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Theoretical Studies of Substituted N-(1H-Benzimidazol-2ylmethyl)-5,6,7,8-Tetrahydro-8-Quinolinamines as CXCR4 Antagonists: QSAR Approach

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Abstract

To identify the essential structural requirements in 2D chemical space for the modulation of the CXCR4 antagonists of Substituted N-(1H-benzimidazol-2ylmethyl)5,6,7,8-tetrahydro-8-quinolinamines. The statistically significant model showed an internal predictive power of 81 % and a predictivity for the external test set of about 79%. It reveals that carbon chain connected should be directly attached with benzimidazole ring for maximal determining activity. Three QSAR models were developed for substituted tetrahydro-8-quinolinamines derivatives based on theoretical molecular descriptors calculated solely from the structures of substituted tetrahydro-8-quinolinamines compounds. The QSAR results showed satisfactory statistical quality.

Keywords: Benzimidazole; CXCR4 antagonists; HIV-1; 2D-QSAR; PLS

Introduction

The human immunodeficiency virus (HIV) is the causative agent of the acquired immunodeficiency syndrome (AIDS). More than 30 million people have died of AIDS-related diseases and currently, there are about 34 million people worldwide infected with HIV [1]. In 2011, the number of new infections was estimated around 2.5 million, while the disease caused 1.7 million deaths. HIV-1 infection is characterized by progressive depletion of CD4+ T cells, immune dysfunction and eventually susceptibility to opportunistic infections and malignancies. HIV-1 evades immune defenses in part by inducing the destruction of both infected and uninfected cells of the immune system [2,3]. HIV-1-mediated apoptosis is largely responsible for CD4+ T cell death, although necrotic cell death has also been reported [4,5]. HIV cell infection is a multi-stage and complex process. It starts with the virus entry [6] into the host membrane. This regimen suppresses the replication of HIV and controls disease progression in HIV-infected patients [7,8]. CXCR4 is a 7-transmembrane chemokine receptor [9]. CXCR4 has only one known natural ligand, stromal cell-derived factor (SDF-1). CXCR4, and its interaction with SDF-1, has been shown to play a role in a number of physiological processes, including the homing of immune cells to sites of inflammation [10] and maintaining the cellular micro-environment of the bone marrow [11]. QSAR is a computerized statistical method which tries to explain the observed variance in the biological effect of compounds as a function of molecular changes caused by the nature of substituent. This approach is based on the assumption that the variations in the properties of the compounds can be correlated with changes in their molecular features [12]. Hence, it was thought appropriate to perform a QSAR study to understand the correlation between the physicochemical parameters and the As CXCR4 antagonists with potent activity against HIV-1 activity of the substituted N-(1H-benzimidazol-2ylmethyl)-5, 6, 7, 8-tetrahydro-8-quinolinamines derivatives reported in the literature. It is expected that such 2D QSAR studies will provide better tools for rational design of promising CXCR4 antagonists with potent activity against HIV-1.

Materials and Method

The goal of our research was to gain further insight into the structural features related to the potent activity against HIV-1 of the title compounds. A training set of twenty two novel amine substituted N-(1H-benzimidazol-2ylmethyl)-5, 6, 7, 8-tetrahydro-8-quinolinamines As CXCR4 antagonists with potent activity against HIV-1 activity reported [13] was taken for the study. The biological activity values [IC_{50} (μM)] reported in literature were converted to their molar units and then further to negative logarithmic scale (pIC_{50}) and subsequently used as the dependent variable for the QSAR analysis. The values of IC_{50} along with the structure of the twenty seven compounds in the series is presented in Table 1. Computations were carried out on a Windows XP workstation using the molecular modeling software package VLife Molecular Design Suite [14]. Compounds were sketched using the 2D draw application and converted to 3D structures. Energy minimization and geometry optimization were conducted using Merck molecular force field (MMFF) and atomic charges, maximum number of cycles were 1000, convergence criteria (RMS gradient) was 0.01 and medium's dielectric constant of 1 by batch energy minimization method [15].

