Original Article

2D and 3D QSAR of Benzimidazole Analogues as Novel HIV-1 Non Nucleoside Reverse Transcriptase Inhibitors

Shital Patil*, Kalyani Asgaonkar, Trupti Chitre, Vedika Bhat, Sayali Ethape, Anagha Sujalegaonkar, Sudeep Bhalekar

Department of Pharmaceutical Chemistry, A.I.S.S.M.S. College of Pharmacy, Near RTO, Kennedy Road, Pune-411001, Maharashtra, INDIA.

ABSTRACT

Context: Acquired Immuno Deficiency Syndrome (AIDS) is a viral disease caused by Human Immunodeficiency Virus. There is an urgent need to identify newer NNRTIs active against these mutant strains Literature survey has revealed that N1-aryl-benzimidazole analogues have significant potential as HIV-1. **Aim:** Pharmacophore optimization of Benzimidazole nucleus as non-nucleoside reverse transcriptase inhibitors using Two Dimensional (2D) and Three Dimensional (3D) QSAR. **Material & Method:** Studies were carried out using V-Life MDS Softwre(4.3 version) using Multiple Linear Regression (MLR) Analysis and Simulated Annealing k Nearest Neighbor Molecular Field Analysis (SA-kNN MFA). **Result & Discussion:** The model generated for 2D QSAR showed significant statistical parameters such as r2 = 0.8847, q2 = 0.7448. The model generated for 3D QSAR showed significant statistical parameter such as q2 = of 0.6695. **Conclusion:** QSAR studies indicated the requirement of certain physicochemical parameters and hydrophobic groups for better Anti HIV activity.

Key words: Molecular Modeling, 2d Qsar, 3d Qsar, Benzimidazole, Anti –HIV.

INTRODUCTION

Acquired Immuno Deficiency Syndrome (AIDS) is a viral disease caused by Human Immunodeficiency Virus type I (HIV type I) in which in-built defense system of body breaks down completely. HIV-1 virus has more virulence and transmiability than HIV-2 and is prevalent globally. Currently, the most commonly used anti-HIV therapy is through the parallel use of drugs that belongs either to the class of nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs/NTRIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease or entry inhibitors and HIV integrase inhibitors.

NNRTIs are structurally diverse group which are more specific and less toxic compounds and binds a specific and allosteric site to the viral enzyme Reverse Transcriptase (RT). NNRTIs non-competitively inhibit RT enzyme, block its mechanism and make it unable to produce a viral DNA. Nevertheless, to date drugs used to treat AIDS under NNRTIs for anti-AIDS therapy are Nevirapine, Delaviridine, Efavirenz, Etravirine and more recently Rilpivirine. The therapeutic efficacy of NNRTIs has been limited by the emergence of drug-resistant mutants (such as Y188C, Y181C, K103N, and L100I) and the severe side effects. Therefore there is an urgent need to identify newer NNRTIs active against these mutant strains with improved pharmacokinetic profile.[1,2]

N1-aryl-benzimidazole analogues have shown a variety of biological activities such as antihistaminic, anti-HIV, anti hepatitis C to name a few.[3-5] Literature survey has

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Correspondence:
Shital Patil,
Department of Pharmaceutical Chemistry, A.I.S.S.M.S. College of Pharmacy, Near RTO, Kennedy Road, Pune-411001, Maharashtra, INDIA.
Tel: 9881203150
E-mail: sheetalnikam1212@yahoo.co.in

www.ijper.org

revealed that N1-aryl-benzimidazole analogues have significant potential as HIV-1 non-nucleoside reverse transcriptase inhibitors.[6-12] Molecular modeling study is an approach that is used to focus on the development of optimal models through variable selection and statistical methods to taper down to highly effective New Chemical Entities (NCE's). Quantitative Structure-Activity Relationships (QSAR) is a widely accepted tool used for finding associations between chemical structures and biological activity.[13] Thus in the present study we have focused on development of Two Dimensional (2D) and Three Dimensional (3D) QSAR studies using Multiple Linear Regression (MLR) Analysis and Simulated Annealing k Nearest Neighbor Molecular Field Analysis (SA-kNN MFA), respectively for a series of N1 –aryl- benzimidazole 2-substituted as novel HIV-1 Non Nucleoside Reverse Trascriptase Inhibitors (NNRTI's).

