International Journal of Scientific Research in Chemical Sciences **Research Paper**
Vol.8, Issue.5, pp.15-18, October (2021) **E-ISSN:** 2455-3174

Toxicity Study and in silico ADME of some selected Anti-HIV agents inhibitors

S.U. Ahanonu[1*], G.A. Shallangwa[2], Y.A. Dallatu[3], A. Ibrahim[4]

[1,2,3,4]Department of chemistry, Ahmadu University, Zaria, Nigeria

[*]*Corresponding Author: favour_saviour@yahoo.com Phone number: 08037680389*

Available online at: www.isroset.org

Received: 18/Jul/2021, Accepted: 20/Oct/2021, Online: 31/Oct/2021

Abstract-Quantitative structural and cytotoxicity relationship (QSCR) has been carried out on twenty pyrindine-4-carboxylate derivatives using genetic function approximation combined with multiple linear regression (GFA-MLR). The following results were obtained by GFA-MLR using three descriptors **AATS6i, MAT57e** and **TDB9s; R-squared, R^2 = 0.888666, Adjusted R-squared, R^2_{adj}= 0.855266, cross validated R-squared, LOO-Q^2_{CV} = 0.710242, Y-randomization, cR^2_p = 0.793663 and external prediction, $R^2_{prediction}$ = 0.8184.** Their physiochemical properties are in agreement with a rule given by Lipinski's rule and results of molecular weight ≤ 500 daltons, hydrogen acceptors of ≤ 10, hydrogen bond donors of ≤ 5 and octanol water partition coefficient ≤ 5 were obtained.
This research provides an understanding on new HIV drugs with reduced toxicity and greater effectiveness.

Keywords-Anti-HIV agents, Toxicity, Validation, Y- randomization, GFA-MLR

I. INTRODUCTION

HIV is a family of diseases involving uncontrolled cell growth with the potential to spread to other body parts. Today, HIV is a serious health problem all over the world. Acquired Immunodeficiency Syndrome (AIDS), characterized by opportunistic infections (T4 cell falls below 200/μL) and opportunistic neoplasms [1]. Acquired Immunodeficiency Syndrome (AIDS), is a type of infection which is brought about by prolonged HIV Virus-1 (cell and is incurable till now [2].

Some drugs are available for the management of HIV but few of them are toxic to other body cells. So, it is now very important to develop new drugs without such toxic effects in the body.

The aim of this research is to study the quantitative structure –cytotoxicity relationship (QSCR), the toxicity, pharmacokinetic and physiochemical properties of these Anti-HIV Agents inhibitors using a computational quantum approach.

II. RELATED WORK

Previous works had been carried out on HIV/AIDS using different compounds and different techniques. To date, there are many computer-aided drug design methods applied in designing and developing novel HIV-1 inhibitors [3]. In this research, toxicity study and In silico ADME of some selected Anti-HIV agents inhibitors were conducted to elucidate the best drug candidate.

III. METHODOLOGY

The inhibitor compounds were extracted from the literature [4]. Cytotoxic activities given in CC_{50} μg/ml were converted into $LogCC_{50}$. The structures were drawn using Chemdraw and energy minimization was conducted by utilizing DFT(density functional theory) with B3LYB(6-311G*) basis set. PaDEL Descriptor software V2.20 was used to calculate the descriptors. Descriptors are defined as mathematical values used to describe accurately the properties of molecules [5]. A total of 1494 were calculated and three were used to develop the model. The three descriptors used are: MATS7e (Moran autocorrelation of lag 7 weighted by Sanderson electronegativity), TDB9s (Moran autocorrelation of lag 7 weighted by Sanderson electronegativity) and AATS6i (Broto-Moreau autocorrelation of lag 6 (log function) weighted by ionization potential).

Data division was carried out using data division software which is one of the components of Theoretical and Cheminformatics laboratory (DTC lab) softwares by utilizing a method called Kennard and stone's algorithm in the percentage of 70%(14 training set) and 30% (6 test set). GFA combined with MLR were used to perform model validation.

