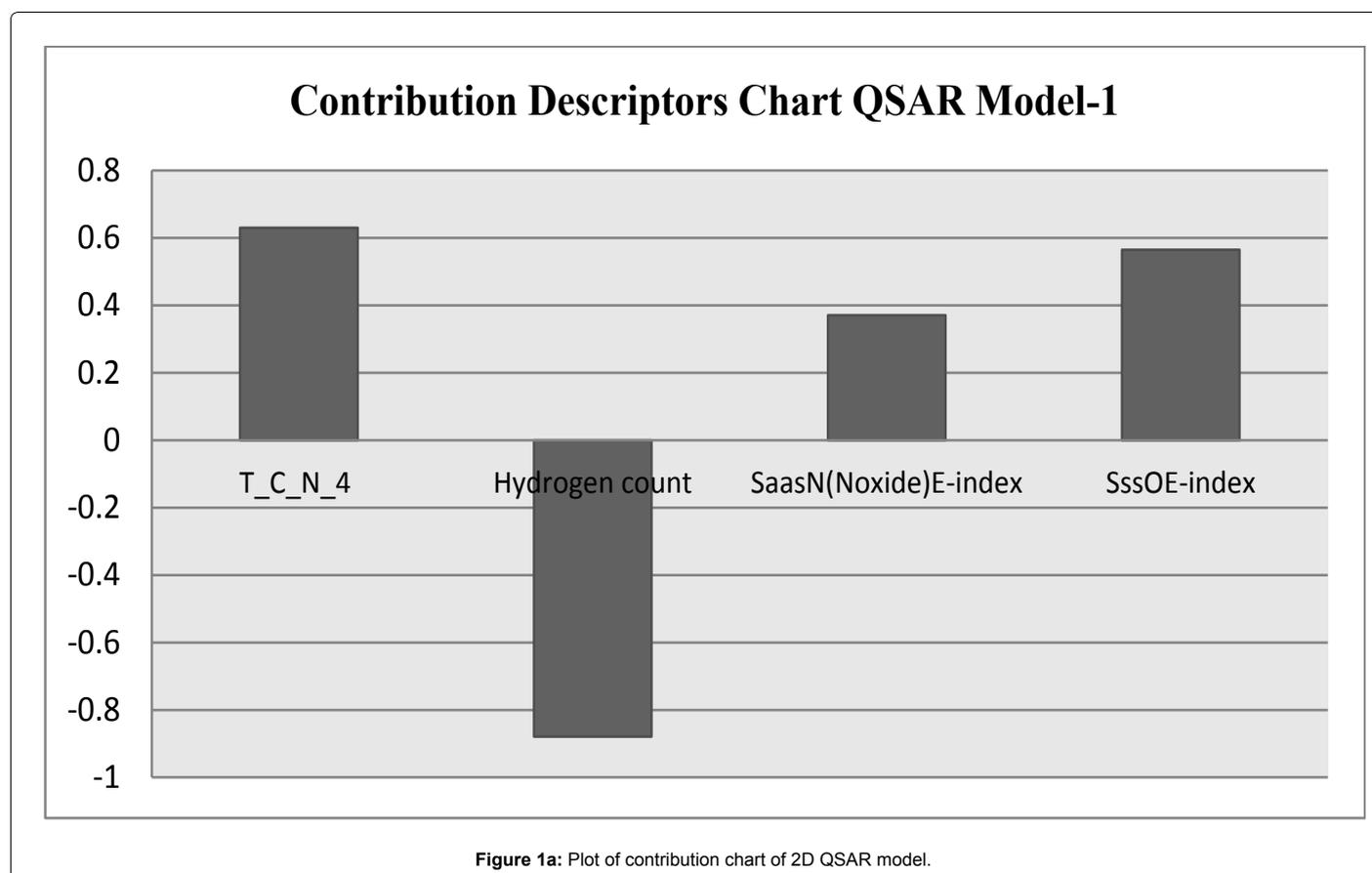


Figure 1a: Plot of contribution chart of 2D QSAR model.