MATERIALS AND METHODS

Computational Details

All the computational studies were carried out using the V-Life sciences, Molecular Design Suite (MDS) version 4.3.[14,15] Molecules were drawn in Chem. Draw Ultra 8.0 and geometry optimization was done using the standard Merck molecular force field (MMFF). The geometry of each molecule was further optimized. The initial conformations were selected and minimized using the Powell method until the root-mean-square deviation 0.001 kcal/mol Å was achieved.[16,17]

Data Set

A data set (27molecules) of N1 –aryl- benzimidazole derivatives with varied chemical and biological activities, reported by Monforte Anna-Maria *et al* for anti-HIV activity, was considered for the QSAR studies.[1] Biological activity expressed in effective concentration (EC) was converted into the corresponding pEC_{50} (pEC_{50} = - log (EC_{50}) values (Table 1). To obtain a predictive QSAR model validation was carried out for which the entire data set was divided into Training and test set using manual selection method. For 2D QSAR 17 molecules were considered in the training set and 5 molecules were considered in test set. For 3D QSAR 20 molecules were considered in the training set and 2 molecules were considered in test set. Uni--Column statistics were generated for uniform representation of the molecules in the training and test sets. While selection of molecules in the training set and test set a care was taken in such a way that biological activities of all compounds in test set lie within the maximum and minimum value range of biological activities of training set of compounds.[11]

2D QSAR studies

Different models were generated for the 2D-QSAR study using MLR method. The MLR analysis was used to correlate biological activities with physicochemical properties. Various 2D descriptors like topological, physicochemical, alignment-independent, and atom-type count descriptors were generated for the geometrically optimized structures. These generated descriptors were further reduced by removing the invariable columns. This was followed by refinement in the selection of descriptors by using the correlation matrix which considers correlation between descriptor with activity as well as correlation between descriptor-descriptor. Variable selection method stepwise forward backward together with MLR regression method was employed to generate statistically significant model.

3D QSAR studies

3D QSAR studies were carried out by kNN MFA method using SA as variable selection method. The selected series of compounds were aligned using the template-based alignment method and template used for alignment is depicted in (Figure 1). Generated models were cross validated using Leave-one-out (LOO) procedure. Different steric, electronic and hydrophobic points were generated and the model generated was evaluated based on different statistical parameters.

RESULT AND DISCUSSION

2D QSAR: The model generated for 2D QSAR showed significant statistical parameters such as r^2=0.8847, q^2=0.7448 (Table 2). 2D QSAR equation was generated along with the fitness plot that indicated the dependence of the biological activity on various different types of the descriptors (Figure 2, Figure 3).

The regression equation obtained is represented as follows:

pEC_{50} = 1.0899 T_N_Cl_3-1.1787 SssOCount -0.4212 XlogP -0.4189 X comp Dipole - 4.8498.

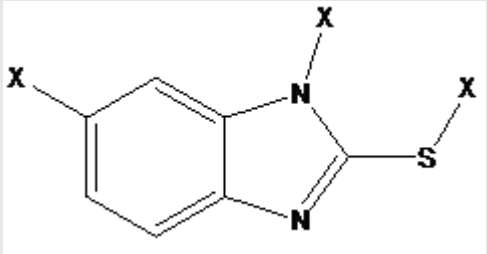


Figure 1: Template used for 3D QSAR.

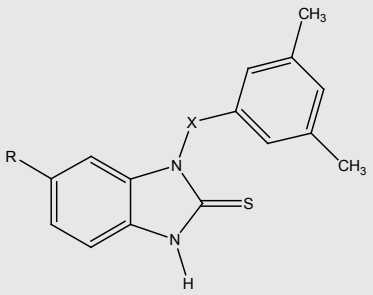
Contribution of descriptors

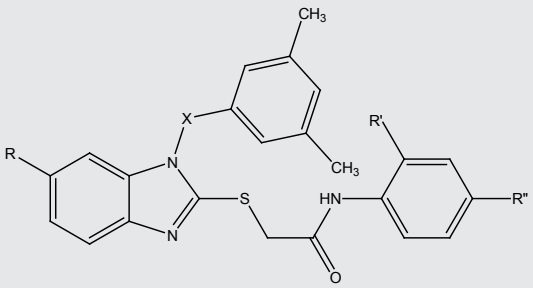
T_N_Cl_3- This descriptor signifies that chlorine should be separated from Nitrogen by 3 bond distance. It is a positively contributing descriptor with a contribution of 35.06%.

SssOCount- This descriptor defines the total no of Oxygen connected with 2 single bonds. Negative Contribution of this descriptor was 37.91%.

