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Original article

QSAR analysis on benzodithiazine derivatives as HIV-1 integrase inhibitors

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Abstract

Objective: Inhibition of HIV-1 integrase is an important strategy for the treatment of HIV and AIDS. Therefore, HIV-1 integrase inhibitory activity of 3-aroyl-1,1-dioxo-1,4,2-benzodithiazines has been analyzed with different physicochemical parameters. **Methods:** In the present work, quantitative structure activity relationship studies were performed on a series of benzodithiazines as HIV-1 integrase inhibitors using the modeling software Win CAChe version 6.1. Multiple linear regression analysis was performed to derive quantitative structure activity relationship models which were further evaluated for statistical significance and predictive power by internal and external validation. **Results:** The best QSAR models were having good correlation coefficient (r) with low standard error of estimation (SEE) and cross validated square of correlation coefficient (q^2). The robustness of the models was checked by Y-randomization test and they were identified as good predictive models. The model for HIV integrase (wt) inhibitory activity of benzodithiazines suggest that the increase of dipole moment (Z) of molecules leads to reduce 3´processing and strand transfer inhibitory activity, substitution with high electro positive groups is conducive for the 3´processing inhibitory activity, and the increase in heat of formation is favorable for 3´-processing and strand transfer inhibitory activity. **Conclusion:** The model for HIV integrase (C65s) inhibitory activity of benzodithiazines suggest that the increase of dipole moment (X) of molecules leads to reduce 3´processing and strand transfer inhibitory activity, and the substitution with high hydrophobic groups is conducive for the 3´processing and strand transfer inhibitory.

Keywords: Human immunodeficiency virus; Integrase; Inhibition; Quantitative Structure Activity Relationship; Benzodithiazines

INTRODUCTION

Among the innumerable viruses, which cause infection and disease in man and animals, there is a large family called retrovirus, the members of which cause cancers and leukemias. Some retroviruses cause immune deficiency in cattle, monkeys and man. These are called immunodeficiency viruses. There are two distinct types of viruses called HIV-1 and HIV-2. Retroviruses have some very interesting properties. Once a person is infected, the infection remains lifelong. In most people the infection causes no disease for a long period. Yet the infected person can be the source of infection for others. Human immunodeficiency virus type1 (HIV-1) Integrase is an enzyme required for viral replication[1,2]. HIV Integrase catalyzes integration of viral DNA into host genome by

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two separate but chemically similar reactions known as 3′processing and DNA strand transfer[3,4]. In 3′ processing IN removes a dinucleotide next to conserved cytosine-adenine sequence from each 3′- end of the viral DNA. IN then attaches the processed 3′- end of the viral DNA to the host cell DNA in the strand transfer reaction. As there is no known human counterpart of HIV Integrase, IN is an attractive target for anti-retroviral drug design[5]. A large number of HIV IN inhibitors have been discovered[6]. However the mechanism of action is incompletely understood[7].

Computational chemistry has developed into an important contributor to rational drug design. Quantitative structure activity relationship (QSAR) modeling results in a quantitative correlation between chemical structure and biological activity. QSAR studies have provided valuable insight in the design and development of HIV-1 reverse transcriptase inhibitors[8], HIV-1 protease inhibitors[9-12] and HIV-1 integrase inhibitors[13,14] were reported. The present group of authors has developed a few quantitative structure-activity relationship models to predict biological activity of different group of compounds[15-26].

As a part of ongoing efforts to design novel molecules with potent anti-HIV activity, a QSAR analysis was performed to relate HIV integrase inhibitory activity of 3-aroyl-1,1-dioxo-1,4,2-benzodithiazine derivatives[27] to its physicochemical properties using WinCAChe version 6.1 (Product of Fujitsu private limited, Japan, http://www.cachesoftware.com/contacts/japan.shtml) modeling software and the QSAR models were generated by STATISTICA version 6 (Soft stat) software. All the HIV integrase inhibitory activities used in the present study were expressed as pIC_{50} or $-logIC_{50}$ where IC_{50} is the micro molar concentration of the compounds producing 50% reduction in the integrase growth.

MATERIALS AND METHODS

General Procedure

Win CAChe 6.1 (molecular modeling software, a product of Fujitsu private limited, Japan), STATISTICA version 6 (Stat Soft, Inc., Tulsa, USA).

