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Quantitative Structure and activity Relationship of 3a, 6a – Dihydro-1H- pyrrolo[3,4-c] pyrazole-4,6-dione Derivatives as anti HIV-1 Agents

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Abstract: A novel series of 3a, 6a – Dihydro-1H- pyrrolo[3,4-c] pyrazole-4,6-dione Derivatives have been reported as better anti-HIV 1 agents. In this study QSAR was carried on a 3a, 6a – Dihydro-1H- pyrrolo[3,4-c] pyrazole-4,6-dione Derivatives as anti HIV – 1 agents. Two different variable selection approaches namely: Genetic function approximation and multi linear regression models were used to predict the HIV-1 inhibition activity. The following were obtained after the model was internally validated: squared correlation coefficient (R^2) of 0.8823, adjusted squared correlation coefficient (R^2_{adj}) of 0.8528 and leave one out (LOO) cross validation coefficient (Q^2_{cv}) of 0.7566. The external validation was carried out to confirm the predictive power of the model and R^2_{pred} of 0.6901 was obtained. The validated model result above showed that the five descriptors which are GATS6c, VR3_Dze, minHCsats, RDF30m and Eze contributed positively to the activity. The result obtained will be very helpful for designing and synthesizing other derivatives with improved anti-HIV activities.

Keywords: *HIV, AIDS, QSAR, 3a 6a – Dihydro-1H- pyrrolo[3,4-c] pyrazole-4,6-dione Derivatives, model validation.*

1. Introduction

Human immunodeficiency virus type 1(HIV-1) is the main causative agent of acquired immunodeficiency syndrome (AIDS) which remains a serious public health problem throughout the world [1].HIV-1 integrase (IN) is a virally encoded enzyme essential for virus replication, which mediates insertion of the double-stranded DNA provirus into the host genome[2]. Integration is the final step before irreversible and productive HIV-1 infection of the target cell [3]. During the past two decades an increasing number of quantitative structure-activity/property relationship (QSAR/QSPR) models have been studied using theoretical molecular descriptors for predicting biomedical, activity, toxicology and technological properties of chemicals.

QSAR was performed on 3a, 6a – Dihydro-1H-pyrrolo[3,4-c] pyrazole-4,6-dione Derivatives dataset. The overall goals of QSAR retain their original essence and remain focussed on the productive ability of the approach and its receptiveness to mechanistic interpretation. QSAR includes all statistical methods by which biological activities (most often expressed by logarithms of equipotent molar activities) are related with structural elements, physiochemical properties or fields (3D QSAR) [4]. Following our interest in this field, our aim is to describe the structure-activity relationships study on 3a, 6a – Dihydro-1H-pyrrolo[3,4-c] pyrazole-4,6-dione Derivatives and develop a QSAR model on these compounds with respect to their 50% effective concentration(EC_{50}).

2. Materials and Methods

The experimental effective concentrations (EC_{50}) in micromole of 3a, 6a – Dihydro-1H-pyrrolo[3,4-c] pyrazole-4,6-dione Derivatives against HIV-1 integrase inhibitors are extracted from a recent publication[5]. For modelling purposes these values are converted into logarithm units ($-\log_{10}EC_{50}$). Table 1 shows the experimental activities in Log EC_{50} of 3a, 6a – Dihydro-1H-pyrrolo[3,4-c] pyrazole-4,6-dione Derivatives. The

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dataset of 35 compounds were divided into 26 training sets to build the model and 9 test sets to validate the model.

