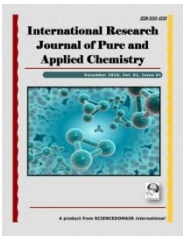

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QSAR Analysis of Some TIBO Derivatives As HIV-1 Reverse Transcriptase Inhibitors

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Authors' contributions

This work was carried out in collaboration between all authors. Author LKO performed the statistical analysis and managed the analysis of the study. Author AMC designed the study. Author AB literature searches. Author MT wrote the first draft of manuscript. Author AT concluded the whole study. All authors read and approved the final manuscript.

Research Article

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ABSTRACT

We performed studies to correlate the biological activity of the TIBO (4,5,6,7-tetrahydro-5-methylimidazo[4,5,1-*j*,*k*][1,4] benzodiazepin-2(1*H*)-one)14 sets of compound with the independent variable (descriptor) to know the structural requirement of the drug receptor binding interaction. Multiple linear regression methods have been applied to linearly correlate dependent (bioactivities) and independent variables. Multiple linear regression (MLR) has been widely used when the number of samples (rows) exceed the amount of descriptors (columns). The result obtained from the regression analysis is good and statistical values of correlation coefficient r= .9264 and standard error of estimation (Se) = .2640 and Fisher ratio (F) = 33.313 proves that the obtained mathematical model from the 14 sets of TIBO compound is best. The role of indicator parameter (I_{Cl} i.e. presence of Cl atom at carbon of six membered ring) is important to reduce the required concentration of the drug and so as index of refraction (η) also plays vital role in this concern.

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Keywords: Anti HIV; biological activity; drug design; NNRTIs; QSAR; regression analysis.

1. INTRODUCTION

Acquired immunodeficiency syndrome (AIDS), caused by infection from the human immunodeficiency virus type 1 (HIV-1), remains a serious global health problem. After years of hard work, a number of inhibitors of reverse transcriptase (RT) and protease (PR) are discovered and introduced in clinical practice [1,2] Unfortunately, all the mono therapies using either RT or PR inhibitors have failed owing to the rapid emergence of HIV-resistant strains, and the long-term goal of eradicating the virus from infected cells is still unattained. However, the use of combinations of both RT and PR inhibitors has resulted in significant increases in disease-free survival [3].This multiple attack is more effective, blocking two different steps of the virus replication cycle and causing a delay in the emergence of resistant strains. Therefore, it is evident that the development of new inhibitors targeted toward other viral proteins is of paramount importance.

Two main categories of HIV RT inhibitors have been discovered to date. The first category of inhibitors is nucleoside analogues (*e.g*., AZT, 3TC, ddI, ddC) and the second category of inhibitors is nonnucleoside analogues. Nevirapine, delaviridine and efavirenz are the only nonnucleoside reverse transcriptase inhibitors (NNRTI) that have received regulatory approval with several NNRTIs (MKC442, Troviridine, S–1153/ AG1549. PNU142721, ACT and HBY1293/GW420867X) are currently undergoing clinical trials. Efavirenz was the first potent anti–HIV drug to be approved by FDA and studies have shown that efavirenz penetrates into the cerebrospinal fluid, a common viral sanctuary. The therapeutic efficacy of the drug is mainly restricted due to the development of viral resistance associated with mutations that include K103N, L100I and Y188L. Reverse transcriptase (RT) plays a central role in the replication of HIV. A number of RT-inhibitors active against both HIV-1 and HIV-2 RT or only against HIV-1 RT have been discussed in the literature [4,5].

Structure-Activity Relationships (SARs) and Quantitative Structure Activity Relationships (QSARs), collectively referred to as (Q)SARs, are theoretical models that relate the structure of chemicals to their biologic activities. (Q)SARs are used to predict the physicochemical, biological (e.g., toxicological) and fate properties of molecules from knowledge of chemical structure. A QSAR is a quantitative relationship between a biological activity (e.g., toxicity) and one or more molecular descriptors that are used to predict the activity. A molecular descriptor is a structural or physicochemical property of a molecule, or part of a molecule, which specifies a particular characteristic of the molecule and is used as an independent variable in a QSAR [6].