A total of 27 molecules were divided into training and a test set to ensure external validation of model derived from the appropriate descriptors. The sphere exclusion method [16] was adopted for division of training and test data set comprising of 22 and 5 molecules, respectively. A large number of theoretical descriptors such as constitutional, physicochemical, topological, estate contribution, polar surface area and semi-empirical type have been computed from the chemical structures of the compounds referred to above with a view to develop structure-activity relationship of N-(1H-benzimidazol-2ylmethyl)-5, 6, 7, 8-tetrahydro-8-quinolinamines compounds. A total of 279 descriptors were calculated by using Molecular Design Suite which was subsequently reduced to 248 descriptors. The descriptors having the same value or almost same value or highly correlated with other descriptors were removed initially.

2D-QSAR model was evaluated using the following statistical measures: N, number of observations The developed (molecules) in the training set; q^2, cross-validated r^2 (by leave one out) which is a relative measure of quality of fit; pred r^2, r^2 for external test set; However, a QSAR model is considered to be predictive, if the following conditions

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are satisfied: $q^2 > 0.6$ and pred_r^2 >0.5 [16].

Results and Discussion

QSAR study of a series of substituted N-(1H-benzimidazol-2ylmethyl)-5, 6, 7, 8-tetrahydro-8-quinolinamines were performed using partial least square regression analysis. Among the number of models generated, the following model has been selected as significant model for further studies.

pIC_{50} =-0.5654(± 0.0276) SssNHcount+0.8742(± 0.0654) SaaCHcount+0.4362(± 0.0834) T_C_N_1

$N_{training}$ = 22, N_{test}= 5, r^2= 0.8176, q^2= 0.7828, F test = 37.436, pred_r^2 = 0.7983

The statistically significant model with r^2 = 0.8176 was considered, as the model 1 showed an internal predictive power of 78 % and a predictivity for the external test set of about 79%. The residuals (observed–predicted activity) were found to be minimal and are presented in Table 2. The developed model explains that the descriptor SssNHcount shows the total number of –NH group connected with two single bonds. Its negative contribution suggests the isobutyl chain linked to –NH group substitution at R position for improved activity. T_C_N_1 (count of number of carbon atoms separated from any nitrogen atom by 1 bonds) contributed positively in the model and is detrimental to biologic activity. SaaCHcount reveals the total number of carbon atom connected with a hydrogen molecule with two aromatic rings, such groups will result in better affinity towards the activity. The Observed activity and Predicted activity pIC_{50} along with residual values are shown in Table 2 and plots of observed vs. predicted values of pIC_{50} are shown in Figure 1a.

pIC_{50} = 0.8063(± 0.1568) SssssCcount -0.7187(± 0.1673) $SsNH_2$count

$N_{training}$ = 22, N_{test}= 5, r^2= 0.7453, q^2= 0.6856, F test = 20.8421, pred_r^2 = 0.7033

The same data set subjected to the PLSR method resulted in r^2 of 0.7653 and q^2 of 68%, with pred_r^2 of 72% (Model 2). As a negative contributing $SsNH_2$count $–NH_2$ group connected with one single bond, its positive contribution in the QSAR model implies that will lead to decreases activity. The descriptor SssssCcount, positive correlation suggests that that activity of benzimidazole derivatives may be increased by increasing the number of carbon bond present in the molecules. The Observed activity and Predicted activity pIC_{50} along with residual values are shown in Table 2 and plots of observed vs. predicted values of pIC_{50} are shown in Figure 1b.

pIC_{50}=0.9754(±0.3273) $SssCH_2$E-index +0.4865(±0.0312) SssOE-index

$N_{training}$ = 22, N_{test}= 5, r^2= 0.7837, q^2= 0.6689, F test = 18.675, pred_r^2 = 0.6717

