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# QSAR Prediction of HIV–1 Reverse Transcriptase Inhibitory Activity of Benzoxazinone Derivatives

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**Abstract**

**Motivation.** Inhibition of HIV–1 reverse transcriptase (RT) is an important strategy for the treatment of HIV and AIDS. Therefore, HIV–1 RT inhibitory activity of benzoxazinone derivatives has been analyzed with different physicochemical parameters.

**Method.** In the present work, quantitative structure–activity relationship (QSAR) studies were performed on a series of benzoxazinones as HIV–1 reverse transcriptase inhibitors using the modeling software WinCAChe version 6.1 and Chem Draw Ultra version 8. The multiple linear regression analysis was performed to derive quantitative structure–activity relationship models that were further evaluated for statistical significance and predictive power by internal and external validation.

**Results.** The best QSAR model was selected having a correlation coefficient ($r$) of 0.833, $r^2$ of 0.694 with standard error of estimation (*SEE*) 0.278 and cross–validated squared correlation coefficient ($r^2_{cv}$) of 0.615. The robustness of the model was checked by Y–randomization test and it was found to be a good predictive model.

**Conclusions.** The model suggest that increase in electron withdrawing groups leads to loss of fit of molecules with the enzyme binding site, which decreases the HIV–1 RT binding affinities. The positive coefficient of $I_{NH}$ showed that the replacement of the 3rd position carbon atom of benzoxazinone with NH is an important determinant for the inhibitory activity. The positive coefficient of $I_{CP}$ indicats that the cyclopropyl group at the $R^1$ position is most favorable for HIV–1 RT inhibitory activity.

**Keywords.** HIV–1 reverse transcriptase inhibitors; quantitative structure–activity relationships; QSAR.

**Abbreviations and notations**

| | |
|---|---|
| HIV–1, human immunodeficiency virus type 1 | RT, reverse transcriptase |
| MLR, multiple linear regression | QSAR, quantitative structure–activity relationships |

## 1 INTRODUCTION

HIV–1 (human immunodeficiency virus type–1) is the pathogenic retrovirus and causative agent of AIDS or AIDS– related complex (ARC) [1,2]. When viral RNA is translated into a polypeptide sequence, it is assembled in a long polypeptide chain, which includes several individual proteins namely, reverse transcriptase, protease, integrase, etc. Before these enzymes become functional,

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they must be cut from the longer polypeptide chain.

Acquired immuno deficiency syndrome (AIDS) is a formidable pandemic that is still wreaking havoc worldwide. The catastrophic potential of this virally caused disease may not have been fully realized. The causative moiety of the disease is human immunodeficiency virus (HIV), which is a retrovirus of the lentivirus family [3]. The following enzymes reverse transcriptase, protease and integrase encoded by the gag and gag–pol genes of HIV play an important role in the virus replication cycle. Among them, viral reverse transcriptase (RT) catalyzes the formation of proviral DNA from viral RNA, the key stage in viral replication. Its central role in viral replication makes RT a prime target for anti–HIV–therapy [4].

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, L1001 and Y188L [5].

In search of effective efavirenz analogues with minimal viral resistance problems, Patel *et al*. synthesized and evaluated a novel set of benzoxazinones (analogues of efavirenz) for their HIV–1 reverse transcriptase inhibitory activity [6]. Balaji *et al*. reported a QSAR study of the above mentioned benzoxazinone derivatives using a combination of P_VSA and pharmacophore feature descriptors [7]. Dutchowicz *et al*. reported a QSAR study of some benzoxazinone derivatives but the maximum correlation coefficient of the model is 0.799 [8]. Leonard *et al*. developed several QSAR models for anti–HIV activities of different group of compounds [9,10]. Several comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA) studies have been carried out for anti–HIV activity of a given set of molecules in rational drug design and related applications [11–19]. The present groups of authors have already reported CoMFA study of the PETT series of compounds [20] and QSAR studies on integrase inhibitors [21] and COX inhibitors [22,23]. QSAR studies of β–ketoamide derivatives [24], flavonoid derivatives [25], cyclooxygenase–2 inhibitors [26], protein tyrosine phosphatase 1B inhibitors [27], and three–dimensional studies on octopamine receptor responsible for the inhibition of sex–pheromone production [28], octopaminergic agonists [29] and tyramine receptor agonist [30], have also been reported.

As a part of ongoing efforts to design novel molecules with potent anti–HIV activity, a QSAR

analysis was performed to relate HIV–1 reverse transcriptase (HIV–1 RT) inhibitory activity of benzoxazinones to its physicochemical properties and to design powerful HIV–1 RT inhibitors.