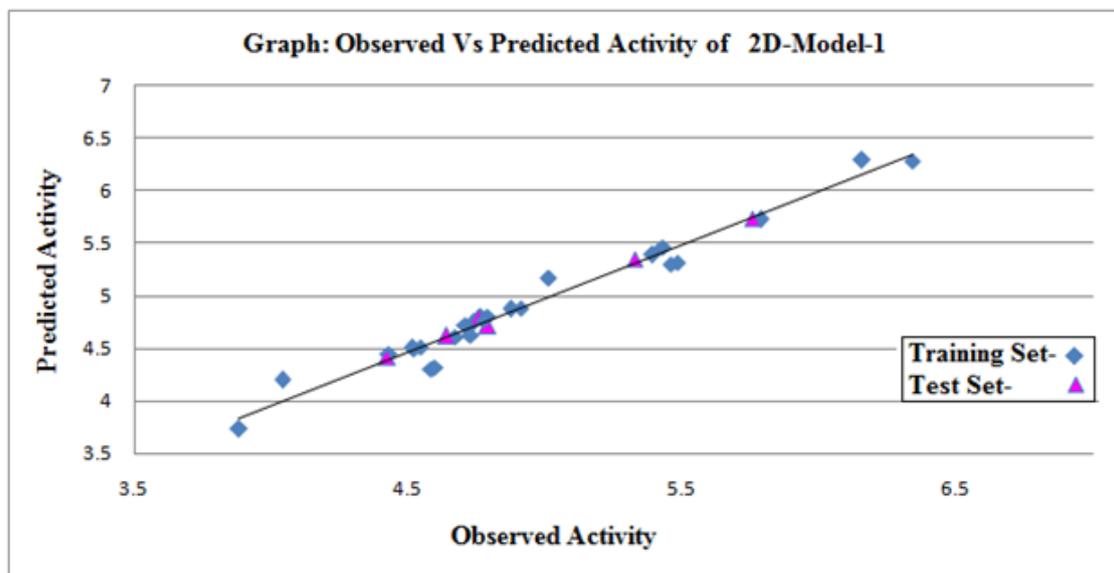


Figure 1b: Graphs of observed vs. predicted activity of 2D QSAR model -1.

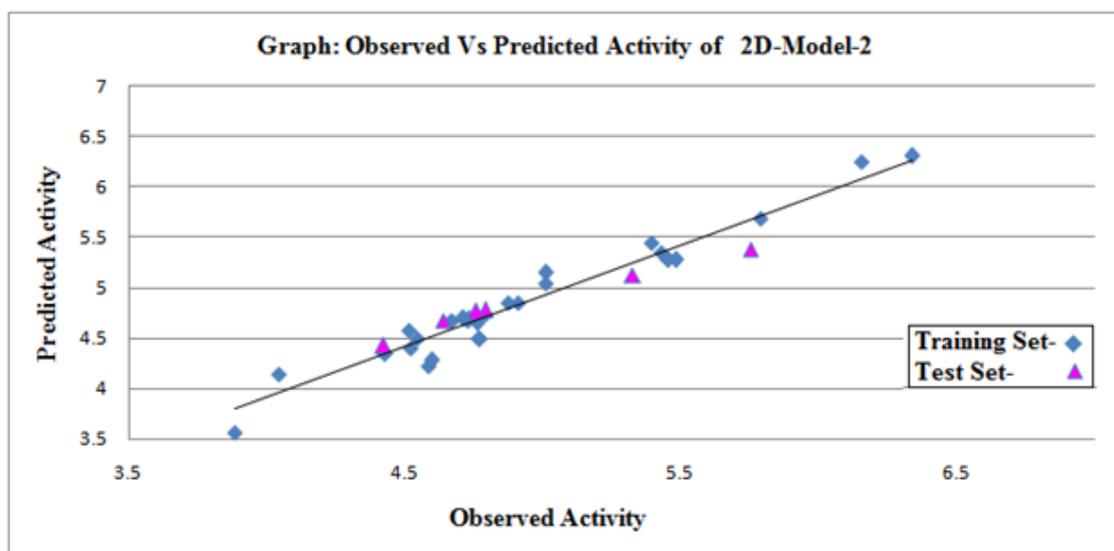


Figure1c: Graphs of observed vs. predicted activity of 2D QSAR model -2.

Parameter	T_C_N_4	Hydrogen count	SaasN(Noxide)E-index	SssOE-index
T_C_N_4	1.0000			
Hydrogen count	0.2165	1.0000		
SaasN(Noxide)E-index	0.4128	0.5395	1.0000	
SssOE-index	0.5914	0.6873	0.8041	1.0000

Table 2: Correlation matrix between descriptors present in the best QSAR model -1.

H-Acceptor Count

$N_{\text{training}}=26$, $N_{\text{test}}=6$, $r^2=0.7194$, $q^2=0.6732$, $F_{\text{test}}=18.2403$, $\text{pred}_r^2=0.6538$

The same data set subjected to the method resulted in r^2 of 0.7194 and q^2 of 67%, with pred_r^2 of 65%. The PolarizabilityAHC descriptor signifies the molecular polarizability using sum of atomic polarizabilities using the atomic hybrid components (AHC) and negative coefficient in the model, suggesting that the increased polarizable groups in the molecules have significant activity on the anti-enteroviruses drug. The descriptor H-Acceptor count explains the number of hydrogen bond acceptor groups present in the molecules. The plots of observed vs. predicted values of pIC_{50} are shown in Figure 1c.