Model 3 with 0.7837 as the coefficient of determination (r^2) was considered using the same molecules in the test and training sets. The model shows an internal predictive power (q^2 = 0.6689) of 67 % and predictivity for the external test set (pred_r^2 = 0.6717) of about 67%. The $SssCH_2$E-index signifies that increase in length of CH_2 atoms chain on that R site is favorable for the activity. SssOE-index indices for number of oxygen atom connected with two single bonds showed positive effect indicated that the activity was increased R may lead to an increase in the activity. The Observed activity and Predicted activity pIC_{50} along with residual values are shown in Table 2 and plots of observed vs. predicted values of pIC_{50} are shown in Figure 1c.

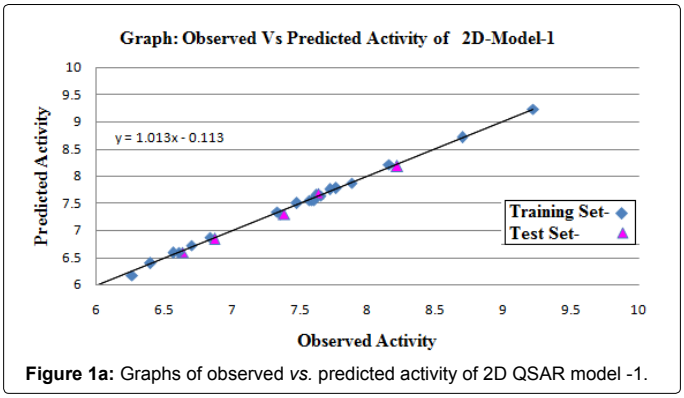


Figure 1a: Graphs of observed *vs.* predicted activity of 2D QSAR model -1.

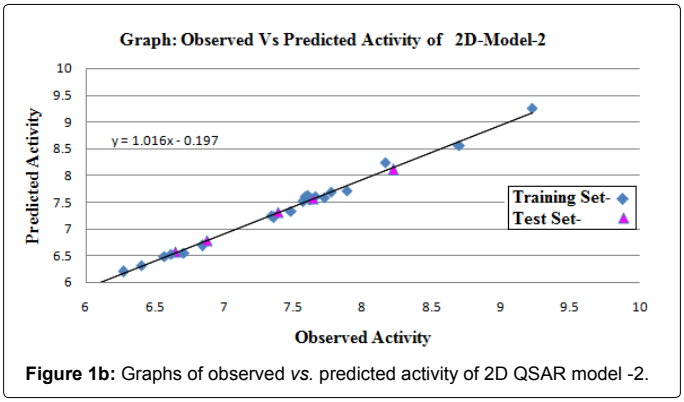


Figure 1b: Graphs of observed *vs.* predicted activity of 2D QSAR model -2.

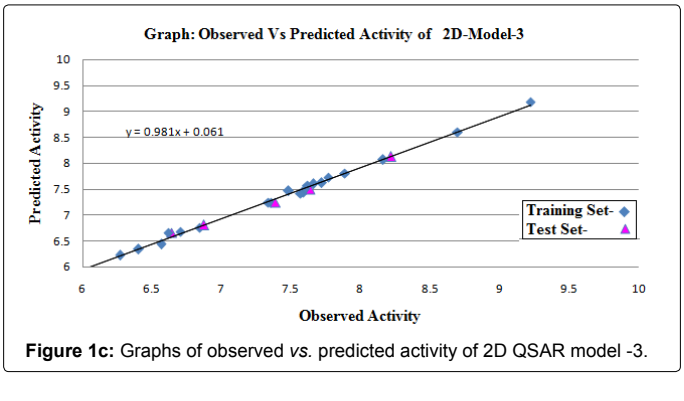
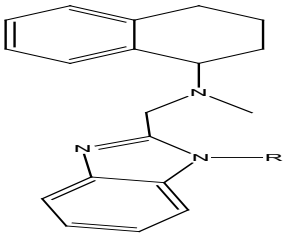
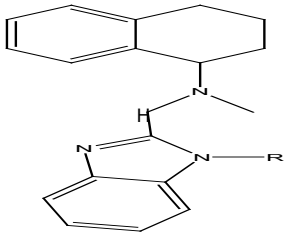
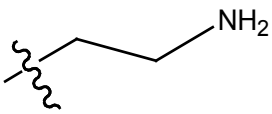
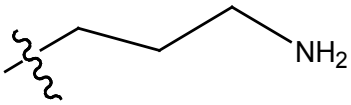
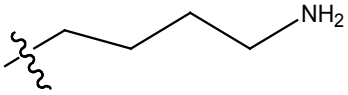
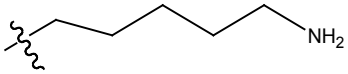
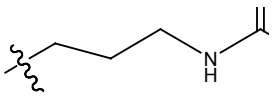