# 2 MATERIALS AND METHODS

## 2.1 Biological Data

A data set of the 36 compounds reported by Patel *et al*. for HIV–1 RT inhibition was used for the QSAR study [6,31]. We have not included compounds 15 and 16 in the first series of compounds reported by Patel *et al*. since they were not exhibiting a well defined HIV–RT inhibitory activity (Table 1). The molar concentrations of the benzoxazinones required to inhibit HIV–1 reverse transcriptase enzyme by 50% were converted to free energy related negative logarithmic values for undertaking the QSAR study.

## 2.2 Molecular Modeling Software

All molecular modeling studies reported here were performed using Win CAChe version 6.1 (Product of Fujitsu private limited, Japan, http://www.cachesoftware.com/contacts/japan.shtml) and Chem Draw Ultra version 8 (Cambridge Soft) modeling software and the QSAR models were generated by STATISTICA version 6 (Softstat) software.

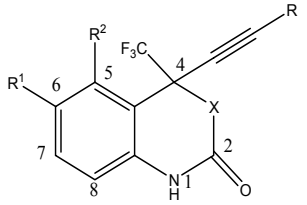
## 2.3 Structural Descriptors

All 36 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. Most stable structure for each compound was generated and used for calculating various physico–chemical descriptors like thermodynamic, steric and electronic values of descriptors. The topological descriptors have been calculated by using Chem Draw Ultra version 8.

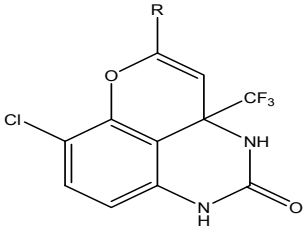
In the present study, the descriptors calculated were dipole moment (DM), total energy at its current geometry after optimization of structure (TE), heat of formation at its current geometry after optimization of structure (HF), highest occupied molecular orbital energies (HOMO), lowest unoccupied molecular orbital energies (LUMO), octanol–water partition coefficient (logP), molar refractivity (MR), solvent accessible surface area (SASA), cluster count, Balaban Index and Wiener Index. We used some indicator variables also to develop the model. Those are $I_{CP}$ (indicator variable is having value 1 if cyclopropyl group is present at R position, otherwise 0), $I_F$ (indicator variable is having value 1 if F is present at aromatic ring of benzoxazinone, otherwise 0), $I_{Cl}$ (indicator variable is having value 1 if Cl is present at aromatic ring of benzoxazinone, otherwise 0), $I_{Phen}$ indicator variable is having value 1 if phenyl group is present at R position, otherwise 0), $I_{3–O}$

(indicator variable is having value 1 if O is present at 3rd position of benzoxazinone, otherwise 0), The other parameters used were $MR^2$, $logP^2$ and $(logP)^{1/2}$. Values of descriptors, which are significant in QSAR models, are shown in Table 2.

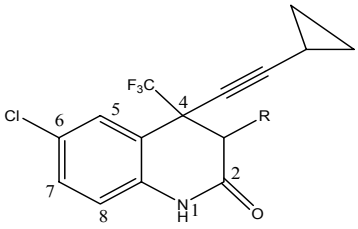
**Table 1.** Structural variation in the benzoxazinone backbone and its HIV–1 RT inhibitory activity