Structure of 3a, 6a – Dihydro-1H- pyrrolo[3,4-c] pyrazole-4,6-dione Derivatives

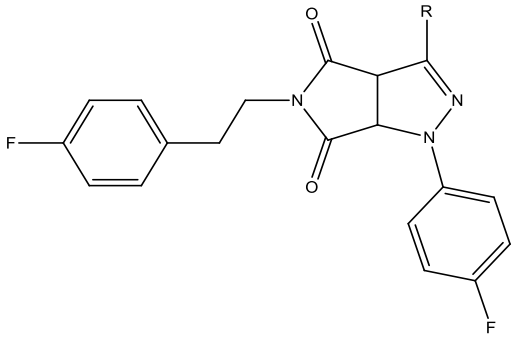


Figure 1. Compounds 1-20

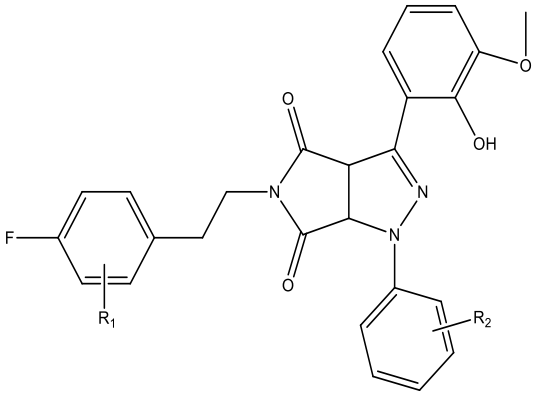


Figure 2. Compound 21-35

Table 1. 3a, 6a – Dihydro-1H- pyrrolo[3,4-c] pyrazole-4,6-dione Derivatives and their respective activities.

Comp No	R	$LogEC_{50}$
1*	2,3-OHPh	4.5786
2	2-OMe, 3-OHPh	5.2700
3	Ph	5.0357
4*	2-OHPh	4.9952
t5	2,4-OHPh	4.4521
6*	2-OH, 3-FPh	5.2411
7*	2-OH, 5-FPh	5.3757
8	2-OH, 3-ClPh	4.6899
9	2-OH, 3-FPh	5.1221
10	2-OH, 3-NO_2Ph	5.3098
11	2-OH, 3-OMePh	5.4001
12	2-OH, 4-OMePh	5.0696
13	2-OH, 5-OMePh	5.3251
14	2-OH, 3-OEtPh	3.9360
15	2-OH, 3-OMe, 5-NO_2Ph	4.3774
16	2,3-OMePh	4.9535
17*	Benzo[1,3]dioxol-4-yl	5.1481
18	2-OH-naphthalene-1-yl	5.3468
19	Thiazol-2-yl	4.4492
20	Pyridine-2-yl	4.5824

Table 2. 3a, 6a – Dihydro-1H- pyrrolo[3,4-c] pyrazole-4,6-dione Derivatives and their respective activities.

Comp No	R_1	R_2	$LogEC_{50}$
21	4F	3F	4.9179
22	4F	2F	3.9475
23	4F	4Cl	4.5940
24	4F	2,4-F	4.1810
25	4F	$4CF_3$	4.4935
26	4F	$4\text{-}SO_2Me$	4.1848
27	4F	$4\text{-}SO_2NH_2$	4.5167
28*	4F	H	4.5432
29	4F	4-Me	5.3872
30	4F	4-OMe	4.6753
31	2F	4F	5.5986
32	3F	4F	4.8854
33*	4Cl	4F	4.9817
34*	H	4F	4.7242
35*	4-OMe	4F	4.0597

*Test set compounds are represented with

2.1. Optimization

The structures of all the compounds were drawn using ChemDraw Ultra module. The drawn structures were imported to Spartan 14 where the 3D structures of the 35 compounds were created. Their energies were minimized by molecular mechanics force fields (MMFF) to remove the strain energy before subjecting it to quantum chemical estimations. DFT (Density Functional Theory) with B3LYP (6-311G*) basis set was employed for complete optimization. The Spartan files of all the optimized molecules were then saved in the SD file format which is the recommended input format in PaDEL Descriptor software V2.20 [6]. The optimization was carried out using Spartan 14.

2.2. Molecular Descriptor Calculations

Descriptors are mathematical values used to describe the properties of molecules. The 35 compounds descriptors calculation was calculated using PaDEL- Descritors software V2.20. A total of 1629 molecular descriptors were calculated.

2.3. Normalization of descriptors

The descriptors' value was values were normalized using Equation 1 in order to give each variable the same opportunity at the onset to influence the model [7].

$$X = \frac{X_i - X_{min}}{X_{max} - X_{min}} \quad (1)$$

Where Xi is the value of each descriptor for a given molecule, Xmax and Xmin are the maximum and minimum value for each column of descriptors X respectively.

2.4. Data Pretreatment

The normalized data were subjected to pretreatment using Data Pretreatment software obtained from Drug Theoretical and Cheminformatics Laboratory (DTC Lab) in order to remove noise and redundant data [6].