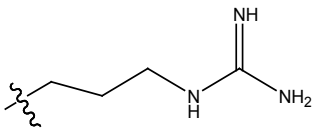
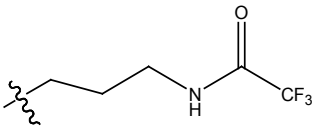
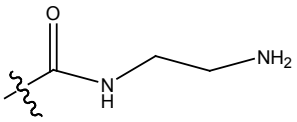
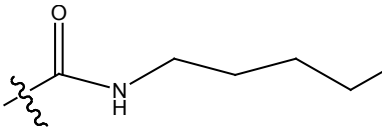
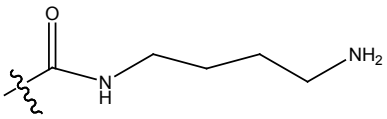
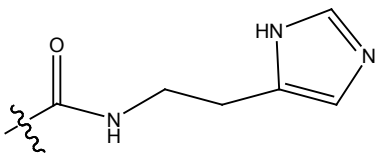
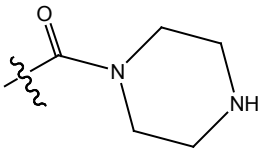
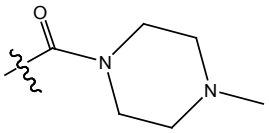
Figure 1c: Graphs of observed *vs.* predicted activity of 2D QSAR model -3.

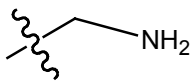
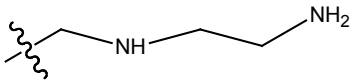
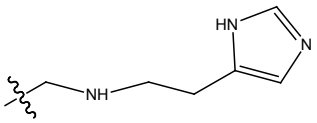
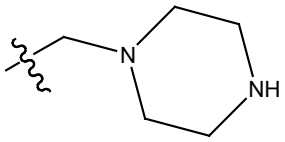
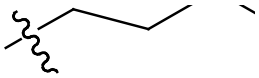
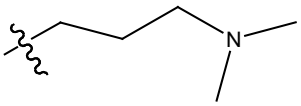
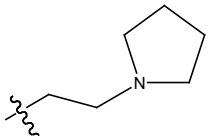
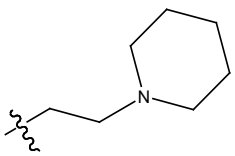
Conclusions

We have developed quantitative structure–activity relationship (QSAR) models for CXCR4 antagonists with potent activity against HIV-1 of the benzimidazole derivative type. Our models would offer help to better comprehend the structure-activity relationships that exist for this class of compounds and also facilitate the design of novel inhibitors with good chemical diversity. Developed QSAR models were found to be statistically significant with excellent predictive power as evident from their statistical characteristics and cross-validation parameters. This may be due to the presence of electron donating groups such as–OCH_3 on ring which linked to the benzimidazole moiety. The results of the present study may be of great help in designing novel substituted N-(1H-benzimidazol-2ylmethyl)-5, 6, 7, 8-tetrahydro-8-quinolinamines with more potent as CXCR4 antagonists with potent activity against HIV-1.