Optimization of molecules structure

A data set of 17 compounds of 3-aroyl-1,1-dioxo-1,4,2-benzodithiazine for HIV-1 integrase activity (Table 1 & 2, Figure 1) was used for the present QSAR study. The molar concentrations of the benzodithiazine compounds required to produce 50% reduction in the HIV integrase enzyme growth and stated as the means of three independent determinations were converted to free energy related negative logarithmic values for undertaking the QSAR study. All 17 compounds structure were built on workspace of Win CAChe 6.1 and energy minimization of the molecules was done using Allinger's MM2 force field followed by semi empirical PM3 method available in MOPAC module until the root mean square gradient value becomes smaller than 0.001 kcal/molÅ. The stable conformations of the molecules were selected automatically by the software when the molecules subjected for optimization. Most stable structure for each compound was generated and used for calculating various physico-chemical descriptors like thermodynamic, steric and electronic values of descriptors.

Table 1. Structure of benzodithiazine derivatives

Comp. No	R1	R2	Ar
1	Me	H	Ph
2	Me	H	4-MeoPh
3	Me	H	4-BrPh
4	Me	H	4-ClPh
5	Me	H	4-FPh
6	Me	H	4-O2NPh
7	Me	H	3-O2NPh
8	Me	H	3,4-diClPh
9	Me	H	4-Ph-Ph
10	Me	H	2-naphthyl
11	H	Me	4-ClPh
12	H	Me	3,4-diClPh
13	H	Me	2-naphthyl
14	H	H	4-ClPh
15	H	H	3-O2NPh
16	H	H	3,4-diClPh
17	H	H	2-naphthyl

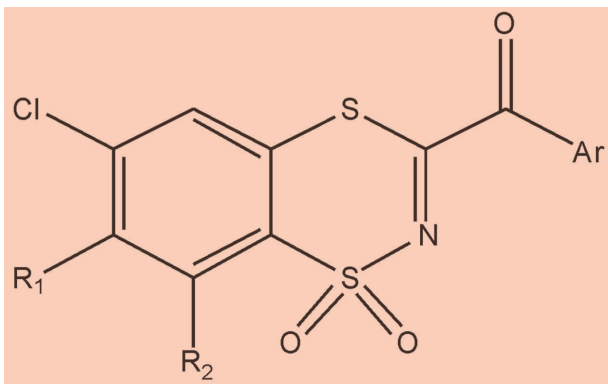

Figure 1. Structure of benzodithiazine clerivatives

Table 2 Integrase inhibitory activity of benzodithiazine derivatives

Comp. No	3′-wt [pIC_{50}(3′-Pwt)]	Int-wt [pIC_{50}(STwt)]	3′c65s [pIC_{50}(3′-PC65s)]	Intc65s [pIC_{50}(STC65s)]
1	-1.079	-1.079	-1.954	-1.954
2	-1.477	-1.519	-2.000	-1.477
3	-1.477	-1.477	-1.813	-1.813
4	-1.477	-1.813	-1.519	-1.519
5	-1.756	-1.623	-1.875	-1.230
6	-1.756	-1.699	-1.041	-1.041
7	-1.176	-0.845	-1.978	-1.903
8	-1.041	-1.000	-1.301	-1.000
9	-1.447	-0.477	-1.255	-1.301
10	-1.431	-1.398	-1.477	-1.176
11	-1.230	-1.398	-1.778	-1.813
12	-1.342	-0.845	-0.903	-0.477
13	-2.000	-1.954	-1.301	-1.301
14	-1.398	-1.301	-2.000	-2.000
15	-1.279	-1.279	-1.792	-1.903
16	-0.903	-0.903	-1.672	-1.301
17	NA	NA	-1.813	-1.544

NA: Not available

Descriptors calculation, QSAR models development and validation

All the calculated descriptors (25 descriptors calculated by Win CAChe 6.1, the complete descriptors data set of all compounds will be provided on request) were considered as independent variable and biological activity as dependent variable. STATISTICA 6 software was used to generate QSAR models by multiple linear regression analysis. Statistical measures used were n-number of compounds in regression, *r*-correlation coefficient, r^2-square of correlation coefficient, *F*- test (Fischer's value) for statistical significance, SEE- standard error of estimation, q^2 or r^2 CV - cross validated square of correlation coefficient and correlation matrix to show correlation among the parameters.