XlogP- This is atom based evaluation of logP. This descriptor signifies ratio of solute concentration in octanol and water and generally termed as Octanol

Table 1: Selected Series with Biological Activity





(1a to 1d)				(2a-d, 8a-d)		
Comp.Code	**R-**	**X-**	**R'-**	**R"-**	**EC 50[a] (μM)**	**pEC 50[b]**
1a	H	CH_2	-	-	27.24	-1.435
1b*	Cl	CH_2	-	-	0.046	1.337
1c	H	SO_2	-	-	1.35	-0.130
1d*	Cl	SO_2	-	-	1.76	-0.245
2a	H	CH_2	Cl	H	42.13	-1.624
2c	H	SO_2	Cl	H	51.93	-1.715
2d	Cl	SO_2	Cl	H	18.64	-1.270
3a	H	CH_2	Br	H	15.02	-1.176
3c	H	SO_2	Br	H	0.18	0.744
3d	Cl	SO_2	Br	H	63.5	-1.802
4a	H	CH_2	NO_2	H	3.91	-0.592
4c	H	SO2	NO_2	H	100.00	-2
4d	Cl	SO2	NO_2	H	37.04	-1.568
5a	H	CH_2	Cl	CH_3	178.93	-2.252
5c	H	SO_2	Cl	CH_3	0.55	0.259
5d	Cl	SO_2	Cl	CH_3	46.41	-1.666
6a	H	CH_2	Cl	COO CH_3	40.30	-1.605
6c	H	SO_2	Cl	$COOCH_3$	162.17	-2.209
6d	Cl	SO_2	Cl	$COOCH_3$	37.56	-1.574
7a	H	CH_2	Cl	SO_2 CH_3	1.93	-0.285
7b	Cl	CH_2	Cl	SO_2 CH_3	70.55	-1.848
7c	H	SO_2	Cl	SO_2 CH_3	0.12	0.920
7d	Cl	SO_2	Cl	SO_2 CH_3	2.61	-0.416
8a	H	CH_2	Cl	SO_2 NH_2	1.02	-0.008
8b	Cl	CH_2	Cl	SO_2 NH_2	86.64	-1.937
8c	H	SO_2	Cl	SO_2 NH_2	18.51	-1.267
8d	Cl	SO_2	Cl	SO_2 NH_2	3.04	-0.482

a= EC 50- Effective concentration, b=EC_{50} = - log(EC_{50})

Table 2: Statistical Results of 2D QSAR and 3D QSAR		
Statistical Data	**2D QSAR**	**3D QSAR**
	(MLR)	**(SA-KNN MFA)**
r^2	0.8847	--
r^2SE	0.2487	--
q^2	0.7448	0.6695
q^2SE	0.3795	0.4643
Pred_r^2	3.0658	-0.5580
Pred_r^2SE	2.0141	1.1611
F-Test	8.6880	--
N	21	20
K Nearest neighbor	--	2
Contributing descriptors	Negatively Contributing-XlogP, XcompDipole, SssOCount Positively Contributing-T_N_Cl_3	Negatively contributing: S_2606,E_2400,S_269 Positively contributing: H_941,H_753,H_95

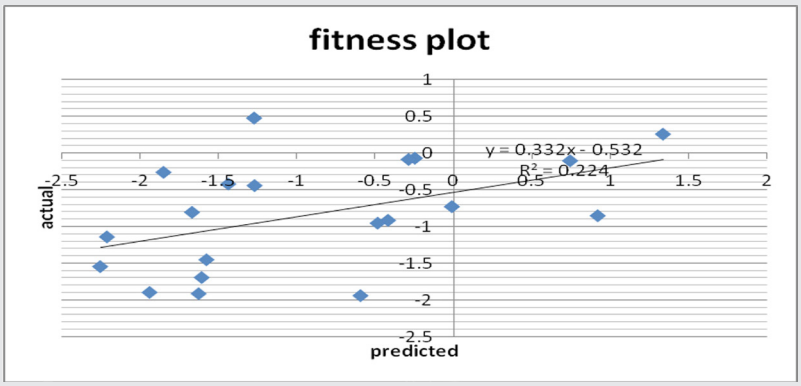


Figure 2: Fitness plot- graph of predicted activity vs observed activity for 2D QSAR .