QSAR analyses of HIV-1 reverse transcriptase inhibitors [7]. HIV-1 protease inhibitors [8,9] and HIV- 1 integrase inhibitors [10] and gp 120 envelope glycoprotein [11] were reported. The present group of authors has developed a few quantitative structure-activity relationship models to predict anti-HIV activity of different group of compounds [12-18].

2. MATERIALS AND METHODS

2.1 Data Set

The TIBO derivatives selected with their activities [19] are listed in Table 1 and the parent structure of the TIBO derivatives is given in the Fig (1).

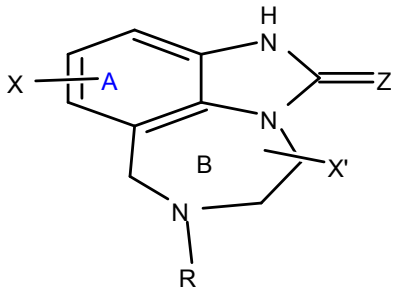

Fig. 1. Parent Structure of TIBO

Table 1. TIBO derivatives Studied and their experimental activities against HIV

No.	X	Z	R	X'	Log (1/C)
1	H	O	$CH_2CH=CH_2$	5-Me	3.17
2	H	O	$CH_2C(Me)=CH_2$	5-Me	3.96
3	H	O	$CH_2CH=CMe$	5-Me	3.33
4	2-Cl	O	$CH_2C(Me)=CH_2$	5-Me	4.77
5	2-Me	O	$CH_2CH=(C_2H_5)_2$	5-Me	4.70
6	2-Cl	O	$CH_2CH=CMe_2$	5-Me	4.66
7	H	S	$CH_2CH=CMe_2$	5-Me	3.26
8	H	S	C_3H_7	5-Me	3.25
9	2-Cl	S	$CH_2CH=CMe_2$	5-Me	4.47
10	2-Cl	S	$CH_2CH_2C_3H_5$	5-Me	4.44
11	2-Cl	S	$CH_2C_4H_7$	5-Me	4.55
12	2-Cl	S	$CH_2CH=(C_2H_5)_2$	5-Me	4.92
13	2-Cl	S	$CH_2C(Me)=CH_2$	4-Me	4.62
14	2,3-Cl	S	$CH_2CH=CMe_2$	5-Me	4.35

2.2 Calculation of the Parameters

All the physicochemical properties viz. MR (Molecular Refractivity), MV (Molecular Volume), Pc (Parachor), η (Index of refraction), ST (Surface Tension), D (density), Pol (Polarizability) were calculated by ACD lab freeware (Chemsketch 5.0) [20]. All the topological parameters and other descriptors were calculated by dragon 5.0 and some non conventional parameter Viz. ASA (Approximate Surface Area) and SAG (Surface Area Grid) is calculated by Hyperchem 6 (demo version) [21].Besides all these parameters, few dummy parameters were also tested i.e.

I_{Cl} Presence of chlorine atom at six membered ring indicated by 1 and absence by 0.
I_{CH2Me2} Presence of $-CH_2Me_2$ group at seven membered ring indicated by 1 and absence by 0.

Table 2 given below shows the value of physico-chemical and indicator parameters which shows the significant relationship with log (1/C).

Table 2. Physico-chemical and indicator parameters used in the model

Compound	η	I_{Cl}	I_{CH2Me2}
1	1.641	0	0
2	1.626	0	0
3	1.637	0	0
4	1.635	1	0
5	1.598	0	0
6	1.632	1	1
7	1.662	0	1
8	1.669	0	0
9	1.670	1	1
10	1.662	1	0
11	1.662	1	0
12	1.646	1	0
13	1.675	1	0
14	1.676	1	1

2.3 QSAR

Quantitative structure–activity relationship (QSAR), in simplest terms, is a method for building computational or mathematical models which attempts to find a statistically significant correlation between structure and function using a chemometric technique. A study of the structure–activity relationships of a lead compound and its analogues may be used to determine the parts of the structure of the lead compound that are responsible for both its beneficial biological activity, that is, its pharmacophore, and also its unwanted side effects. This information may be used to develop a new drug that has increased activity, a different activity from an existing drug and fewer unwanted side effects. Structure–activity relationships are usually determined by making minor changes to the structure of a lead to produce analogues and assessing the effect these structural changes have on biological activity.

