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Original Research Article

Quantum and Statistical Study for Evaluating the Cytotoxicity Ability of Some Pyrazole Derivatives as Potent Anti Hiv-1 Agents Inhibitors

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ABSTRACT

A series of 20 compounds isolated from some pyrazole derivatives were subjected to cytotoxicity test against HIV–1. Two statistical approaches namely: Genetic Function Algorithm (GFA) and Multi Linear Regression Analysis (MLRA) were effectively used. Best three descriptors which are: VR2_Dzv, VR1_Dzp and PubchemFP824 were selected for the Quantitative structural and activity relationship (QSAR) using the two aforementioned statistical approaches. The results obtained were as follows: R-squared (R^2) of 0.9698, adjusted squared (R^2_{adj}) of 0.9607, cross validated R-squared (LOO- Q^2_{cv}) value of 0.9299 and external prediction ability (R^2_{pred}) of 0.6827. The result proved that the compounds are attractive platform and clinically viable for developing anti HIV-1 drugs. Multivariate statistics with chemical descriptors molecular shape and polarizability may be useful for the evaluation of cytotoxicity of pyrazole.

Keywords: *QSCR*, Pyrazole Derivatives, Anti-HIV-1, Validation, Cytotoxicity, MLR

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Introduction

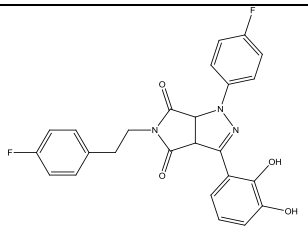
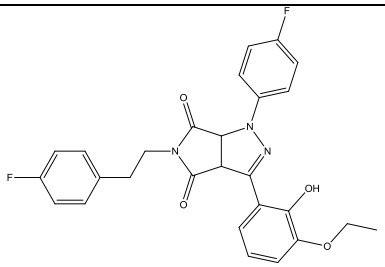
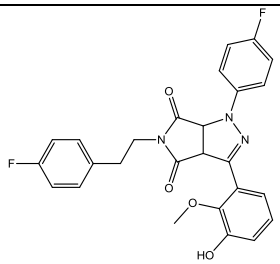
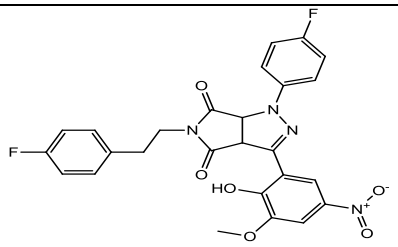
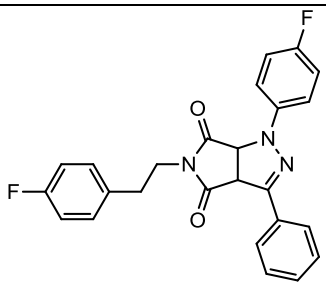
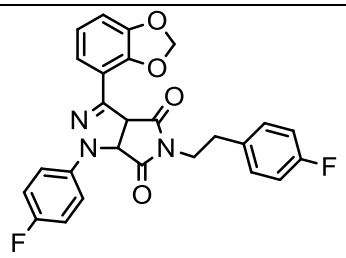
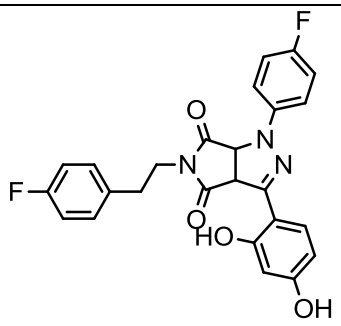
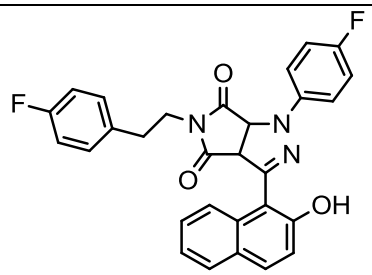
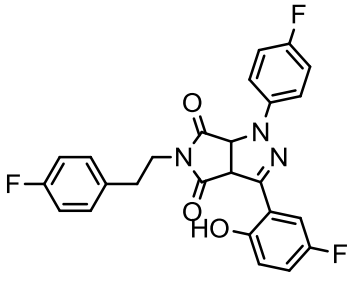
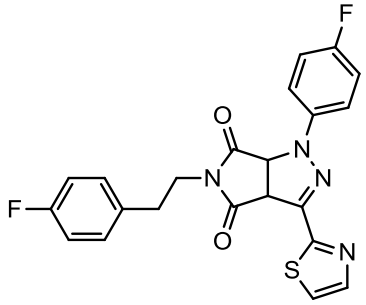
Cytotoxity is the tendency of a drug to prevent cell division or destroy the growth of other cells. Acquired Immunodeficiency Syndrome (AIDS) which is caused by Human Immunodeficiency Virus-1 (HIV-1) cell is still incurable till now. This means that there is no particular drug that can cure it. Without treatment, HIV can gradually destroy the immune system and advance to AIDS. It is the final stage of infection with HIV. Scientists have done several researches on finding the cure but only came up with developing certain drugs called antiretroviral therapy (ART) which can only slow down the HIV-1 replication in the body. The drugs are as follows: Nucleosides reverse transcriptase inhibitors (NRTIs), Non- nucleosides reverse transcriptase inhibitors (NNRTIs), Integrase inhibitors, Protease inhibitors.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 [1]. QSAR studies of anti-HIV activity represent an emerging and exceptionally important topic in the area of computer-aided drug design [2]. It provides a discussion of several qualitative approximations of the structure activity relationship to search the preferred conformations to establish correlations between structural parameters and the various properties of the investigated macromolecules and improving the conception of new therapeutic drugs [3]. The aim of this work is to use Quantitative structure and cytotoxicity relationship (QSCR) to interpret how toxic pyrazole derivatives are to HIV-1 in the body and how they are very effective as potent Anti HIV-1 agents using different statistics techniques such as Genetic Function Algorithm (GFA) and Multi Linear Regression Analysis (MLRA).