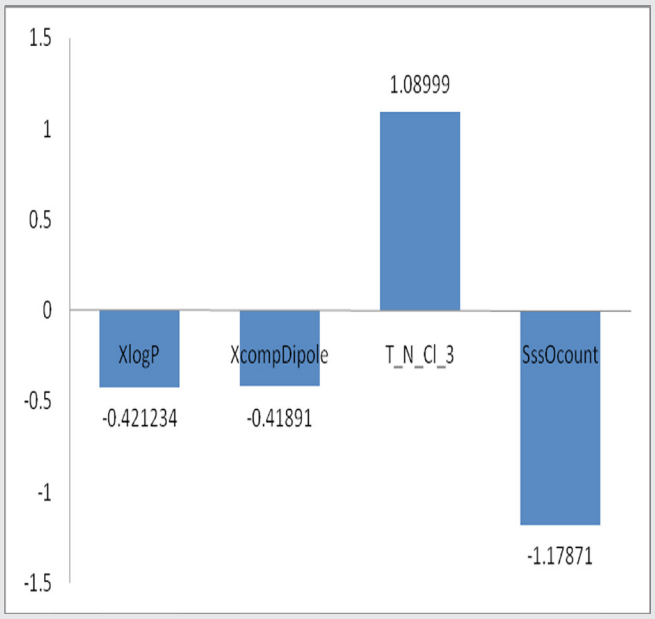


Figure 3: Contribution plot of Descriptors for 2D QSAR.

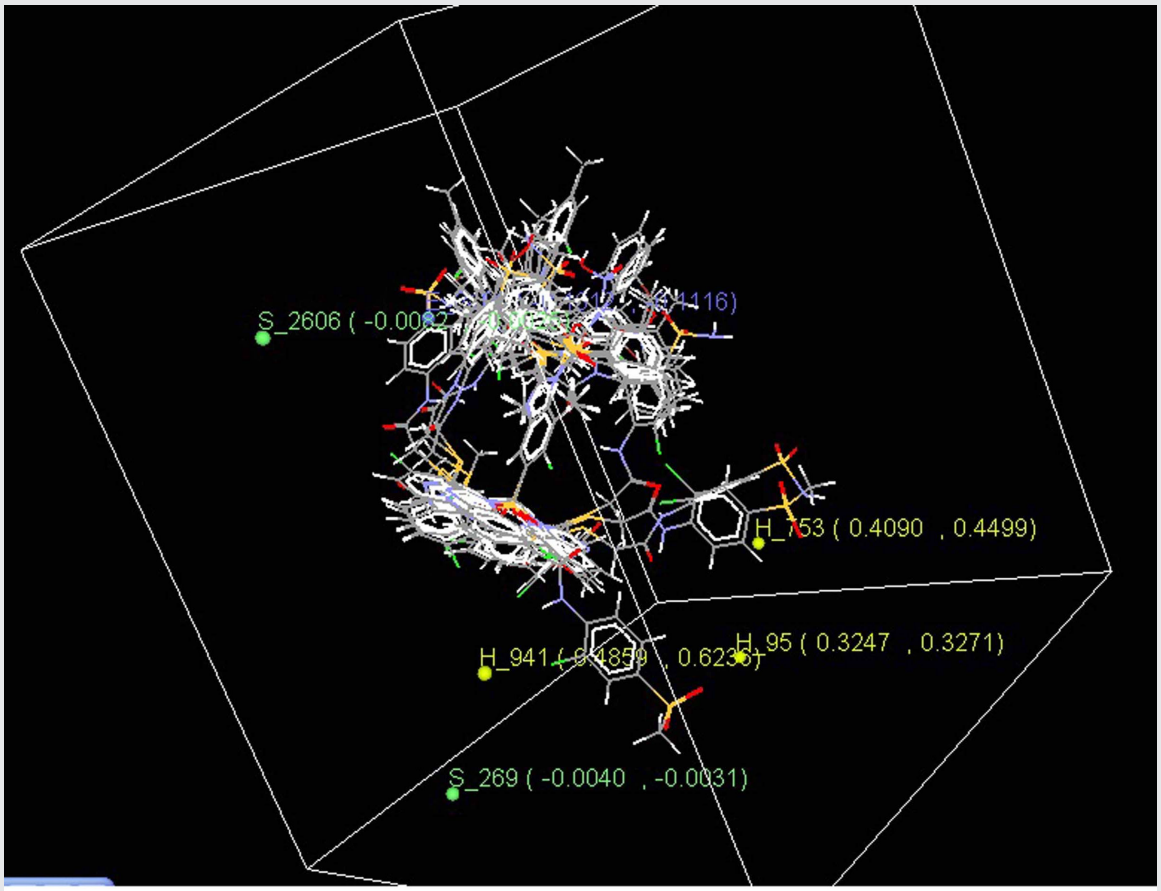


Figure 4: Alignment of the optimized molecules using 3D QSAR.

Water partition Coefficient. Negative Contribution of this descriptor was 13.54%.

X comp Dipole- X Component of Dipole moment. Negative Contribution of this descriptor was 13.47%.