To obtain a significant correlation, it is essential that appropriate descriptors be used, regardless of whether they are theoretical, empirical or derived from readily available experimental characteristics of structures. Many descriptors reflect simple molecular properties and can thus provide insight into the physicochemical nature of the activity/property under consideration [22-24].

In the present data set only physical properties of the compound taken for the correlation between the activity and the structure. Some of the indicator parameters also taken into account. The effort made to correlate the concentration of the drug with the physical parameters and to determine that which property is responsible to the lower concentration of the drug. In a QSAR study, generally, the quality of a model is expressed by its fitting ability and prediction ability, and of these the prediction ability is the more important.

The QSAR studies enable the scientists to establish reliable quantitative relationship to derive the QSAR model and predict the activity of novel molecules prior to their synthesis. These studies reduce the trial and error element in the design of compounds by establishing mathematical relationships between physical, chemical, biological, or environmental

activities of interest and measurable or computable parameters such as physicochemical, electronic, topological, or stereochemistry.

The main success of the QSAR method is the possibility to estimate the characteristics of new chemical compounds without the need to synthesize and test them. This analysis represents an attempt to relate structural descriptors of compounds with their physicochemical properties and biological activities. This is widely used for the prediction of physicochemical properties in the chemical, pharmaceutical, and environmental spheres. This method included data collection, molecular descriptor selection, correlation model development, and finally mode evaluation. QSAR studies have predictive ability and simultaneously provide deeper insight into mechanism of drug receptor interactions [25-26].QSAR studies are of importance in molecular biochemistry. It is essential that appropriate descriptors are employed, whether they are theoretical, empirical or derived from available experimental characteristics of structure to obtain significant correlation.

The activities and properties are related using the general mathematical function,
B.A. = f [structure (physicochemical descriptors as structural parameters)]. Hence, biological activity is a function of physicochemical descriptors.

The relationship is often not a mathematical expression derived by statistical or related techniques. The parameters describe structural and physiochemical properties as independent variables and the biological activities as dependent variable for usage in multiple linear regression (MLR) analysis.

2.4 Regression Analysis

All the calculated descriptors and indicator parameters considered as independent variable and biological activity as dependent variable. “ANALYSIS” software was used to generate QSAR models by multiple linear regression analysis. Statistical measures used were the number of compounds in regression n, the correlation coefficient (r), the squared correlation coefficient (r^2), the F–test (Fischer’s value) for statistical significance F, the standard error of estimation (Se). The squared correlation coefficient (or coefficient of multiple 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.

3. RESULTS & DISCUSSION

The statistical quality of the developed equations was judged by the parameters such as correlation coefficient (r), standard error of estimate (Se), Fisher ratio (F test). The number of developed equations was high, so further analysis was based on statistical significant parameters, namely r, Se, F and maximum limit of inter–correlation among parameters used in the generation of equations. Among several generated models, some statistically significant QSAR models were selected for discussion. We limited our study up to bi-

parametric combinations, as there are 14 sets of compound in our data set, so we cannot go for tri-parametric combinations as per the rule of thumb.

The value of mono-variate parameter from correlation matrix is as follows-
MR= 0.68414, MV= .72874, Pc= .7060, Pol= .6838, I_{Cl}= .7848

We also found the value of Standard error (Se), Fisher Ratio (F) and Quality Factor (Q). The Table 3 given below shows the full details of the values.