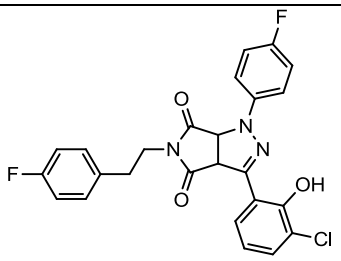
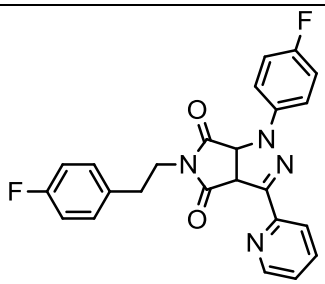
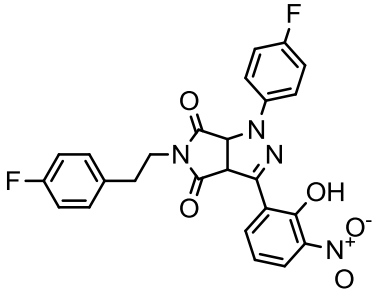
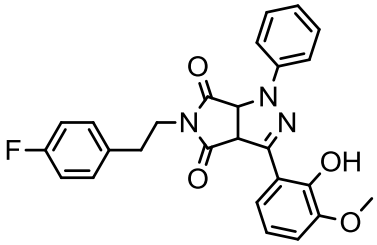
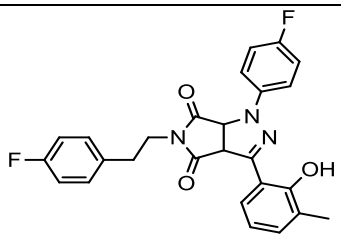
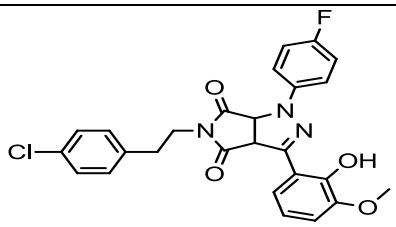
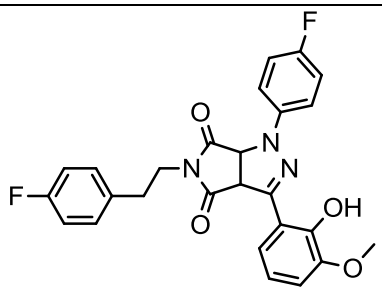
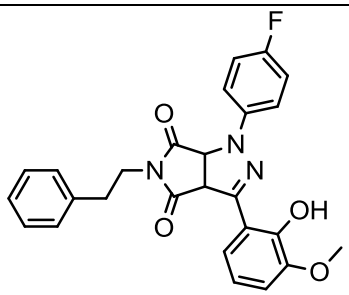
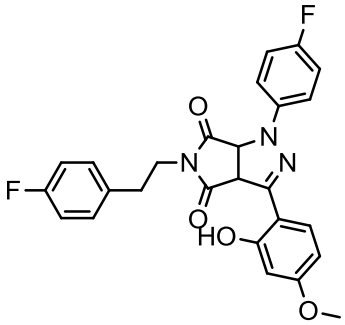
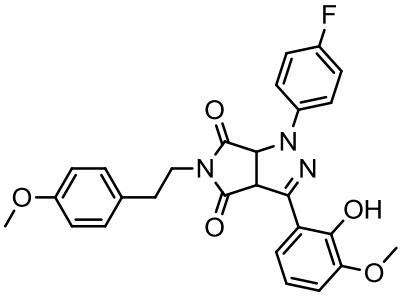
Materials and Methods