2.5. Data Division

Data Division software obtained from Drug Theoretical and Cheminformatics Laboratory (DTC Lab) by employing Kennard and Stone's algorithm was used in order to obtain validated QSAR models from the dataset. The dataset was divided into 26 training and 9 tests set in the percentage of 75% and 25% respectively which table 1 clearly shows.

2.6. Model Validation

Validation of the model was performed using Material studio software version 8 by utilizing Genetic Function Approximation (GFA) method. The importance of model validation could now be regarded as a collective wisdom within the community of molecular modellers [8].

LOF (Friedman's lack of fit) was one of the methods used to validate the model. The formula is given in equation 2 below.

$$LOF = \frac{SEE}{(1-\frac{c+d\times p}{m})2} \quad \text{..... (2)}$$

where SEE is the standard error of estimation, c is the number of descriptors, p is the number of independent parameters, m is the number of samples and d =1. The advantage of using LOF rather than SSE is that LOF do not decrease with increase in the number of descriptors. The lower value of LOF in QSAR indicates that the model has a good predictive power.

The second parameter is cross- validation which is based on leave one out (LOO) or leave some out (LSO) cross validation procedure. The outcome from this procedure is the cross-validation parameters. They include PRESS (predicted residual sum of squares), SSY (sum of the squares of the response values), S_{press} (uncertainty of precision), Q^2_{cv} overall predicted ability and PSE (predictive square Error). Frequently Q^2_{cv} is used as a criterion of both robustness and predictive ability of the model. High value of Q^2_{cv} (for instance >0.5) is an indicator of the high predictive power of the QSAR model.

$$Q^2_{cv} = 1- \frac{\sum(Y_{cal} - Y_{obs})^2}{\sum(Y_{obs} - \bar{Y})^2} \quad (3)$$

Correlation coefficient between the predicted and observed activities, R^2 is the third parameter for validating a model but not a complete useful measure of stability of a model. R^2 varies directly with the increase in number of descriptors.

$$R^2 = 1- \frac{\sum(Y_{obs} - Y_{cal})^2}{\sum(Y_{obs} - \bar{Y})^2} \quad (4)$$

Y_{obs}, Y_{cal} and $\bar{Y}$ are the observed activity, the calculated activity and the mean observed activity of the samples in the training set, respectively.
Another parameter is adjusted squared correlation coefficient (R^2_{adj}). The formula for calculating R^2_{adj} is:

$$R^2_{adj} = \frac{R^2 - P(n-1)}{n-p+1} \quad (5)$$

P in equation 5 is the number of independent variables in the model.
The coefficient of determination of the test set was calculated with the formula in equation (6) below.

$$R^2_{predicted} = \frac{\sum(Ypred_{test} - Yexp_{test})^2}{\sum(Yexp_{test} - \bar{Y}_t)^2} \quad (6)$$

2.7. Y Randomization

Y randomization is carried out only with training set compounds to guarantee the created QSAR model is strong and not inferred by chance. It was carried out by randomly shuffling the dependent variable while keeping the independent variables unaltered. The dependent variable is the activity while the independent variable is the descriptor. The randomized R^2 and Q^2 obtained must have lower values after several trials than the original R^2 and Q^2 to confirm that the model developed is robust.

Coefficient of determination for Y-Randomization, cR^2_p must be greater than 0.5 for passing this test [9].

Table 3. Summary of GFA Analysis

Analysis type	Genetic Function Approximation
Response column	BJR: activity
Number of rows in model	26
population	1000
Maximum generations	2000
Initial terms per equations	5
Maximum equation length	5
Constant equation length	Yes
Number of top models returned	4
Scoring Function	Friedman LOF
Scaled LOF smoothness parameter	0.50000000
Mutation probability	0.10000000
Linear spine	No
Quadratic spine	No
Random number seed	9999
Minimum prediction fraction for term inclusion	1.000000e-004
Number of variables requested for plot	5

3. Results and Discussion

A QSAR examination was performed to investigate the structure Activity relationship of 35 compounds as potent Anti-HIV 1. In order to assemble a good QSAR model for anti-HIV a decent predictive power Kennard-stone was used to divide the data set into a training set of 26 compounds which was used to develop the model and a test set of 9 compounds which was used to utilize the predictive ability of the built model. Table 4a and 4b below show the experimental, predicted and residual values for 3a, 6a – Dihydro-1H- pyrrolo[3,4-c] pyrazole-4,6-dione Derivatives. The low residual

values between the experimental and the predicted activity show that the model is of high predictability.