The higher frequency of occurrence of positively contributing descriptors in NCE's may lead to increase in biological activity whereas the negatively contributing descriptors should be avoided while designing the NCE's.

3D QSAR

The energy minimized molecules were properly aligned on the selected template (Figure 4). The model generated for 3D QSAR showed significant statistical parameter such as q^2 of 0.6695 (Table 2).

Interpretation of 3D QSAR studies

In 3D QSAR studies, 3D data points generated around Benzimidazole pharmacophore were used to optimize the electrostatic and steric requirements of the Benzimidazole nucleus for anti-HIV activity. The points generated in KNN MFA 3D QSAR model are negatively contributing S_2606,E_2400,S_269 and Positively contributing H_941,H_753,H_95 (Figure 3b).

These points suggested the significance and requirement of less electrostatic, steric and more hydrophobic groups for maximum biological activity of Benzimidazole analogues.

The points generated around the pharmacophore were used to correlate chemical nature of substituents around benzimidazole ring with their observed activity.

CONCLUSION

The present study was aimed to derive 2D and 3D QSAR models for optimization of pharmacophore to identify key structural fragments required for anti HIV activity. Results obtained from statistically significant models indicated the requirement of physicochemical descriptors like T_N_Cl_3 which is positively contributing to the anti-HIV activity from 2D QSAR whereas 3D QSAR gave an insight to the importance of hydrophobic groups that increase the biological activity.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ABBREVIATIONS USED

HIV type I: Human Immunodeficiency Virus type I; **QSAR:** Quantitative structure–activity relationship; **MLR:** Multiple Linear Regression; **kNN MFA:** k Nearest Neighbor Molecular Field Analysis; **AIDS:** Acquired Immuno Deficiency Syndrome; **HIV-2;** NRTIs/NTRIs: Nucleoside/nucleotide reverse transcriptase inhibitors; **NNRTIs:** Non-nucleoside reverse transcriptase inhibitors; **NCE's:** New Chemical Entities; **MDS:** Molecular Design Suite; **MMFF:** Merck molecular force field; **EC:** Effective concentration; **SA:** Simulated annealing.

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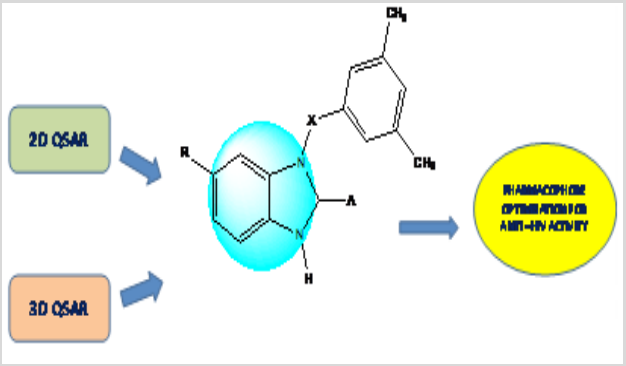
PICTORIAL ABSTRACT



SUMMARY

- Molecular modelling approach was used to design novel Benzimidazole analogues as anti HIV agents. The present study was aimed to derive 2D and 3D QSAR models for optimization of pharmacophore to identify key structural fragments required for anti HIV activity . Two Dimensional (2D) and three dimensional (3D) Quantitative structure–activity relationship (QSAR) studies were carried out for a series containing benzimidazole nucleus with Anti-HIV Activity using Multiple Linear Regression (MLR) and k Nearest Neighbor Molecular Field Analysis (kNN MFA)method respectively. Results obtained from statistically significant models were used to derive the optimized benzimidazole pharmacophore for better Anti HIV activity.

About Authors

Shital Patil- M.Pharm: Assistant Professor in Dept. of Pharmaceutical chemistry. Her area of research includes drug design, synthesis of Anti HIV and Anti TB entities.

Kalyani Asgaonkar- M.Pharm: Assistant Professor in Dept. of Pharmaceutical chemistry. Her area of research includes drug design, synthesis of Anti HIV and Anti TB entities.

Dr.Trupti Chitre- M.Pharm, Ph.D: Associate Professor in Dept. of Pharmaceutical chemistry. Her area of research includes drug design, synthesis of Anti HIV and Anti TB entities.

Vedika Bhat: Undergraduate students of AISSMS College of Pharmacy.

Sayali Ethape: Undergraduate students of AISSMS College of Pharmacy.

Sudeep Bhalekar: Undergraduate students of AISSMS College of Pharmacy.

Anagha Sujalegaonkar: Post graduate student in department of Pharmaceutical chemistry in AISSMS College of Pharmacy.

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