The 50% cytotoxic concentration (CC_{50}) of the 20 compounds was given in micromole from the publication [4]. They were converted into $LogCC_{50}$ which was the required standard for modelling according to the equation (1) below.

$$pCC_{50} = -\log_{10}CC_{50} \qquad (1)$$

Table 1: pCC_{50} values and structures of the Pyrazole derivatives used in the QSAR**.**

S/N	Structures	pCC_{50}	S/N	Structures	pCC_{50}
1[a].		**3.3636**	11[b].		**4.0444**
2[a].		**4.4074**	12[a].		**3.3894**
3[a].		**3.8308**	13[b].		**3.6528**
4[a].		**3.7608**	14[a].		**5.0443**
5[a].		**3.7992**	15[a].		**3.8002**

6[b].		**3.4795**	16[a].		**3.8243**
7[b].		**4.3051**	17[a].		**3.3590**
8[a].		**3.8224**	18[a].		**4.1541**
9[a].		**3.3769**	19[a].		**3.3598**
10[b].		**4.6704**	20[b].		**3.6588**

Training set compounds are represented by superscript a while test set compounds are represented by superscript b.

Energy Minimization/optimization

The structures on Table 1 above were drawn using Chemdraw software. The drawn structures were imported to Spartan 14 to convert them to 3D structures. Energy minimization of the structures was carried by using molecular force fields (MMFF). DFT (Density Functional Theory) with B3LYP (6-311G*) basis set was employed for complete optimization **[1].**

Computational details of Descriptors

The descriptors of the compounds used in this work were calculated using PaDEL- Descriptors software V2.20. Molecular descriptors are calculated for chemical compounds and used to develop quantitative structure and cytotoxicity relationship (QSCR) models for predicting the biological activities of novel compounds [5].

Data Division

The compounds were subjected to data division which utilized data division software from Drug Theoretical and Cheminformatics Laboratory DTC Lab where Kennard and Stone's algorithm was effectively used to divide them into 14 training sets and 6 test sets compounds.

Variable Selection

The training set compounds were imported to Material Studio for variable selection and eventually model building using Genetic Function Approximation (GFA). This was done by highlighting the activity in form of pCC_{50} which was in the last column of the training set. The three descriptors used to build the QSAR models are: VR2_Dzv, VR1_Dzp and PubchemFP824.

Model Development

GFA-MLR technique was used to develop and evaluate a stable, robust and reliable model. It is good for generating QSCR equations when one is dealing with a large number of descriptors. It can build linear, higher-order, polynomials, splines and other non-linear equations. In GFA algorithm incorporates Friedman's LOF error measure which estimates the most appropriate number of features, resists overfitting and allows control over the smoothness of fit. It automatically selects which features are to be used in the models.

Model Validation

The importance of model validation could now be regarded as a collective wisdom within the community of molecular modellers [6]. The QSCR model is validated using two parameters: Internal and external parameters. Internal validation is used to develop the mode while the external validation is to validate the model by ensuring that it is robust and stable.

Internal Validation Parameters

The internal Validation parameters used to develop the QSAR model are as follows: standard errors of regression coefficient , R^2(squared correlation coefficient, R^2_{adj}(adjusted squared correlation coefficient, Q^2(leave one out cross validated coefficient, F-test , Y-randomization, Friedman's LOF etc. The root mean square error (*RMSE*) is dispersion degree of random error, presenting a more intuitive index of the fitting ability of the model [7]. Standard Error, root mean square error (RMSE) and root mean square error prediction (RMSEP) must be low for a better predictive ability of a model.

$$\text{RMSE} = \sqrt{\sum_{i=1}^{n}(Y_{obs} - Y_{pred})^2}\ . \qquad (2)$$

The residual value which is obtained by the difference between the observed and predicted activity of the training sets compounds must also be low an indication for robustness of the model.