S. No	R	IC_{50} (μM)	pIC_{50}	Training/test set
1		1.35	5.869	Training
2		0.197	6.705	Training
3		0.044	7.356	Training
4*		0.144	6.841	Test
5		0.228	6.642	Training
6		0.017	7.769	Training

7*		0.026	7.585	Test
8		0.243	6.614	Training
9		0.027	7.568	Training
10		0.134	6.872	Training
11		0.396	6.402	Training
12*		0.019	7.721	Test
13		0.046	7.337	Training
14		0.033	7.481	Training

15		1.3	5.886	Training
16*		0.54	6.267	Test
17		0.041	7.387	Training
18		0.013	7.886	Training
19		0.024	7.619	Training
20		0.022	7.657	Training
21		0.023	7.638	Training
22		0.025	7.602	Training

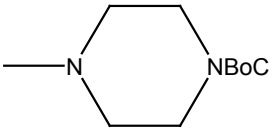
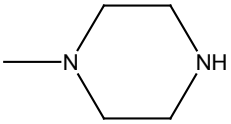
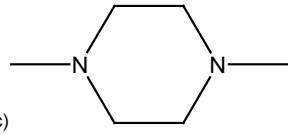
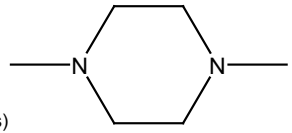
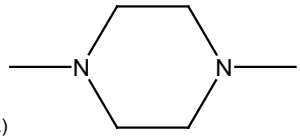
23		0.271	6.567	Training
24		0.006	8.221	Test
25	 (rac)	0.002	8.698	Training
26	 (s)	0.0006	9.221	Training
27	 (R)	0.0069	8.161	Training

Table 1: Structures and Anti-HIV activity for N-1 substituted benzimidazoles.

Com	Model-1		Model-2		Model-3	
	Pred.	Res.	Pred.	Res.	Pred.	Res.
1	5.799	0.07	5.833	0.036	5.913	-0.044
2	6.724	-0.019	6.551	0.154	6.681	0.024
3	7.296	0.06	7.217	0.139	7.239	0.117
4	6.875	-0.034	6.689	0.152	6.757	0.084
5	6.596	0.046	6.571	0.071	6.662	-0.02
6	7.774	-0.005	7.697	0.072	7.725	0.044
7	7.556	0.029	7.609	-0.024	7.435	0.15
8	6.599	0.015	6.526	0.088	6.657	-0.043
9	7.545	0.023	7.509	0.059	7.419	0.149
10	6.838	0.034	6.782	0.09	6.806	0.066

11	6.396	0.006	6.317	0.085	6.339	0.063
12	7.755	-0.034	7.584	0.137	7.618	0.103
13	7.341	-0.004	7.251	0.086	7.246	0.091
14	7.498	-0.017	7.328	0.153	7.465	0.016
15	5.904	-0.018	5.729	0.157	5.756	0.13
16	6.173	0.094	6.198	0.069	6.223	0.044
17	7.291	0.096	7.311	0.076	7.244	0.143
18	7.867	0.019	7.709	0.177	7.803	0.083
19	7.648	-0.029	7.545	0.074	7.577	0.042
20	7.634	0.023	7.613	0.044	7.603	0.054
21	7.679	-0.041	7.565	0.073	7.496	0.142
22	7.546	0.056	7.624	-0.022	7.514	0.088
23	6.585	-0.018	6.488	0.079	6.433	0.134
24	8.181	0.04	8.103	0.118	8.127	0.094
25	8.714	-0.016	8.553	0.145	8.596	0.102
26	9.233	-0.012	9.260	-0.039	9.187	0.034
27	8.214	-0.053	8.238	-0.077	8.067	0.094

Table 2: Observed and Predicted activities with residue according to 2D QSAR models.

Acknowledgements

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