Table 4a. Experimental, Predicted and Residual values of training set of 3a, 6a – Dihydro-1H- pyrrolo[3,4-c] pyrazole-4,6-dione Derivatives.

S/N	Experimental	predicted values	Residual
2	5.3098	5.363592	-0.05379
3	5.4001	5.391676	0.008424
5	5.0696	5.212068	-0.14247
8	5.3251	5.336812	-0.01171
9	3.936	3.918456	0.017544
10	4.3774	4.505073	-0.12767
11	4.39535	4.453602	-0.05825
12	5.3468	5.160046	0.186754
13	4.4492	4.213953	0.235247
14	5.27	5.057108	0.212892
15	4.5824	4.672004	-0.0896
16	4.9179	5.087736	-0.16984
18	3.9475	4.184707	-0.23721
19	4.594	4.64802	-0.05402
20	4.181	4.128223	0.052777
21	4.4935	4.466479	0.027021
22	4.1848	4.339639	-0.15484
23	4.5167	4.182111	0.334589
24	5.3872	5.086451	0.300749
25	5.0357	5.233731	-0.19803
26	4.6753	4.852069	-0.17677
27	5.5986	5.331183	0.267417
29	4.8854	4.852921	0.032479
30	4.4521	4.597567	-0.14547
31	4.6899	4.663171	0.026729
32	5.1221	5.205051	-0.08295

Table 4b. Experimental, Predicted and Residual values of test set of 3a, 6a – Dihydro-1H- pyrrolo[3,4-c] pyrazole-4,6-dione Derivatives.

S/N	Activity	Predicted values	Residual
1	4.5786	5.301255	-0.72266
4	5.1481	5.315982	-0.16788
6	4.5432	4.83087	-0.28767
7	4.9817	4.694192	0.287508
17	4.7242	4.95784	-0.23364
28	4.0597	3.703689	0.356011
33	4.9952	4.988736	0.006464
34	5.2411	5.729365	-0.48827
35	5.3757	5.577769	-0.20207

Table 5. Validation parameters from material studio.

	Equation 1	Equation 2	Equation 3	Equation 4
Friedman LOF	0.15497	0.156554	0.157166	0.158315
R-squared	0.882272	0.881068	0.880603	0.879731
Adjusted R-squared	0.852839	0.851335	0.850754	0.849663
Cross validated R-squared	0.756607	0.781141	0.725727	0.789124
Significant Regression	Yes	Yes	Yes	Yes

Significance-of-regression F-value	29.976495	29.632662	29.501762	29.258665
Critical SOR F-value (95%)	2.732939	2.732939	2.732939	2.732939
Replicate points	0	0	0	0
Computed experimental error	0	0	0	0
Lack-of-fit points	20	20	20	20
Min expt. error for non-significant LOF (95%)	0.146632	0.147379	0.147667	0.148206

The Genetic Algorithm -Multi linear Regression (GA-MLR) study led to the selection of five descriptors which were used to assemble a linear model for calculating predictive activity on HIV-1. Four QSAR model was models were built but only the first was used due to statistical significance. The parameter of model 1 which was $R^2_{predicted}$ was calculated. The validation parameters in Table 5 above were in agreement with the threshold value reported in Table 6. It showed that the model was stable and robust.

Table 6. Minimum recommended values of validation parameters for a generally acceptable QSAR model

Name	Symbol	Value
Coefficient of Determination	R^2	≥0.6
Confidence interval at 95% confidence level	P(95%)	<0.05
Difference between R^2 and Q^2	R^2 - Q^2	≤0.3
Cross validation coefficient	Q^2	≥0.6
Minimum number of external test set	$N_{ext.test\ set}$	≥0.5
Coefficient of Determination for Y-Randomization	cR^2_p	>0.5

The model number 1 used is:

pEC_{50} = 3.101882593*GATS6c – 0.185597104*VR3_DZe + 4.934195547*minHCsats – 0.157014990*RDF30m + 8.505034001*E2e – 0.318780476

Table 7. Pearson's correlation for descriptors used in the QSAR optimization model

	Name	GATS6c	VR3_Dze	minHCsats	RDF30m	E2e
Name	1					
GATS6c	-0.062	1				
VR3_Dze	0.185	0.040	1			
minHCsats	0.220	0.030	0.934	1		
RDF30m	0.0312	-0.155	-0.786	-0.736	1	
E2e	-0.189	-0.308	-0.810	-0.784	0.792	1

The correlation shown in Table 7 above was an indication that the five descriptors used in the QSAR optimization model do not show high correlation.