R-squared is formula is given in equation (3) below. It is the most commonly used internal validation parameter. For a QSAR model to be robust and reliable, the R^2 value must be greater than or equal to 0.6.

$$R^2 = 1 - \frac{\sum(Y_{predicted} - Y_{obs})^2}{\sum(Y_{obs} - \bar{Y})^2} \qquad (3)$$

The cross validated R-squared is defined in equation (4) below.

$$Q^2 = 1 - \frac{\sum(Y_{obs} - Y_{predicted})^2}{\sum(Y_{obs} - \bar{Y})^2} \qquad (4)$$

From equations 2, 3 and 4, Y_{obs}, $Y_{predicted}$ and $\breve{Y}$ are the observed activity, the calculated activity and the mean observed activity of the samples in the training set, respectively.

R^2 adjusted is given in the equation (5) below.

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

Its value must also be greater than 0.6 for a model to be reliable.

External Validation Parameters

R-squared predicted is the most important used to determine the stability and reliability of the model developed using internal validation parameters. The developed model must be subjected to external validation using test set compounds for the model to be stable, robust and reliable. Its value must be greater than 0.6 for the validated model to be robust. It is defined using the formula given in equation (6) below.

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

Results and Discussion

Table 2: Pearson's correlation Coefficient

	VR2_Dzv	*VR1_Dzp*	*PubchemFP824*
VR2_Dzv	1		
VR1_Dzp	0.638114843	1	
PubchemFP824	0.388415877	0.649387495	1

The equation for model number 1 used in the QSCP

pCC_{50} = - 0.011052656 * VR2_Dzv **+ 0.001883744 *** VR1_Dzp **- 0.640477245 ***: PubchemFP824 **+ 3.200372616**

Table 3: Experimental, Predicted and Residual values of training set pyrazole Derivatives

Actual values for BJR : Cytotoxicity	Equation 1: Predicted values	Equation 1: Residual values
3.3769	3.273714	0.103186
3.8243	3.877961	-0.05366
3.8308	3.865105	-0.03431
3.7608	3.758338	0.002462
3.7992	3.875522	-0.07632
3.3636	3.1912	0.1724
3.359	3.447502	-0.0885
4.4074	4.370353	0.037047
3.3894	3.380614	0.008786
3.8224	3.848685	-0.02629
3.8002	3.848637	-0.04844
3.3598	3.402274	-0.04247
4.1541	4.241358	-0.08726
5.0443	4.910937	0.133363

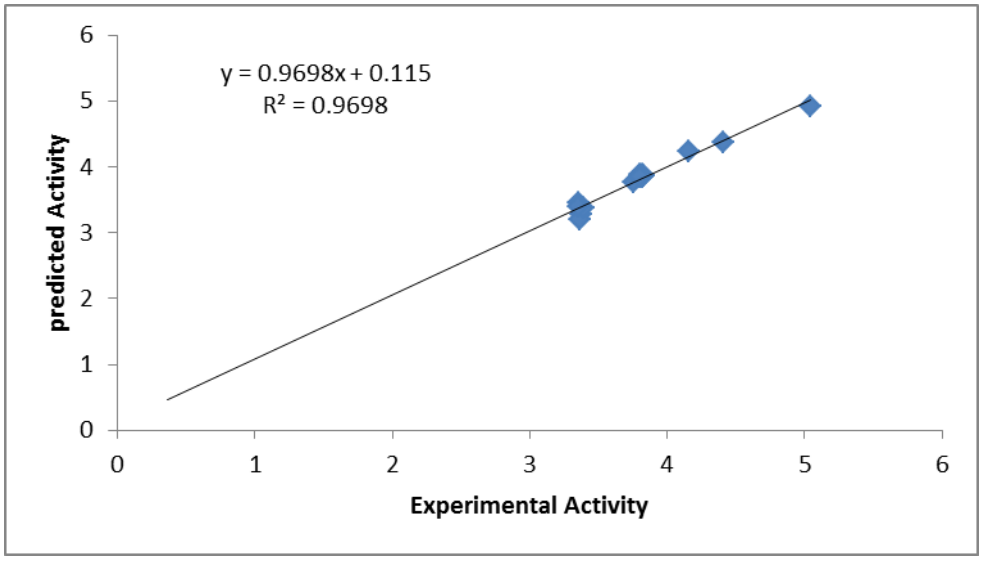


Figure 1: plot of predicted activity against experimental activity of training set