Table 1a: Biological activity of training set compounds

No	X	R^1	R^2	CC_{50} (μM)
1	CH2	Ph	OEt	234.02
2	CH_2	4-FPh	OEt	323.32
5	$CH(CH_3)$	Ph	OEt	320.09

7	NH	4-ClPh	OEt	135.46
9	CH_2CH_2	3-FPh	OEt	176.42
10	CH_2CH_2	4-FPh	OEt	13.16
11	CH_2CH_2	4-ClPh	OEt	145.43
12	CH_2CH_2	4-MePh	OEt	15.45
13	CH_2CH_2	4-SO_2NH_2	OEt	173.46
14	CH_2CH_2	4-OMePh	OEt	232.97
15	CH_2CH_2	3,4-OMePh	OEt	33.52
16	CH_2CH_2	Indol-3-yl	OEt	26.73
17	CH_2CH_2	4-MePh	NH(4-FBn)	164.60
19	CH_2CH_2	4-MePh	$NHCH_2CH(CH_2CH_2)$	306.17

Table 1b: Biological activities of test set compounds

No	X	R^1	R^2	CC_{50} (μM)
3	CH_2	2-OMePh	OEt	395.39
4	CH_2	4-OMePh	OEt	243.69
6	NH	4-FPh	OEt	213.01
8	CH_2CH_2	Ph	OEt	376.18
18	CH_2CH_2	4-MePh	NH(2-OMeBn)	215.82
20	$CH_2CH(Ph)$	Ph	OEt	25.22

Validation of the model is divided into two

1. Internal validation
2. External validation

Internal validation is used to develop a model and its parameters are: R^2 (squared correlation coefficient), R^2_{adj}(Adjusted squared correlation coefficient), Q^2(leave one out cross validated coefficient), Y-randomization, F-test , Freedman's LOF etc. For the built model to be robust $R^2 > 0.6$, $R^2_{adj} > 0.6$, $Q^2 > 0.6$, F-value > 2.09 [6] and $cR^2_p > 0.6$ [7].

External validation is the best method of validating a model. R-squared predicted is the most important used to determine the stability and reliability of the model developed using internal validation parameters [2]. For the model to be robust, strong and reliable the $R^2_{predicted} \geq 0.6$.

Physiochemical properties and druglikeness of the inhibitors were predicted by using the SwissADME website (htt:swissadme.ch) [8]. The criteria for drug potency are stated by rule of five of Lipniski as follows.

Molecular weight ≤ 500 daltons, hydrogen bond acceptors ≤ 10, hydrogen bond donors ≤ 5 and octanol/water partition coefficient ≤ 5. They are in multiples of five that is why it is called rule of five.

IV. RESULTS AND DISCUSSION

Equation for the model: pCC_{50} = - 0.89783552(**AATS6i**) + 6.194696713(**MATS7e**) + 0.078889411(**TDB9s)** + 48.508232691

Table 2: Validation parameters from material studio

Validation parameters	
Friedman LOF	0.159948
R-squared	0.888666
Adjusted R-squared	0.855266
Cross validated R-squared	0.710242
Significant Regression	Yes
Significance-of-regression F-value	26.606568
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%)	0.139227

R^2 value reported in **Table 2** which is greater than 0.6 means that the model is robust.

In Table 2 above, Friedman LOF has a low value and this is in line with a strong model. LOO cross-validated R-squared analysis revealed that the difference between R-squared (R^2) and cross validation R-squared (Q^2_{cv}) must be less than 0.3 for the model to be significant. The result obtained showed that R^2- Q^2_{cv} is less than 0.3 (0.888666 – 0.710242 = 0.178424).The robustness of the model was justified.

Table 3: Pearson's correlation for descriptors used in the QSAR optimization mode

	AATS6i	*MATS7s*	*TDB9s*
AATS6i	1		
MATS7s	0.012753	1	
TDB9s	0.541047	- 0.16895	1

The Pearson's correlation between the descriptors in **Table 3** shows that the descriptors used in the validation of the model do not show any strong relationship. The value of 1 means strong relationship. There is a strong correlation of 1 between the same descriptor used in validating the model as reported in **Table 3.**

Table 4: **Y-Randomization**

Model	R	R^2	Q^2
Original	0.933644	0.871691	0.745602
Random 1	0.502183	0.252187	-0.75394
Random 2	0.335339	0.112452	-0.41926
Random 3	0.416622	0.173574	-0.61092
Random 4	0.568479	0.323169	-0.04913
Random 5	0.418754	0.175355	-1.12289
Random 6	0.355374	0.126291	-1.95036
Random 7	0.260989	0.068115	-1.93573

Random 8	0.470104	0.220998	-0.82519
Random 9	0.215628	0.046495	-0.7335
Random 10	0.317503	0.100808	-1.03326

Random Models Parameters

Average r :	0.386097
Average r^2 :	0.159944
Average Q^2 :	-0.94342
cRp^2 :	0.793663

Y-Randomization is one of the methods used to determine how reliable a developed model is. For the model to be reliable the Y0randomization value must be greater than 0.5. In this study, the Y- randomization value of 0.793663 in **Table 4** shows that the developed model is strong and reliable. It is in conformity with its threshold value [7].