The square of correlation coefficient (or coefficient of determination) r^2 is a relative measure of fit by the regression equation. Correspondingly, it represents the part of the variation in the observed data that is explained by the regression. The correlation coefficient values closer to 1.0 represent the better fit of the regression. The F-test reflects the ratio of the variance explained by the model and the variance due to the error in the regression. High values of the F-test indicate that the model is statistically significant. Standard deviation is measured by the error mean square, which expresses the variation of the residuals or the variation about the regression line. Thus standard deviation is an absolute measure of quality of fit and should have a low value for the regression to be significant.

The predictive ability of the generated correlations was evaluated by cross validation method employing a leave-one-out scheme. Validation parameters considered were cross validated r^2 or q^2, standard deviation based on predicted residual sum of squares (SPRESS) and standard error of prediction (SDEP). The predictive ability of the selected model was also confirmed by leave some (33%) out method [$r^2CVext_{(LSO)}$][28].

The robustness of a QSAR model was checked by Y - randomization test. In this technique, new QSAR models were developed by shuffling the de-

pendent variable vector randomly and keeping the original independent variable as such. The new QSAR models are expected to have low r^2 and q^2 values. If the opposite happens then an acceptable QSAR model can not be obtained for the specific modeling method and data.

RESULTS

In the present study we tried to develop best QSAR model to explain the correlation between the physico-chemical parameters (Table 3) and HIV-1 integrase inhibitory activity of benzodithiazine derivatives.

Table 3 Selected physico-chemical parameters of benzodithiazine derivatives

Comp. No	DVX	DVZ	HF	HOMO	logP	BK1
1	0.351	0.005	-15.249	-9.630	4.046	16.844
2	0.393	0.000	-61.518	-9.520	3.793	18.781
3	-1.095	0.004	-7.073	-9.691	4.838	17.811
4	-0.874	0.005	-21.772	-9.657	4.564	17.811
5	-1.155	0.005	-58.734	-9.700	4.185	17.811
6	-5.109	0.006	-30.151	-9.864	3.999	19.753
7	-0.806	0.003	-29.939	-9.858	3.999	19.753
8	-1.875	0.003	-26.907	-9.448	5.082	18.781
9	1.203	0.004	1.568	-9.442	5.730	21.240
10	1.418	0.692	-5.895	-9.145	5.048	19.322
11	-2.120	0.002	-18.220	-9.601	4.564	17.811
12	-2.639	0.004	-23.207	-9.526	5.082	18.781
13	-0.506	0.003	5.428	-8.984	5.048	19.322
14	-2.324	3.162	-23.238	-9.504	3.874	17.811
15	-5.041	0.004	-13.238	-9.859	3.532	18.781
16	-2.607	0.002	-17.720	-9.415	4.615	17.811
17	-1.156	0.006	10.896	-9.003	4.581	18.367

DVX: Dipole vector X, DVZ: Dipole vector Z, HF: Heat of formation, HOMO: Highest occupied molecular orbital, logP: Partition coefficient, BK1: Shape index order 1.

Integrase (wt) 3′-processing (3′-Pwt)

The best equation received for 3′processing (3′-Pwt) inhibitory activity was

$pIC_{50}(3'\text{-Pwt}) = 1.627 (\pm 1.005) - 0.210 (\pm 0.059)\ DVZ + 0.005 (\pm 0.001)\ HF + 0.302 (\pm 0.210)\ HOMO$ (1)

$n = 16$, $r^2 = 0.663$, $r^2_{adj} = 0.579$, $SEE = 0.184$, $F = 7.88$, $P < 0.01$, $q^2 = 0.560$

The rule-of-thumb for the optimal number of descriptors in a QSAR model is that the number of descriptors should equal one-sixth to one-third the number of molecules in the training Set. Based on rule-of-thumb we have considered three parameters to develop QSAR model for the present series consist of 16 compounds.

The residual of observed and calculated activity of compound number 12 was found two times larger than standard deviation of the Eq. 1. Hence they were removed as outliers, we rebuilt the models with 15 compounds and got the following Eq. 2:

$pIC_{50}(3'\text{-Pwt}) = 3.600 (\pm 1.959) - 0.226 (\pm 0.052)\ DVZ + 0.006 (\pm 0.001)\ HF + 0.505 (\pm 0.207)\ HOMO$ (2)

$n = 15$, $r^2 = 0.766$, $r^2_{adj} = 0.702$, $SEE = 0.160$, $F = 12.01$, $P < 0.001$, $q^2 = 0.685$, $S_{PRESS} = 0.172$, SDEP = 0.151.