1–19



20–23



24–36

| No. | R | $R^1$ | $R^2$ | X | $IC_{50}$ (nM) | $pIC_{50}$ (M) |
|---|---|---|---|---|---|---|
| **1** | Cyclopropyl | H | F | O | 78 | 7.108 |
| **2** | Ethyl | H | F | O | 127 | 6.896 |
| **3** | n–Propyl | H | F | O | 156 | 6.807 |
| **4** | Isopropyl | H | F | O | 102 | 6.991 |
| **5** | Cyclopropyl | $NO_2$ | H | O | 209 | 6.679 |
| **6** | Ethyl | $NO_2$ | H | O | 276 | 6.559 |
| **7** | n–Propyl | $NO_2$ | H | O | 304 | 6.517 |
| **8** | Isopropyl | $NO_2$ | H | O | 199 | 6.701 |
| **9** | Cyclopropyl | $NH_2$ | H | O | 802 | 6.096 |
| **10** | Ethyl | $NH_2$ | H | O | 1894 | 5.723 |
| **11** | n–Propyl | $NH_2$ | H | O | 1506 | 5.822 |
| **12** | Isopropyl | $NH_2$ | H | O | 896 | 6.048 |
| **13** | Cyclopropyl | $NHCH_3$ | H | O | 608 | 6.216 |
| **14** | Isopropyl | $NHCH_3$ | H | O | 473 | 6.325 |
| **15** | Cyclopropyl | Cl | $CH_3$ | NH | 70 | 7.155 |
| **16** | Phenyl | Cl | $CH_3$ | NH | 144 | 6.842 |
| **17** | 3–Pyridyl | Cl | $CH_3$ | NH | 139 | 6.857 |
| **18** | Cyclopropyl | Cl | H | NH | 54 | 7.267 |
| **19** | Phenyl | Cl | H | NH | 174 | 6.759 |
| **20** | Cyclopropyl | – | – | – | 90 | 7.046 |
| **21** | Phenyl | – | – | – | 244 | 6.613 |
| **22** | 3–Pyridyl | – | – | – | 122 | 6.914 |
| **23** | H | Cl | H | C | 130 | 6.886 |
| **24** | O–3,3–Dimethylallyl | Cl | H | C | 1434 | 5.843 |
| **25** | O–Cyclopropylmethyl | Cl | H | C | 1051 | 5.978 |
| **26** | O–n–Propyl | Cl | H | C | 440 | 6.357 |
| **27** | OBn | Cl | H | C | 1572 | 5.804 |
| **28** | O–2–Pyridylmethyl | Cl | H | C | 438 | 6.358 |
| **29** | O–3–Pyridylmethyl | Cl | H | C | 129 | 6.889 |
| **30** | O–4–Pyridylmethyl | Cl | H | C | 1296 | 5.887 |
| **31** | O–2–Fluorobenzyl | Cl | H | C | 1776 | 5.751 |
| **32** | O–3–Fluorobenzyl | Cl | H | C | 899 | 6.046 |
| **33** | O–4–Fluorobenzyl | Cl | H | C | 1019 | 5.992 |
| **34** | O–2–Aminobenzyl | Cl | H | C | 1455 | 5.837 |
| **35** | O–3–Aminobenzyl | Cl | H | C | 412 | 6.385 |
| **36** | O–4–Aminobenzyl | Cl | H | C | 241 | 6.618 |

**Table 2.** Descriptors for quantitative model of HIV–1 RT inhibitory activity of benzoxazinones

| No. | LUMO | logP | $I_{CP}$ | $I_F$ | $I_{3-NH}$ | $I_{NP}$ | $logP^2$ |
|---|---|---|---|---|---|---|---|
| **1** | –0.753 | 3.283 | 1 | 1 | 0 | 0 | 10.779 |
| **2** | –0.827 | 3.451 | 0 | 1 | 0 | 0 | 11.913 |
| **3** | –0.913 | 3.868 | 0 | 1 | 0 | 1 | 14.968 |
| **4** | –0.748 | 3.781 | 0 | 1 | 0 | 0 | 14.300 |
| **5** | –1.544 | 3.07 | 1 | 0 | 0 | 0 | 9.424 |
| **6** | –2.350 | 3.244 | 0 | 0 | 0 | 0 | 10.523 |
| **7** | –2.327 | 3.193 | 0 | 0 | 0 | 1 | 10.195 |
| **8** | –1.582 | 3.575 | 0 | 0 | 0 | 0 | 12.780 |
| **9** | –0.433 | 2.322 | 1 | 0 | 0 | 0 | 5.393 |
| **10** | –0.422 | 2.490 | 0 | 0 | 0 | 0 | 6.203 |
| **11** | –0.360 | 2.908 | 0 | 0 | 0 | 1 | 8.456 |
| **12** | –0.419 | 2.820 | 0 | 0 | 0 | 0 | 7.956 |
| **13** | –0.401 | 2.621 | 1 | 0 | 0 | 0 | 6.873 |
| **14** | –0.383 | 3.120 | 0 | 0 | 0 | 0 | 9.735 |
| **15** | –0.532 | 2.878 | 1 | 0 | 1 | 0 | 8.288 |
| **16** | –0.595 | 3.818 | 0 | 0 | 1 | 0 | 14.577 |
| **17** | –0.743 | 2.481 | 0 | 0 | 1 | 0 | 6.155 |
| **18** | –0.572 | 2.615 | 1 | 0 | 1 | 0 | 6.842 |
| **19** | –0.601 | 3.555 | 0 | 0 | 1 | 0 | 12.638 |
| **20** | –0.658 | 1.994 | 0 | 0 | 1 | 0 | 3.976 |
| **21** | –0.755 | 3.680 | 0 | 0 | 1 | 0 | 13.544 |
| **22** | –1.002 | 2.343 | 0 | 0 | 1 | 0 | 5.490 |
| **23** | –0.544 | 3.475 | 1 | 0 | 0 | 0 | 12.078 |
| **24** | –0.451 | 3.906 | 1 | 0 | 0 | 0 | 15.259 |
| **25** | –0.497 | 4.005 | 1 | 0 | 0 | 0 | 16.047 |
| **26** | –0.527 | 4.914 | 1 | 0 | 0 | 0 | 24.150 |
| **27** | –0.505 | 4.001 | 1 | 0 | 0 | 0 | 16.006 |
| **28** | –0.603 | 3.577 | 1 | 0 | 0 | 0 | 12.796 |
| **29** | –0.586 | 3.577 | 1 | 0 | 0 | 0 | 12.796 |
| **30** | –0.509 | 5.072 | 1 | 0 | 0 | 0 | 25.729 |
| **31** | –0.546 | 5.072 | 1 | 0 | 0 | 0 | 25.729 |
| **32** | –0.561 | 5.072 | 1 | 0 | 0 | 0 | 25.729 |
| **33** | –0.489 | 4.111 | 1 | 0 | 0 | 0 | 16.904 |
| **34** | –0.485 | 4.111 | 1 | 0 | 0 | 0 | 16.904 |
| **35** | –0.459 | 4.111 | 1 | 0 | 0 | 0 | 16.904 |
| **36** | –0.506 | 4.269 | 1 | 0 | 0 | 0 | 18.229 |