Table 5: Experimental, predicted and residual values of training set compounds

Experimental values	Predicted values	Residual Values
3.6307	3.657901	-0.0272
3.4904	3.4787	0.0117
3.4947	3.695383	-0.20068
3.8682	3.61772	0.25048
3.7535	3.67063	0.08287
4.8807	4.909736	-0.02904
3.8373	3.923618	-0.08632
4.8111	4.510315	0.300785
3.7608	3.83092	-0.07012
3.514	3.641821	-0.12782
4.4747	4.734802	-0.2601
4.573	4.407423	0.165577
3.6327	3.761192	-0.12849
3.7836	3.665239	0.118361

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 [2]. The low residual values obtained in table 5 above indicated the robustness of the model.

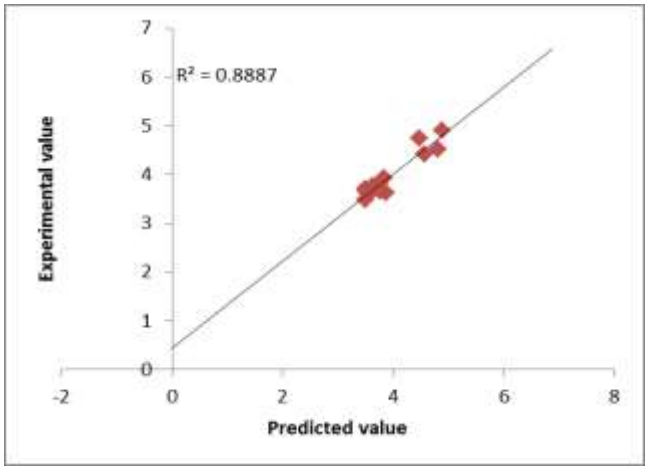

Figure 1: Plot of Experimental value against predicted value of training set.

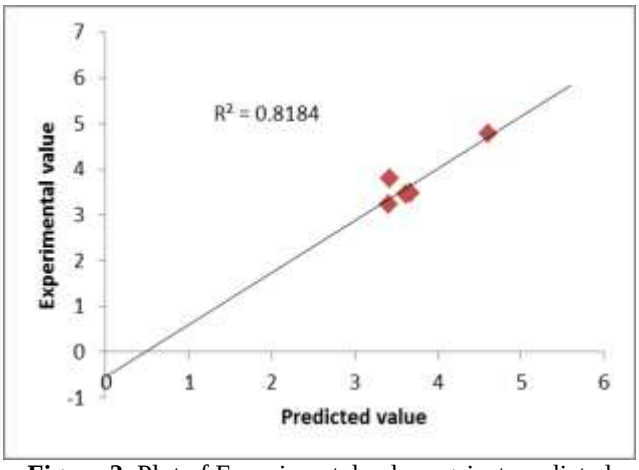

Figure 2: Plot of Experimental value against predicted value of test set.

The linearityof plots in Figure 1 and 2 above for the experimental values against the predicted values of training (0.888666) and test set(R^2 predicted of 0.8184) respectively used in this study indicated that the model is strong with an excellent predictability. **Table 6**: Physiological properties and Druglikeliness of the inhibitors

	Formula	Molecular weight(g/mol)	nH-bond donor	nH-bond acceptor	n Octanol/water partition coefficient
1.	$C_{17}H_{14}N_2O_5$	326.30	1	6	1.81
2.	$C_{17}H_{13}FN_2O_5$	344.29	1	7	3.32
3.	$C_{18}H_{16}N_2O_6$	356.33	1	7	1.85
4.	$C_{18}H_{16}N_2O_6$	356.33	1	7	1.85
5.	$C_{18}H_{16}N_2O_5$	340.33	1	6	2.11
6.	$C_{16}H_{12}ClN_3O_5$	361.74	2	6	2.07
7.	$C_{16}H_{12}ClN_3O_5$	361.74	2	6	2.07

8.	$C_{18}H_{16}N_2O_5$	340.33	1	6	2.13
9.	$C_{18}H_{15}FN_2O_5$	358.32	1	7	2.43
10.	$C_{18}H_{15}FN_2O_5$	358.32	1	7	2.46
11.	$C_{18}H_{17}N_3O_7S$	419.41	2	9	1.43
12.	$C_{19}H_{18}N_2O_5$	354.36	1	6	2.46
13.	$C_{18}H_{17}N_3O_7S$	419.41	2	9	0.90
14.	$C_{19}H_{18}N_2O_5$	370.36	1	7	2.13
15.	$C_{20}H_{20}N_2O_2$	400.38	1	8	2.13
16.	$C_{20}H_{17}N_3O_5$	379.37	2	6	2.27
17.	$C_{24}H_{20}FN_3O_4$	433.43	2	6	3.24
18.	$C_{25}H_{23}N_3O_5$	445.47	2	6	2.91
19.	$C_{21}H_{21}N_3O_4$	379.41	2	5	2.44
20.	$C_{24}H_{20}N_2O_5$	316.43	1	6	3.32