Model - 2 showed good correlation coefficient (r) of 0.875 between descriptors (HF, DVZ and HOMO) and HIV-1 integrase (wt) 3′processing inhibitory activity. Square of correlation coefficient (r^2) of 0.766 explained 76.6% variance in biological activity. This model also indicated statistical signifi-

cance > 99.9% with $F = 12.01$. Cross validated square of correlation coefficient of this model was 0.685, which showed the good internal prediction power of this model. There was no inter-correlation between selected descriptors (Table 4).

Table 4 Correlation matrix of physico-chemical descriptors and HIV-1 integrase (3'-Pwt) inhibitory activities of benzodithiazine derivatives

	pIC_{50}	DVZ	HF	HOMO
pIC_{50}	1			
DVZ	-0.577	1		
HF	0.534	-0.017	1	
HOMO	0.436	0.072	0.528	1

Integrase (wt) strand transfer (STwt)

The best equation received for HIV-1 integrase strand transfer (STwt) inhibitory activity was

pIC_{50}(STwt) = 7.249 (±2.549) - 0.181 (±0.018) DVZ + 0.005 (±0.001) HF + 0.884 (±0.214) HOMO (3)

$n = 16$, $r^2 = 0.639$, $r^2_{adj} = 0.549$, $SEE = 0.270$, $F = 7.08$, $P < 0.001$, $q^2 = 0.505$, $S_{PRESS} = 0.260$, SDEP = 0.242.

Where HF - heat of formation, HOMO - highest occupied molecular orbital and DVZ - dipole moment vector Z.

Model - 3 showed good correlation coefficient (r) of 0.799 between descriptors (HF, DVZ and HOMO) and HIV-1 integrase (wt) strand transfer inhibitory activity. Square of correlation coefficient (r^2) of 0.639 explained 63.9% variance in biological activity. This model also indicated statistical significance > 99.9% with $F = 7.08$. Cross validated square of correlation coefficient of this model was 0.505, which showed the good internal prediction power of this model. The calculated and predicted (LOO) activities of the compounds by the above models are shown in Table 8. There was no inter-correlation between selected descriptors (Table 5).

Table 5 Correlation matrix of physico-chemical descriptors and HIV-1 integrase (STwt) inhibitory activities of benzodithiazine derivatives

	pIC_{50}	DVZ	HF	HOMO
pIC_{50}	1			
DVZ	-0.321	1		
HF	0.552	-0.017	1	
HOMO	0.678	0.072	0.528	1

Integrase (C65s) 3'-processing (3'-PC65s)

The best equation received for 3' processing (3'-PC65s) inhibitory activity was

pIC_{50}(3'-PC65s) = -5.533 (±0.936) + 0.442 (±0.105) logP - 0.106 (±0.031) DVX + 0.095 (±0.005) BK1 (4)

$n = 17$, $r^2 = 0.713$, $r^2_{adj} = 0.647$, $SEE = 0.206$, $F = 10.79$, $P < 0.001$, $q^2 = 0.625$, $S_{PRESS} = 0.199$, SDEP = 0.186.

Where logP - partition coefficient, BK1 - shape index 1 and DVX - dipole moment vector X. The calculated and predicted (LOO) activities of the compounds by the above models are shown in Table 8.

Model - 4 showed good correlation coefficient (r) of 0.844 between descriptors (BK1, DVX and logP) and HIV-1 integrase (C65s) 3'processing inhibitory activity. Square of correlation coefficient (r^2) of 0.713 explained 71.3% variance in biological activity. This model also indicated statistical significance > 99.9% with F = 10.79. Cross validated square of correlation coefficient of this model was 0.647, which showed the good internal prediction power of this model. There was no inter-correlation between selected descriptors (Table 6).

Table 6 Correlation matrix of physico-chemical descriptors and HIV-1 integrase (3'-PC65s) inhibitory activities of benzodithiazine derivatives

	pIC_{50}	DVX	logP	BK1
pIC_{50}	1			
DVX	-0.059	1		
logP	0.533	0.445	1	
BK1	0.358	0.116	0.388	1

Integrase (C65s) strand transfer (STC65s)

The best equation received for HIV-1 integrase strand transfer (STC65s) inhibitory activity was

pIC_{50}(STC65s) = -5.138 (±0.762) + 0.730 (±0.152) logP - 0.101 (±0.004) DVX - 0.013 (±0.000) HF(5)

$n = 17$, $r^2 = 0.644$, $r^2_{adj} = 0.562$, $SEE = 0.274$, $F = 7.85$, $P < 0.001$, $q^2 = 0.526$, $S_{PRESS} = 0.264$, SDEP = 0.247.