Table 3. Statistical Parameter for Monovariate descriptor

Parameter	r	Se	F	Q
MR	.6841	.4897	10.558	1.396
MV	.7287	.4598	13.590	1.584
Pc	.7060	.4755	11.928	1.484
Pol	.6839	.4899	10.543	1.395
I_{Cl}	.7848	.4161	19.248	1.886

From the above Table 3 it is very clear that the indicator parameter (I_{Cl}) is the best monovariate parameter and the value of Se, F and Q also shows the importance of the parameter. So from the above table we found the best mathematical model is as follows-

$$\text{Log } (1/C) = .9858\ (\pm.2247)\ I_{Cl} + 3.6117 \quad (1)$$

The biological activity is expressed as 1/C, where *C* is the concentration of drug required to achieve a defined level of biological activity. (The reciprocal of the concentration (1/C) is used, since more active drugs will achieve a defined biological activity at lower concentration). Besides physico-chemical parameters several indicator variables with a value of unity or zero were also found significant. They were observed in many of the models in association with other parameters. Eq. (1) clearly indicated that the role of indicator parameter is really essential to achieve the required lower concentration of the drug. All though the indicator parameters are dummy parameters but govern the importance in indication of presence or absence of any particular group or atom at a specific substitution. The indicator variable I_{Cl} was used to investigate the effect of the -Cl linkage. Here, the chlorine atom substitution at six membered ring of the TIBO derivatives shows the positive correlation with log (1/C), which means that as we increase the magnitude of this substitution the concentration of the drug become low. Among the halogens, -Cl shows better result, suggesting a moderately electronegative group would be more effective to achieve required lower concentration of the drug.

The step up method allow us to introduce the new parameter in best mono-parameter results so, from here we tested various bi-parametric combinations to determine the role of other parameters with the indicator parameter. The role of indicator parameter is very important and now the combination of other parameter with indicator parameter will definitely give some better finding about the concentration of the drug. Though we have tried every possible combination for bi-parametric model and choice of the selection of the best model depends on the higher magnitude of r and F and lower standard error of estimation (Se). The Table 4 given below shows only those result which give the value >.90 with the combination of other parameter.

Table 4. Statistical Parameter for bi-parametric combinations

Combinations	r	Se	F	Q
I_{Cl} + η	.9264	.2640	33.313	3.509
I_{Cl} + ST	.9054	.2978	25.009	3.040
I_{Cl} + D	.9203	.2744	30.416	3.353
I_{Cl} + RBN	.9074	.2947	25.654	3.079

Not only the value of r is important to know the lower concentration of the drug but some other statistical parameters like Se (Standard error of estimation), F (Fisher Ratio) and Q (Quality factor) are also important. So, from the above Table 4 it is clear that the indicator parameter along with index of refraction (η) gives the better mathematical model and the value of Se and F also indicate that this one is best model. The mathematical model leads to find out the important structural requirement of the drug to know the required concentration of the drug. The equation for the best mathematical model is as follows-

$$\text{Log } (1/C) = 1.2722\ (\pm.1571)\ I_{Cl} - 15.5513\ (\pm3.5856)\ \eta + 29.0977 \quad (2)$$

PRESS= .7666, SSY= 4.6430, r^2_{adj} = .8325, r^2_{cv}= .8349

In Eq. (2) the magnitude of index of refraction is much higher than the indicator parameter. In general refractive index correlates in a manner somewhat similar to density but different from molecular volume. Index of refraction (η) shows negative correlation with the log (1/C), it means decrease in the index of refraction of molecules responsible for the required lower concentration of the drug molecule. Thus, molecule having less index of refraction will require less quantity i.e. the concentration to achieve the 50% inhibition.

$$MR = \frac{n^2 - 1}{n^2 + 2} \times \frac{M}{D}$$

Where, n= index of refraction, M= Molecular weight and D= Density

Index of refraction- The index of refraction (IR) of a medium is the ratio of the speed of light in vacuum to its velocity in the medium. By definition, the refractive index of a vacuum is 1, for air the value is 1.008. Index of refraction is the property of the molecule which is somewhat associated with the other properties like MR, D and Molecular weight.