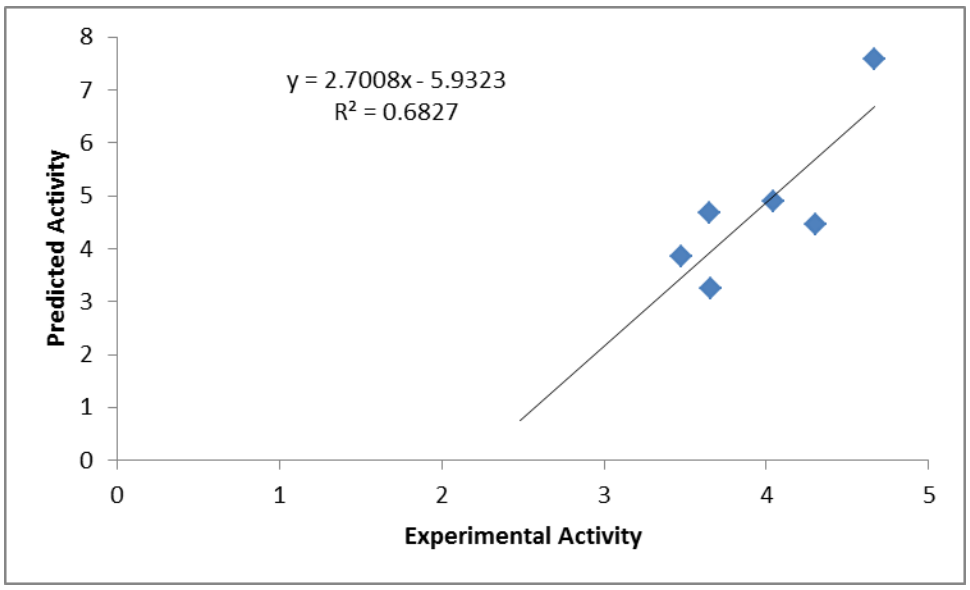


Figure 2: plot of predicted activity against experimental activity of test set

Table 4: Descriptors and Occurrences in population

Variable	Abbreviation	Occurrences in population
Citotoxicity	Y	
VR2_Dzv	X385	5
VR1_Dzp	X410	509
PubchemFP824	X1627	192

Table 5: Univariate statistics of Pyrazole derivatives data

Statistics Parameters	Training set	Test set
Number of sample used	14	6
Range	1.6853	1.1909
Maximum	5.0443	4.6704
Minimum	3.3590	3.4795
Mean	3.8066	3.9685

Table 6: Validation Parameters from Material Studio

Friedman LOF	0.040296
R-squared	0.96979
Adjusted R-squared	0.960727
Cross validated R-squared	0.929874
Significant Regression	Yes
Significance-of-regression F-value	107.0067
Critical SOR F-value (95%)	3.871034
Replicate points	0
Computed experimental error	0
Lack-of-fit points	10
Min expt. error for non-significant LOF (95%)	0.069882

The Table 2 above shows the Pearson's correlation Coefficient of the three descriptors used in the QSCR. The highest value obtained was 0.649387495. The lower values of Pearson's correlation Coefficient indicate that there is no relationship between the descriptors used in the QSCR. A correlation of 1 means very strong relationship.

The Experimental, Predicted and Residual values of training set pyrazole reported in Table 3 shows low residual values between the experimental and predicted activity. The low values indicate that the developed model was very robust and stable.

Table 5 shows the univariate analysis of activity values of training set and test set compounds. From the table 6 the test set range was within the training set range. Hence Kennard Stone Algorithm was able to generate a test set that is a good reflection of the training set [8].

Table 6 above shows the validation parameter from material studio, the difference between the R^2 and R_{adj}^2 value less than 0.3 indicates that the number of descriptors involved in the QSAR model is acceptable [9].

Also, the large f-value indicates that the model is not a chance occurrence [10].

Figure 1 which is a plot of predicted activity against experimental activity of training set confirmed the robustness of the QSCR developed with R- squared value of 0.9698.

Figure 2 which is a plot of predicted activity against experimental activity of test set also confirmed the robustness of the QSCR developed with R- squared value of 0.6827.

Conclusion

In this work, Quantitative Structure Cytotoxicity Relationship (QSCR) between 20 pyrazole inhibitor Derivatives and their respective cytotoxicity in pCC_{50} was accounted for. The three descriptors namely: **VR2_Dzv, VR1_Dzp and PubchemFP824** played a significant role in the development of the model and its validation with R-squared values of 0.9698 and 0.6827 for training and test set respectively. Robustness and stability of the model was confirmed by these results. It can be inferred that the stability and reliability of the model obtained by this QSCR can be helpful to design and synthesize other pyrazole derivatives.

Acknowledgement

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