Where logP - partition coefficient, HF - heat of formation and DVX - dipole moment vector X. The calculated and predicted (LOO) activities of the compounds by the above models are shown in Table 8.

Model - 5 showed good correlation coefficient (r)

of 0.802 between descriptors (HF, DVZ and logP) and HIV-1 integrase (C65s) strand transfer inhibitory activity. Square of correlation coefficient (r^2) of 0.644 explained 64.4% variance in biological activity. This model also indicated statistical significance > 99.9% with F = 7.85. Cross validated square of correlation coefficient of this model was 0.526, which showed the good internal prediction power of this model. There was no inter-correlation between selected descriptors (Table 7).

The robustness of the selected models (2, 3, 4 and 5) was checked by Y - randomization test. The low r^2 and q^2 values (Table 9) indicated that good results in our original models were not due to a chance correlation or structural dependency of the training set. The maximum VIF value of the selected descriptors was 1.215.

Table 7 Correlation matrix of physico-chemical descriptors and HIV-1 integrase (STC65s) inhibitory activities of benzodithiazine derivatives

	pIC_{50}	DVX	HF	logP
pIC_{50}	1			
DVX	-0.194	1		
HF	0.243	0.117	1	
logP	0.611	0.445	0.516	1

Table 8 Calculated and predicted HIV-1 integrase inhibitory activities of benzodithiazine derivatives

Comp. No	pIC_{50}							
	3′ Pwt by Eq. 2		Int-wt by Eq. 3		3′ PC65s by Eq. 4		Int-C65s by Eq. 5	
	Cal	Pred	Cal	Pred	Cal	Pred	Cal	Pred
1	-1.361	-1.393	-1.342	-1.372	-2.175	-2.096	-2.027	-2.056
2	-1.576	-1.569	-1.470	-1.425	-2.106	-2.168	-1.631	-1.573
3	-1.335	1.301	-1.356	-1.327	-1.580	-1.617	-1.404	-1.364
4	-1.404	-1.396	-1.398	-1.355	-1.724	-1.750	-1.441	-1.436
5	-1.616	-1.612	-1.617	-1.613	-1.862	-1.860	-1.222	-1.218
6	-1.508	-1.529	-1.615	-1.595	-1.340	-1.549	-1.317	-1.447
7	-1.368	-1.369	-1.238	-1.280	-1.795	-1.887	-1.757	-1.833
8	-1.213	-1.223	-1.093	-1.110	-1.296	-1.296	-0.896	-0.863
9	-1.309	-1.374	-0.992	-1.119	-1.102	-0.901	-1.096	-0.086
10	-1.367	-1.362	-1.330	*1.324	-1.609	-1.616	-1.522	-1.621
11	-1.372	-1.383	-1.289	-1.280	-1.292	-1.585	-1.359	-1.323
12	*	*	0.669	-0.581	-1.216	-1.184	-0.865	-1.012
13	-2.030	-2.289	-1.842	-1.987	-1.405	-1.409	-1.469	-1.504
14	-1.419	-1.427	-1.535	-1.627	-1.875	-1.855	-1.779	-1.974
15	-1.309	-1.311	-1.164	-1.154	-1.646	-1.654	-1.878	-1.859
16	-1.031	-1.025	-0.660	-0.538	-1.518	-1.688	-1.279	-1.276
17	NA	NA	NA	NA	-1.634	-1.621	-1.813	-1.909

NA: Not available, *: outlier, Cal: calculated activity, Pred: predicted activity

Table 9 Results of Y - randomization test for HIV-1 integrase inhibitory activity of benzodithiazine derivatives

Iteration	Eq. 2		Eq. 3		Eq. 4		Eq. 5	
	r^2	q^2	r^2	q^2	r^2	q^2	r^2	q^2
1	0.024	0.012	0.032	0.006	0.143	0.016	0.184	0.034
2	0.074	0.009	0.056	0.001	0.015	0.010	0.032	0.005
3	0.058	0.006	0.039	0.023	0.021	0.019	0.010	0.002
4	0.186	0.034	0.134	0.008	0.130	0.023	0.101	0.041
5	0.155	0.036	0.092	0.052	0.022	0.001	0.093	0.009