$\text{pIC}_{50}=0.4375(\pm 0.1434) \text{ SsCH}_3 \text{ count}+0.3370(\pm 0.1590) \text{ SsOHE-index}$

$N_{\text{training}}=26$, $N_{\text{test}}=6$, $r^2=0.7194$, $q^2=0.6882$, $F_{\text{test}}=13.468$, $\text{pred}_r^2=0.6102$

Model 3 with the same data set was performed, which resulted in a coefficient of correlation of 0.7494 and external predictivity of 61%. The developed regression model-3 reveals that the descriptor SsOHE-index which is topological state indices for number of -OH group connected with one single bond at R1 substitution site is inversely proportional to activity which means that branching with hydroxyl atom is detrimental for activity. SsCH₃ count positive coefficient of this descriptor signifies the importance of methyl group for activity. The above all models are validated by predicting the biological activities of the training and test

molecules, as indicated in Table 3. The plots of observed vs. predicted values of pIC_{50} are shown in Figure 1d.

Conclusion

Here, we show that the quantitative structure-activity relationship (QSAR) method commonly used to predict the physicochemical properties of chemical compounds can be applied to predict the toxicity of benzimidazole analogues as anti-enteroviruses drug. The models reliably predict the toxicity of all considered compounds, and the methodology is expected to provide guidance for the future design of safe anti-enteroviruses agents. On the basis of discussion given earlier we could conclude that benzimidazole analogues must have T_C_N_4, SaasN (Noxide) E-index and SssOE-index values for enhanced inhibition activity. Talking about the effects of the SssOE-index on the bioactivity of derivatives of benzimidazole analogues, the developed QSAR model suggests that a positive SssOE-index will definitely be favorable to the activity. The suggested substitutions are -CH₃, -OH, methoxy and two substitutions simultaneously at R1- and R2- positions for the improved and potent anti-enterovirus activities. We hope that the current study provides better insight into the designing and development of more potent benzimidazole-4-carboxamide inhibitors as anti-enterovirus drug in the future.

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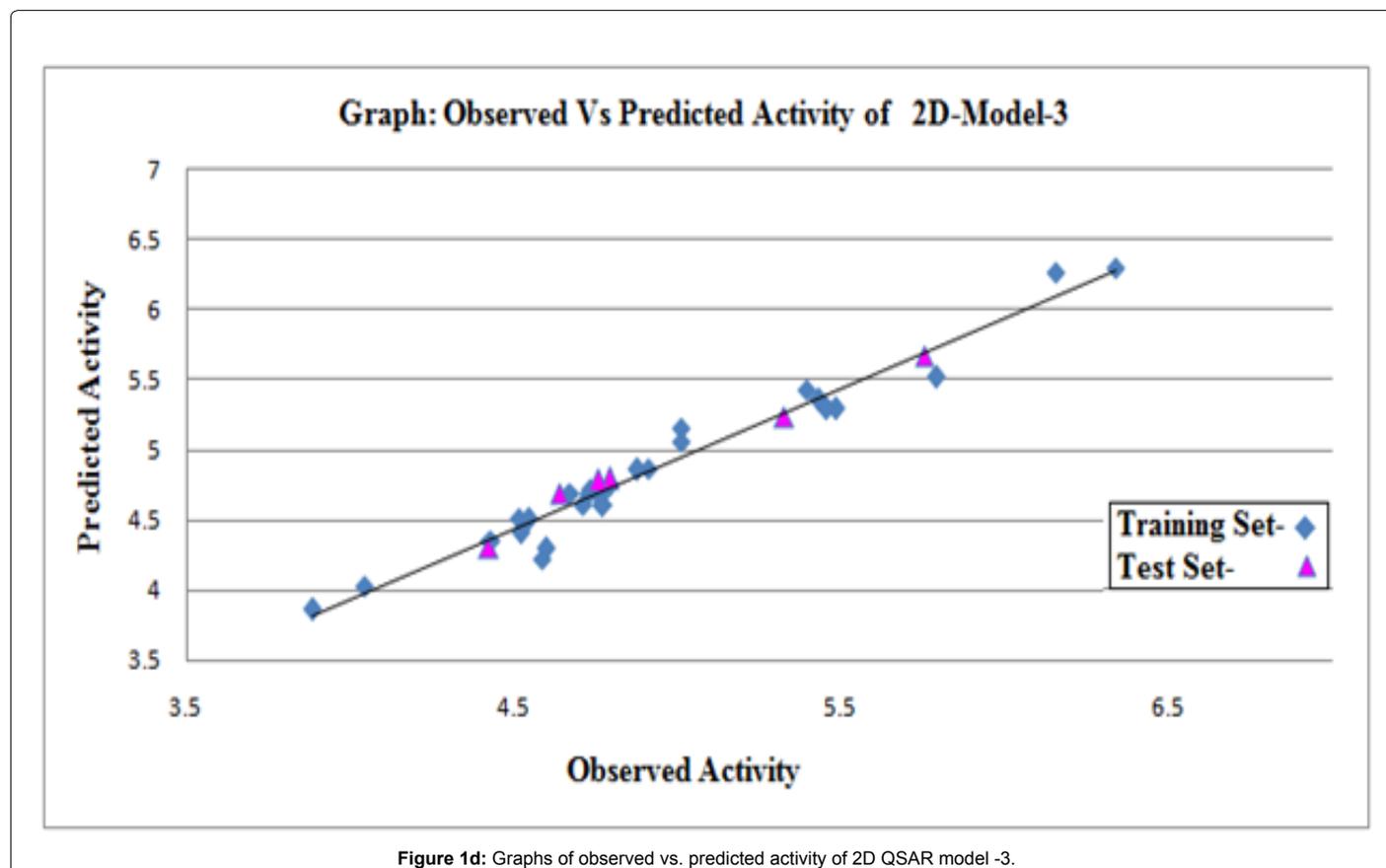