All the twenty compounds were analysed and the result in **Table 6** above shows that the compounds are in conformity with rule of five of Lipniski which states that molecular weight ≤ 500 daltons, hydrogen bond acceptors ≤ 10, hydrogen bond donors ≤ 5 and octanol/water partition coefficient ≤ 5 [9]. The result obtained showed that the compounds are relatively small molecules and moderately lipophilic. Compound 13 is hydrophilic due to its low octanol water partition coefficient of 0.90. These compounds have good oral bioavailability and not probable to toxicity. Molecules with high molecular weight are very bulky and difficult to be distributed. Compound 20 is easily absorbed, diffused and transported due to its low molecular weight.

V. CONCLUSION AND FUTURE SCOPE

In this research, the result obtained by 20 inhibitors confirmed that they are orally bioavailable and not probable to toxicity. The model developed with the three descriptors **AATS6i, MAT57e** and **TDB9s** was reliable, strong and robust. Computational analysis of the inhibitors gives excellent information about the drugs and will be used to produce drugs with more reduced toxicity.

ACKNOWLEDGMENT

The authors are grateful to the department of chemistry,Ahmadu Bello University, Zaria.

REFERENCES

[1]. K. Roy, J. Leonard, "QSAR modelling of HIV-1 reverse transcriptase inhibitor 2-amino-6-arylsulfonylbenzonitriles and congeners using molecular connectivity and t-state parameters, "Bioorg Medicinal. Chemistry, **Vol.12, Issue. 4, pp. 745-754, 2004.**

[2]. A.S.Ugochukwu, , G. A. Shallangwa, A. Uzairu., "Quantum and statistical study for evaluating the cytotoxicity ability of some pyrazole derivatives as potent Anti HIV-1 agents inhibitors, "International journal of New Chemistry, **Vol. 8 Issue. 2, pp. 131-141, 2021.**

[3]. F. Ooms, "Molecular modeling and computer aided drug design. Examples of their applications in medicinal chemistry, "*Current medicinal chemistry*, **Vol. *7 Issue.* 2, pp. 141-158, 2000.**

[4]. G. Liu, R. Luo, X. ZHANG, Y. ZHOU, J. LI, Y. ZHENG, H. Liu, "Synthesis and Evaluation of Anti-HIV Activities of Novel 7-Hydroxy-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine-4-carboxylate Derivatives, "Medicinal chemistry, **Vol.4 Issue. 8, pp. 573-580, 2014.**

[5]. S.U. Ahanonu, S. U, G. A. Shallangwa, U. Adamu, "Quantitative structure and activity relationship of 3a, 6a – Dihydro-1H- pyrrolo[3,4-c] pyrazole-4,6-dione "Turkish Computational and Theoretical Chemistry, **Vol. 4, Issue. 1, pp. 32 – 38, 2020.**

[6]. A. Tropsha, "Best practices for QSAR model Development, Validation and Explitation, "Mol. Inf, **Vol. 29, Issue. 6, pp. 476-488, 2010.**

[7]. K. Roy, "Some aspects of validation of predictive quantitative structure-activity relationship models, "Expert Opinion On Drug Discovery, **Vol. 2, Issue. 12, pp. 1567-1577, 2007.**

[8]. S. A. Asma, A. S. Hassan, A. M. Naglah, "In vitro cytotoxicity and druglikeness of pyrazolines and pyrindines bearing benzofuran moiety, "Journal of Applied pharmaceutical science, **Vol. 10, Issue. 4, pp. 142-148, 2020.**

[9]. C. A. Lipinski, F. Lombardo, B. W. Dominy, P. J.Feeney, "Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings, "Journal of Advanced Drug Delivery. Reviews, **Vol. 46 Issue. 1, pp. 3-26, 2001**.

ATHORS PROFILE

Mr S U Ahanonu is a graduate of Industrial chemistry from Imo State university, Owerri. He specializes in computational chemistry and has published many research papers in reputable journals.

Dr. G A Shallangwa holds B.Sc, M.Sc and Ph.D in physical chemistry. He is a lecturer in Ahmadu Bello university, Zaia. He has over 167 publications.

Dr. Y.A. Dallatu holds B.Sc. M.Sc and Ph.D in analytical chemistry. He is currently a lecturer in Ahmadu Bello university, Zaria.

Dr. Ibrahim Abdulkadir holds B.Sc, M.Sc and Ph.D in Inorganic chemistry and he is currently a lecturer in Ahmadu Bello University, Zaria.