## 2.4 Statistical Computation

All the calculated descriptors and indicator variables were considered as independent variable and biological activity as dependent variable. STATISTICA 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 *SEE*, the cross–validated correlation coefficient $r^2_{cv}$, and thecorrelation matrix to show correlation among the parameters.

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.

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 $r^2$, standard deviation based on predicted residual sum of squares ($S_{PRESS}$) and standard error of prediction ($S_{DEP}$). Leave 33% out cross validation (*LGO*, leave group out) was also performed for the selected model to explore its predictivity. The predictive ability of the selected model was also confirmed by external $r^2_{\mathrm{CVext}}$ which is also denoted with $q^2$:

$$q^2 = 1 - \frac{\sum \left(Y_{obs} - Y_{pre}\right)^2}{\sum \left(Y_{obs} - Y_{mean}\right)^2}$$

Tropsha et al considered a QSAR model is predictive, if the following conditions are satisfied: $r^2_{CVext} > 0.5$ and $r^2 > 0.6$. The robustness of a QSAR model was checked by Y – randomization test. In this technique, new QSAR models were developed by shuffling the dependent variable vector randomly and keeping the original independent variable as such. The new QSAR models are expected to have low $r^2$ and $r^2_{\mathrm{cv}}$ values. If the opposite happens then an acceptable QSAR model can not be obtained for the specific modeling method and data.

## 3 RESULTS AND DISCUSSION

The statistical quality of the developed equations was judged by the parameters like explained variance *(%EV)*, correlation coefficient (*r*), standard error of estimate (*SEE*), *F* test, *LOO* cross–validation $r^2$ ($r^2_{CV}$), $S_{PRESS}$ and $S_{DEP}$. The number of developed equations was high, so further analysis was based on statistical significant parameters, namely *r*, *SEE*, $r^2_{\mathrm{cv}}$, *F* and maximum limit of inter–correlation among parameters used in the generation of equation. Among several generated models, some statistically significant QSAR models were selected for discussion. The correlation matrix for the variables used in QSAR equations is shown in Table 3. We extended our study for six–parametric correlations as they are permitted for a data set of 36 compounds in accordance with the lower limit of rule of thumb.

$$\begin{gathered} \mathrm{pIC_{50}} = 5.7847\ (\pm 0.149) - 0.3694\ (\pm 0.111)\ LUMO + 0.2363\ (\pm 0.117)\ I_{CP} \\ + 0.8072\ (\pm 0.163)\ I_F + 0.8354\ (\pm 0.130)\ I_{NH} \\ n = 36 \quad r = 0.815 \quad \%EV = 66.4 \quad F_{(4,31)} = 15.33 \quad p<0.001 \quad SEE = 0.287 \\ PRESS = 3.086 \quad r^2_{CV} = 0.600 \quad S_{PRESS} = 0.316 \quad S_{DEP} = 0.297 \\ VIF \text{ of: } LUMO = 1.199 \quad I_{CP} = 1.471 \quad I_F = 1.147 \quad I_{NH} = 1.272 \end{gathered} \tag{1}$$

Model–1 shows good correlation coefficient ($r$) of 0.815 between LUMO, $I_{CP}$, $I_F$, $I_{NH}$ and HIV–1 RT inhibitory activity. Square correlation coefficient ($r^2$) of 0.664 explains 66.4% variance in biological activity. This model also indicates statistical significance > 99.9% with F values $F_{(4,31)}$ = 15.33. Cross validated squared correlation coefficient of this model was 0.600, which shows the good internal prediction power of this model.