Molecular Refractivity (MR) - It is the measures of volume occupied by a group of atoms or atoms and is a measure of the susceptibility of the molecule to become polarized. It is a measure of overall bulkiness and is related to London dispersion forces using $MR=4\Pi N\alpha/3$, where N is Avogadro number and α is the polarizability of the molecule. It gives no information about shape.

Density (D) - This parameter is related to bulk and size of the substituent.

One important observation is obtained with the bi-parametric combination is that the index of refraction doesn't shows good relationship in mono-parametric combination whereas it shows higher correlation with indicator parameter in bi-parametric combinations. Because of the small pool of the data set, we cannot go for further combinations and consider eq. (2) as a best mathematical model.

Validation of QSAR model- The quality of predictive power of generated QSAR model is depends upon $\mathbf{r^2_{cv}}$ statistics, called cross-validated, which is the indicator of the predicting ability of the model. It is obtained by PRESS (Predictive Residual Sum of Squares) and SSY (Sum of Square of Response value).In this study, r^2_{adj} and r^2_{CV} are taken as a proof of the high predictive ability of the model. A high value of these statistical characteristics is considered as a proof of the high predictive ability of the models. The value of PRESS is smaller than SSY, another indication of the statistical significance of the prediction. To be a reasonable QSAR model, PRESS/SSY should be smaller (0.165 in this case).

The Table 5 is the value of observed and calculated Log (1/C) along with residual for eq. (1). Fig. (2) shows the graph between observed and calculated Log (1/C) for eq. (1) and this graph shows, no linearity for the 14 sets of TIBO compound. Table 6 is the value of observed and calculated Log (1/C) along with residual for eq. (2). Fig. (3) is the graph between observed and calculated Log (1/C) for eq. (2), shows much better linearity between observed and calculated value and hence we consider eq. (2) is the best mathematical model and can be useful to know the structural requirements of the drug molecule to achieve the lower concentration of the TIBO derivatives for as an anti-HIV agent.

Table 5. The value of observed and calculated Log (1/C) along with residual for Fig 2

Comp No	Observed Log (1/C)	Calculated Log (1/C)	Residual
1	3.17	3.612	-0.442
2	3.96	3.612	0.348
3	3.33	3.612	-0.282
4	4.77	4.598	0.172
5	4.70	3.612	1.088
6	4.66	4.598	0.062
7	3.26	3.612	-0.352
8	3.25	3.612	-0.362
9	4.47	4.598	-0.128
10	4.44	4.598	-0.158
11	4.55	4.598	-0.048
12	4.92	4.598	0.322
13	4.62	4.598	0.022
14	4.35	4.598	-0.248

Table 6. The value of observed and calculated Log (1/C) along with residual for Fig. 3

Comp No	Observed Log (1/C)	Calculated Log (1/C)	Residual
1	3.17	3.578	-0.408
2	3.96	3.811	0.148
3	3.33	3.64	-0.310
4	4.77	4.944	-0.173
5	4.70	4.247	0.453
6	4.66	4.990	-0.330
7	3.26	3.251	0.008
8	3.25	3.143	0.107
9	4.47	4.399	0.070
10	4.44	4.524	-0.083
11	4.55	4.524	0.026
12	4.92	4.772	0.147
13	4.62	4.321	0.298
14	4.35	4.306	0.044