Figure 1d: Graphs of observed vs. predicted activity of 2D QSAR model -3.

Com.	pIC ₅₀	2D QSAR Model-1		2D QSAR model-2		2D QSAR model-3	
		Pred.	Res.	Pred.	Res.	Pred.	Res.
1	4.5142	4.5025	0.0117	4.5760	-0.0618	4.5071	0.0071
2	3.8827	3.7289	0.1538	3.5602	0.3225	3.8565	0.0262
3	5.3914	5.3884	0.003	5.4473	-0.0559	5.4269	-0.0355
4	6.3381	6.2834	0.0547	6.3064	0.0317	6.3004	0.0377
5	5.7878	5.7266	0.0612	5.6906	0.0972	5.5156	0.2722
6	5.7544	5.7311	0.0233	5.3742	0.3802	5.6645	0.0899
7	4.585	4.3007	0.2843	4.2214	0.3636	4.2154	0.3696
8	4.0423	4.198	-0.1557	4.1349	-0.0926	4.0298	0.0125
9	4.5436	4.5063	0.0373	4.4956	0.048	4.5016	0.042
10	5.4294	5.4625	-0.0331	5.3463	0.0831	5.3545	0.0749
11	5.0118	5.167	-0.1552	5.1459	-0.1341	5.1551	-0.1433
12	4.7904	4.7947	-0.0043	4.7327	0.0577	4.7427	0.0477
13	4.5199	4.4922	0.0277	4.3954	0.1245	4.4066	0.1133
14	4.91	4.8786	0.0314	4.8533	0.0567	4.8641	0.0459
15	4.4294	4.4415	-0.0121	4.3402	0.0892	4.3485	0.0809
16	4.6716	4.6075	0.0641	4.6685	0.0031	4.6838	-0.0122
17	5.4814	5.318	0.1634	5.2743	0.2071	5.2891	0.1923
18	4.4236	4.4157	0.0079	4.4208	0.0028	4.296	0.1276
19	4.8728	4.8718	0.001	4.8432	0.0296	4.8571	0.0157
20	4.5968	4.3168	0.28	4.2768	0.32	4.2922	0.3046

21	4.6401	4.6168	0.0233	4.6745	-0.0344	4.6896	-0.0495
22	4.7904	4.713	0.0774	4.777	0.0134	4.7922	-0.0018
23	5.4559	5.3027	0.1532	5.2753	0.1806	5.2891	0.1668
24	4.7644	4.7937	-0.0293	4.6479	0.1165	4.6622	0.1022
25	6.1549	6.2882	-0.1333	6.2505	-0.0956	6.2649	-0.11
26	4.7351	4.7429	-0.0078	4.7058	0.0293	4.7216	0.0135
27	5.0087	5.1679	-0.1592	5.042	-0.0333	5.055	-0.0463
28	5.3251	5.3506	-0.0255	5.1184	0.2067	5.2311	0.094
29	4.7099	4.7151	-0.0052	4.6927	0.0172	4.6025	0.1074
30	4.7281	4.6212	0.1069	4.675	0.0531	4.6914	0.0367
31	4.7594	4.7977	-0.0383	4.7604	-0.001	4.7762	-0.0168
32	4.7721	4.7702	0.0019	4.4842	0.2879	4.6009	0.1712

Table 3: Predicted activities according to QSAR models results of 2-substituent-1H-benzimidazole-4-carboxamide.

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