**Table 3.** Pearson correlation matrix of parameters used in QSAR models

| | $pIC_{50}$ | LUMO | logP | $I_{CP}$ | $I_F$ | $I_{3–NH}$ | $I_{NP}$ |
|---|---|---|---|---|---|---|---|
| $pIC_{50}$ | 1 | | | | | | |
| LUMO | –0.283 | 1 | | | | | |
| logP | –0.374 | 0.133 | 1 | | | | |
| $I_{CP}$ | –0.249 | 0.359 | 0.4136 | 1 | | | |
| $I_F$ | 0.376 | –0.062 | 0.038 | –0.217 | 1 | | |
| $I_{NH}$ | 0.546 | 0.051 | –0.398 | –0.328 | –0.188 | 1 | |
| $I_{NP}$ | –0.051 | –0.301 | –0.071 | –0.337 | 0.213 | –0.161 | 1 |

$$\begin{gathered} pIC_{50} = 6.1784\ (\pm 0.272) - 0.3622\ (\pm 0.107)\ LUMO + 0.2953\ (\pm 0.118)\ I_{CP} \\ + 0.8235\ (\pm 0.159)\ I_F + 0.7722\ (\pm 0.131)\ I_{NH} - 0.116\ (\pm 0.068)\ logP \\ n = 36 \quad r = 0.833 \quad \%EV = 69.4 \quad F_{(5,30)} = 13.62 \quad p<0.001 \quad SEE = 0.278 \\ PRESS = 2.965 \quad r^2_{CV} = 0.615 \quad S_{PRESS} = 0.314 \quad S_{DEP} = 0.291 \\ VIF \text{ of: } LUMO = 1.201 \quad I_{CP} = 1.606 \quad I_F = 1.151 \quad I_{NH} = 1.381 \quad logP = 1.330 \end{gathered} \tag{2}$$

Model–2 shows good correlation coefficient ($r$) of 0.833 between LUMO, $I_{CP}$, $I_F$, $I_{NH}$, logP and HIV–1 RT inhibitory activity. Square correlation coefficient ($r^2$) of 0.694 explains 69.4% variance in biological activity. This model also indicates statistical significance > 99.9% with $F$ values $F_{(5,30)}$ = 13.62. Cross validated squared correlation coefficient of this model was 0.615, which shows the good internal prediction power of this model.

$$\begin{gathered} pIC_{50} = 5.1272\ (\pm 0.837) - 0.3378\ (\pm 0.108)\ LUMO + 0.3011\ (\pm 0.117)\ I_{CP} \\ + 0.7777\ (\pm 0.161)\ I_F + 0.7949\ (\pm 0.131)\ I_{NH} - 0.5026\ (\pm 0.471)\ logP - 0.0855\ (\pm 0.064)\ logP^2 \\ n = 36 \quad r = 0.843 \quad \%EV = 71.1 \quad F_{(6,29)} = 11.93 \quad p<0.001 \quad SEE = 0.276 \\ PRESS = 2.970 \quad r^2_{CV} = 0.615 \quad S_{PRESS} = 0.320 \quad S_{DEP} = 0.291 \\ VIF \text{ of: } LUMO = 1.237 \quad I_{CP} = 1.609 \quad I_F = 1.208 \quad I_{NH} = 1.405 \end{gathered} \tag{3}$$

Model–3 shows good correlation coefficient ($r$) of 0.843 between descriptors LUMO, $I_{CP}$, $I_F$, $I_{NH}$, logP, $logP^2$ and HIV–1 RT inhibitory activity. Square correlation coefficient ($r^2$) of 0.711 explains 71.10% variance in biological activity. This model also indicates statistical significance > 99.9% with $F$ values $F_{(6,29)}$ = 11.93. Cross–validated squared correlation coefficient of this model was 0.615, which shows the good internal prediction power of this model

$$\begin{gathered} pIC_{50} = 2.119\ (\pm 3.129) - 0.336\ (\pm 0.108)\ LUMO + 0.301\ (\pm 0.117)\ I_{CP} + 0.780\ (\pm 0.160)\ I_F \\ + 0.798\ (\pm 0.131)\ I_{NH} - 1.292\ (\pm 0.905)\ logP + 4.405\ (\pm 3.384)\ logP^{1/2} \\ n = 36 \quad r = 0.843 \quad \%EV = 71.1 \quad F_{(6,29)} = 11.89 \quad p<0.001 \quad SEE = 0.276 \\ PRESS = 3.018 \quad r^2_{CV} = 0.609 \quad S_{PRESS} = 0.323 \quad S_{DEP} = 0.294 \\ VIF \text{ of: } LUMO = 1.244 \quad I_{CP} = 1.609 \quad I_F = 1.203 \quad I_{NH} = 1.413 \end{gathered} \tag{4}$$