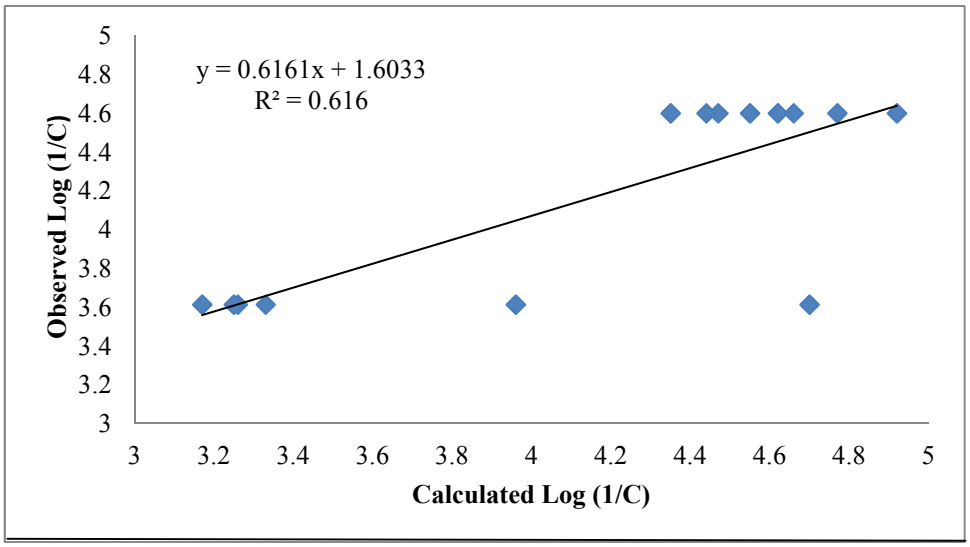

Fig. 2. Graph between observed and calculated Log (1/C)

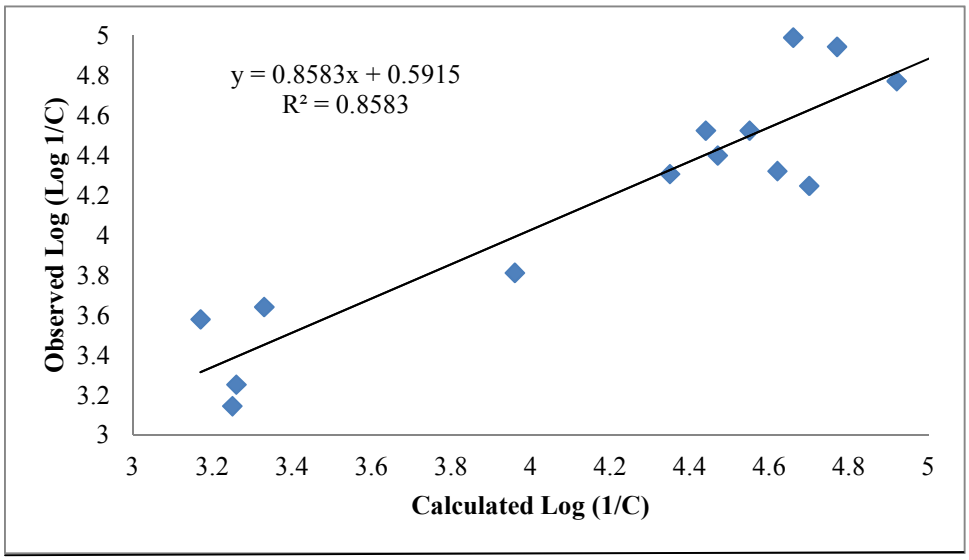

Fig. 3. Graph between observed and calculated Log (1/C)

4. CONCLUSION

In the present investigation, a QSAR study was performed using 14 TIBO derivatives. The relationship between the inhibitory activity and various descriptors is established by multiple regression analysis using ANALYSIS. The analysis has produced good predictive and statistically significant QSAR models. The values of statistical data are r = 0.9264, Se = 0.2640. The predicted activity shows linear relationship with observed activity. The negative contribution of η (index of refraction) on the biological activity (concentration of the drug molecule) showed that the lower concentration of the drug can be achieved with reducing

value of η. The positive coefficient of I_{Cl} showed that the presence of chlorine atom on six membered ring of carbon atom of TIBO is most favorable for HIV–1 RT inhibitory activity. Thus proper substitutions of the group with high molar refractivity probably required for the lower concentration of the drug. The effect of modification at this site will be the subject of further optimization and investigation i.e. 3D-QSAR study. The best QSAR mathematical models are used to predict inhibitory activity of the investigated TIBO derivatives, and close agreement between experimental and predicted values was obtained. The low residual activity and high cross-validated r^2 values (r^2_{CV}) observed indicate the predictive ability of the developed QSAR models.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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