The Y-randomization in table 8 below with cR^2_p > 0.5 shows that QSAR model is strong and not inferred by chance. It is also in agreement with the threshold values in Table 6.

Table 8. Y-Randomization

Model	R	R^2	Q^2
Original	0.821036	0.674101	0.342265
Rand. 1	0.383917	0.147392	-2.05655
Rand. 2	0.283951	0.080628	-1.49508
Rand. 3	0.453379	0.205553	-9.82142
Rand. 4	0.455922	0.207865	-0.34115
Rand. 5	0.331781	0.110078	-2.97162
Rand. 6	0.389811	0.151952	-1.87279
Rand. 7	0.419556	0.176027	-5.89422
Rand. 8	0.362969	0.131746	-1.02703
Rand. 9	0.453342	0.205519	-4.73414
Rand. 10	0.502091	0.252096	-6.46537

Random Models Parameters	
Average r :	0.403672
Average r^2 :	0.166886
Average Q^2 :	-3.66794
cRp^2 :	0.586998

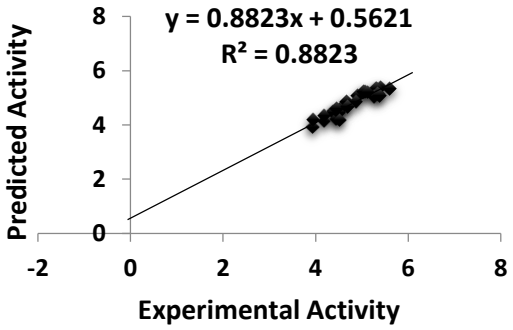


Figure 3. Plot of Predicted Activity against Experimental Activity of training set.

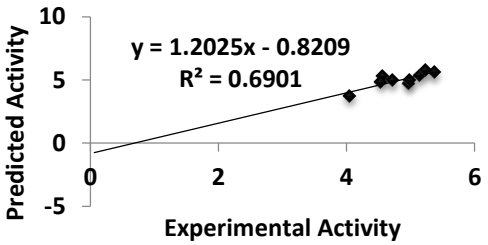
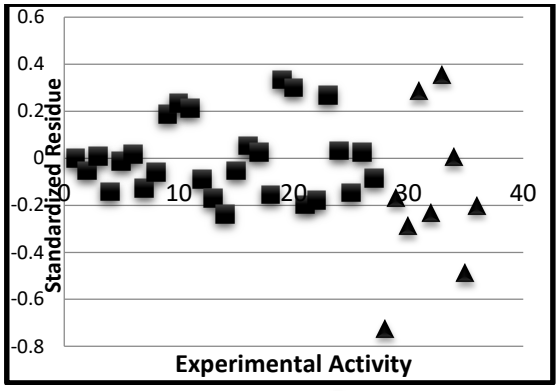


Figure 4. Plot of Predicted Activity against Experimental Activity of test set.



Training set ■ Test set ▲

Figure 5. Plot of Standardized Activity verses Experimental Activity

4. Conclusion

This work reported Quantitative Structure Activity Relationship (QSAR) between 3a, 6a – Dihydro-1H- pyrrolo[3,4-c] pyrazole-4,6-dione Derivatives and their respective activities in pEC_{50}. Result from the model showed that pEC_{50} of the studied molecules against HIV-1 was affected by five descriptors namely: GATS6c, VR3_DZe, minHCsats, RDF30m and E2e. The internal and external validation confirmed the robustness and stability of the model. Stability obtained by external validation indicates that the model can be used to design other 3a, 6a – Dihydro-1H- pyrrolo[3,4-c] pyrazole-4,6-dione Derivatives with improved anti-HIV 1 activity.

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