Model–4 shows good correlation coefficient ($r$) of 0.843 between descriptors LUMO, $I_{CP}$, $I_F$, $I_{NH}$,

logP, $(\log P)^{1/2}$ and HIV–1 RT inhibitory activity. Square correlation coefficient ($r^2$) of 0.711 explains 71.10% variance in biological activity. This model also indicates statistical significance > 99.9% with *F* values $F_{(6,29)}$ = 11.82. Cross–validated squared correlation coefficient of this model was 0.609, which shows the good internal prediction power of this model.

$$\begin{gathered} pIC_{50} = 6.206\ (\pm 0.275) - 0.377\ (\pm 0.109)\ LUMO + 0.263\ (\pm 0.124)\ I_{CP} + 0.835\ (\pm 0.160)\ I_F \\ + 0.743\ (\pm 0.136)\ I_{NH} - 0.117\ (\pm 0.068)\ logP - 0.166\ (\pm 0.151)\ I_{nP} \\ n = 36 \quad r = 0.837 \quad \%EV = 70.1 \quad F_{(6,29)} = 11.38 \quad p<0.001 \quad SEE = 0.289 \\ PRESS = 2.939 \quad r^2_{CV} = 0.605 \quad S_{PRESS} = 0.318 \quad S_{DEP} = 0.294 \\ VIF \text{ of: } LUMO = 1.755 \quad I_{CP} = 1.160 \quad I_F = 1.233 \quad I_{NH} = 1.465 \quad logP = 1.338 \quad I_{nP} = 1.285 \end{gathered} \tag{5}$$

Model–5 shows good correlation coefficient (*r*) of 0.837 between descriptors LUMO, $I_{CP}$, $I_F$, $I_{NH}$, logP, $I_{NP}$ and HIV–1 RT inhibitory activity. Square correlation coefficient ($r^2$) of 0.701 explains 70.10% variance in biological activity. This model also indicates statistical significance > 99.9% with *F* values $F_{(6,29)}$ = 11.37. Cross–validated squared correlation coefficient of this model was 0.605, which shows the good internal prediction power of this model.

In model–3, 4 and 5, we have included one more independent variable than model–2 but there was no change in internal predictivity compare to model–2. Hence the model–2 was selected as best model. We obtained a statistically more significant and good model when we removed some outliers (compound number 23 and 29, because the residual of experimental and calculated value is two times larger than the standard deviation value of the model) from the series to make the model (model–6).

$$\begin{gathered} pIC_{50} = 6.060\ (\pm 0.224) - 0.3722\ (\pm 0.088)\ LUMO + 0.228\ (\pm 0.099)\ I_{CP} \\ + 0.853\ (\pm 0.130)\ I_F + 0.822\ (\pm 0.108)\ I_{NH} - 0.89\ (\pm 0.056)\ logP \\ n = 34 \quad r = 0.893 \quad \%EV = 79.8 \quad F_{(5,28)} = 22.15 \quad p<0.001 \quad SEE = 0.228 \\ PRESS = 1.968 \quad r^2_{CV} = 0.730 \quad S_{PRESS} = 0.256 \quad S_{DEP} = 0.244 \end{gathered} \tag{6}$$

In order to explore the predictive power of the selected model, the data set of 36 benzoxazinone derivatives was divided (approximately 2:1) into a training set (24 compounds) and a test set (12 compounds). The selection of training and test set was made manually such that each and every compound present at least one time in test set. Using the above criteria we made three training and test set. The QSAR equations for the training set compounds are given in table 4.

The predictive ability of model–2 was also confirmed by external $r^2_{CVext}$. The selected QSAR model is predictive as it satisfies all the conditions mentioned above ($r^2_{CVext}$ = 0.526, $r^2$ = 0.715). The variables used in the selected model have no mutual correlation (Table 3) and the calculated and predicted activities are given in Table 5. The robustness of the selected model was checked by Y–randomization test and results are given in Table 6.