The predictive ability of these models (2, 3, 4 and 5) was also confirmed by leave 33 % out cross validation. All the four models showed good predictivity. The equations received from the leave 33 % out cross validation technique were

Leave 33% out cross-validation equation for model - BIP4 (number of cycles 3)

$pIC_{50}(3'Pwt) = 2.502 (\pm 1.812) - 0.255 (\pm 0.051)$ DVZ + 0.005 (±0.001) HF + 0.391 (±0.206) HOMO (6)

$r^2_{CVextLSO} = 0.573$, $r^2_{LSO} = 0.678$

Leave 33% out cross-validation equation for model - BIS3 (number of cycles 3)

$pIC_{50}(STwt) = 7.214 (\pm 2.759) - 0.230 (\pm 0.037)$ DVZ + 0.007 (±0.002) HF + 0.905 (±0.303) HOMO (7)

$r^2_{CVextLSO} = 0.509$, $r^2_{LSO} = 0.610$

Leave 33% out cross-validation equation for model - BICP3 (number of cycles 3)

$pIC_{50}(3'PC65s) = -5.362 (\pm 1.059) + 0.483 (\pm 0.122)$ logP - 0.047 (±0.012) DVX + 0.076 (±0.006) BK1(8)

$r^2_{CVextLSO} = 0.575$, $r^2_{LSO} = 0.680$

Leave 33% out cross-validation equation for model - BICS3 (number of cycles 3)

$pIC_{50}(STC65s) = -5.478 (\pm 0.918) + 0.799 (\pm 0.181)$ logP - 0.044 (±0.004) DVX - 0.015 (±0.000) HF (9)

$r^2_{CVextLSO} = 0.508$, $r^2_{LSO} = 0.632$

Consequently Eq. 2 was considered as most suitable model for wt 3´processing inhibitory activity, Eq. 3 was selected as best model for wt strand transfer inhibition activity, Eq. 4 was considered as most suitable model for C65s 3´processing inhibitory activity and Eq. 5 was selected as best model for C65s strand transfer inhibition activity with both high statistical significant and excellent predictive ability. The variables used in the selected models had no mutual correlation (Table 4-7). These models showed good correlation coefficient between descriptors and HIV integrase 3´processing (wt and C65s) and strand transfer (wt and C65s) inhibitory activity.

DISCUSSION

In model - 2 and 3, the negative contribution of DVZ on the biological activity shows that the increase of dipole moment (Z) of molecules lead to reduce HIV integrase (wt) 3´processing and strand transfer inhibitory activity, the positive coefficient of HOMO shows that the substitution with high electro positive groups is conducive for the HIV integrase (wt) 3´processing inhibitory activity of benzodithiazine, and the positive coefficient of HF shows that the increase in heat of formation is favorable for activity. HOMO is the highest energy level in the molecule that contains electrons. When a molecule acts as a Lewis base in bond formation, the electrons are supplied from the molecules HOMO. Molecules with high HOMOs are more able to donate their electrons and hence they are relatively reactive compared to molecules with low lying HOMOs, thus the HOMO descriptor should measure the nucleophilicity of a molecule.

In model - 4 and 5, the negative contribution of DVX on the biological activity shows that the increase of dipole moment (X) of molecules lead to reduce HIV integrase (C65s) 3´processing and strand transfer inhibitory activity, and the positive coefficient of logP shows that the substitution with high hydrophobic groups is conducive for the HIV integrase (C65s) 3´processing and strand transfer inhibitory activity of benzodithiazine. But, in the model - 4 shape index 1 (BK1) is contributed negatively and in the model - 5 HF is contributed negatively. Based on the developed QSAR model, new HIV integrase inhibitors of benzodithiazine derivatives can be designed with caution.

CONCLUSION

The proposed models, due to the high internal and external predictive ability, can therefore act as a useful aid to the costly and time consuming experiments for determining the molar concentration of a compound required to achieve 50% inhibition in HIV-1 integrase activity. Our results lead to the conclusion that the HIV-1 integrase inhibitory activities of benzodithiazine derivatives could be increased if substituents that bring about changes in the molecule as mentioned above are attached to it.

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