**Table 4.** Prediction of inhibitory activity of test set compounds in three crossvalidation cycle leave 33%–out) based on the descriptor set of model–2

| Cycle | Test set compounds | Training set compounds | Regression coefficient | | | | | | $r^2_{CVex}$ |
|---|---|---|---|---|---|---|---|---|---|
| | | | Intercept | LUMO | logP | $I_{CP}$ | $I_F$ | $I_{3–NH}$ | |
| 1 | 1, 4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34. | Rest of the compound ($n$ = 24) | 6.322 | –0.358 | –0.136 | 0.311 | 0.716 | 0.679 | 0.594 |
| 2 | 2, 5, 8, 11, 14, 17, 20, 23, 26, 29, 32, 35. | Rest of the compound ($n$ = 24) | 6.002 | –0.377 | –0.119 | 0.302 | 0.978 | 0.924 | 0.565 |
| 3 | 3, 6, 9,12, 15, 18, 21, 24, 27, 30, 33, 36. | Rest of the compound ($n$ = 24) | 6.213 | –0.358 | –0.110 | 0.302 | 0.793 | 0.726 | 0.514 |

**Table 5.** Experimental, Calculated and Predicted ($pIC_{50}$) (M) activity values for HIV–1 RT Inhibitors

| Compd. No. | Exp. act. | Calc. act. | | | Pred. act. | | |
|---|---|---|---|---|---|---|---|
| | | Model–1 | Model–2 | Model–3 | Model–1 | Model–2 | Model–3 |
| **1** | 7.1079 | 7.1067 | 7.187 | 7.189 | 7.106 | 7.234 | 7.236 |
| **2** | 6.8961 | 6.897 | 6.899 | 6.9 | 6.898 | 6.901 | 6.902 |
| **3** | 6.8068 | 6.929 | 6.882 | 6.878 | 6.972 | 6.909 | 6.904 |
| **4** | 6.9913 | 6.868 | 6.833 | 6.835 | 6.824 | 6.774 | 6.778 |
| **5** | 6.6798 | 6.591 | 6.675 | 6.687 | 6.571 | 6.674 | 6.689 |
| **6** | 6.559 | 6.653 | 6.652 | 6.652 | 6.708 | 6.707 | 6.706 |
| **7** | 6.5171 | 6.644 | 6.649 | 6.646 | 6.716 | 6.724 | 6.719 |
| **8** | 6.7011 | 6.369 | 6.335 | 6.365 | 6.307 | 6.265 | 6.297 |
| **9** | 6.0958 | 6.181 | 6.361 | 6.281 | 6.186 | 6.426 | 6.341 |
| **10** | 5.7226 | 5.941 | 6.042 | 5.991 | 5.985 | 6.126 | 6.071 |
| **11** | 5.8221 | 5.917 | 5.97 | 5.987 | 5.939 | 6.005 | 6.027 |
| **12** | 6.0476 | 5.939 | 6.002 | 6.006 | 5.918 | 5.992 | 5.997 |
| **13** | 6.216 | 6.169 | 6.314 | 6.294 | 6.166 | 6.331 | 6.308 |
| **14** | 6.3251 | 5.926 | 5.954 | 5.992 | 5.843 | 5.874 | 5.916 |
| **15** | 7.1549 | 7.053 | 7.104 | 7.141 | 7.023 | 7.089 | 7.137 |
| **16** | 6.8416 | 6.84 | 6.722 | 6.795 | 6.84 | 6.692 | 6.781 |
| **17** | 6.8569 | 6.895 | 6.931 | 6.894 | 6.901 | 6.943 | 6.9 |
| **18** | 7.267 | 7.068 | 7.148 | 7.146 | 7.015 | 7.111 | 7.108 |
| **19** | 6.7594 | 6.842 | 6.754 | 6.831 | 6.856 | 6.753 | 6.851 |
| **20** | 7.0457 | 6.864 | 6.957 | 6.807 | 6.835 | 6.938 | 6.682 |
| **21** | 6.6126 | 6.899 | 6.796 | 6.869 | 6.944 | 6.836 | 6.941 |
| **22** | 6.9136 | 6.991 | 7.041 | 6.969 | 7.003 | 7.063 | 6.982 |
| **23** | 6.886 | 6.222 | 6.266 | 6.326 | 6.184 | 6.225 | 6.271 |
| **24** | 5.843 | 6.188 | 6.183 | 6.239 | 6.208 | 6.203 | 6.274 |
| **25** | 5.978 | 6.205 | 6.187 | 6.237 | 6.218 | 6.199 | 6.258 |
| **26** | 6.3565 | 6.216 | 6.092 | 6.011 | 6.208 | 6.056 | 5.939 |
| **27** | 5.8035 | 6.208 | 6.191 | 6.241 | 6.231 | 6.214 | 6.276 |
| **28** | 6.358 | 6.244 | 6.276 | 6.336 | 6.238 | 6.271 | 6.334 |
| **29** | 6.8894 | 6.238 | 6.269 | 6.33 | 6.201 | 6.232 | 6.278 |
| **30** | 5.8873 | 6.209 | 6.068 | 5.949 | 6.228 | 6.097 | 5.969 |
| **31** | 5.7505 | 6.223 | 6.081 | 5.962 | 6.249 | 6.136 | 6.032 |
| **32** | 6.046 | 6.228 | 6.086 | 5.967 | 6.239 | 6.093 | 5.941 |
| **33** | 5.9918 | 6.202 | 6.172 | 6.214 | 6.214 | 6.184 | 6.232 |
| **34** | 5.8371 | 6.2 | 6.171 | 6.213 | 6.222 | 6.192 | 6.242 |
| **35** | 6.3851 | 6.191 | 6.161 | 6.204 | 6.179 | 6.147 | 6.189 |
| **36** | 6.6179 | 6.208 | 6.159 | 6.186 | 6.184 | 6.128 | 6.154 |

**Table 6.** Y – Randomization test

| Iteration | $r^2$ | $r^2_{CV}$ |
|---|---|---|
| 1 | 0.117 | 0.021 |
| 2 | 0.127 | 0.017 |
| 3 | 0.109 | 0.027 |
| 4 | 0.116 | 0.007 |
| 5 | 0.081 | 0.005 |

According to the QSAR models listed above, it was found that the equation 2 is statistically significant. The internal predictive ability of the equation 2 is better than the equation 1, 3, 4 and 5. From the overall consideration of statistical parameters equation 2 was considered to be the best predictive QSAR model for predicting HIV–1 RT inhibitor activity of benzoxazinone derivatives.

In model–4, we have included $(logP)^{1/2}$ instead of $logP^2$ in model–3 but there was no change in correlation coefficient and predictivity. The model–4 explains the influence of hydrophobicity (logP) value of benzoxazinone derivatives on their HIV–1 RT inhibitory activity. In model–2 and 3 the negative coefficient of logP and $logP^2$, respectively, and in model–4 the positive coefficient of $(logP)^{1/2}$ indicates that the substituent in benzoxazinone nucleus is having less hydrophobicity is conducive to activity and hydrophilic is detrimental to activity but in the same time high hydrophobicity is also detrimental to HIV–1 RT inhibitory activity. Meanwhile the substituent at $R^1$ position should be bulky but not a straight chain. These findings are from the positive contribution of $I_{CP}$ and negative coefficient of $I_{NP}$ (model–5). These findings from our QSAR study is confirming the QSAR study reported by Balaji *et al* [7], but the authors used only 14 compounds in that reported work. The number of compounds used to make QSAR model was less, so they got good square correlation coefficient ($r^2 > 0.9$). Because, there is no structural diversity and there is no sufficient range of biological activity. The authors have not done any external validation to prove the predictive power of the developed model. But, in our present QSAR study we have used 36 benzoxazinone derivatives which are structurally well diverse and having sufficient range of biological activity and we did external validation to prove the predictivity of the developed model.

The variables used in the selected model have no mutual correlation (Table 4). This model showed good correlation coefficient ($r$) of 0.833 between LUMO, $I_{CP}$, $I_F$, $I_{NH}$, logP and and HIV–1 RT inhibitory activity. Square correlation coefficient ($r^2$) of 0.694 explains 69.4% variance in biological activity. The predictive ability of the selected model was also confirmed by external $r^2_{CVext}$ method. The $r^2_{CVext}$ value of the selected model is greater than the prescribed value. The robustness of the selected model was checked by Y–randomization test. The low $r^2$ and $r^2_{CV}$ values (Table 6) indicate that the good results in our original model are not due to a chance correlation or structural dependency of the training set.

## 4 CONCLUSIONS

In the present investigation, a QSAR study was performed using 36 benzoxazinone derivatives using Win CAChe 6.1. The relationship between the inhibitory activity and various descriptors is established by multiple regression analysis using STATISTICA 6. The analyses have produced good predictive and statistically significant QSAR models. These models were cross validated with the leave–one–out (*LOO*) method. The values of statistical data are $r = 0.833$, $\%EV = 69.4$, $F_{(5,30)} = 13.62$, $p<0.001$, $SEE = 0.278$, $PRESS = 2.965$, $r^2_{CV} = 0.615$, $S_{PRESS} = 0.314$, $S_{DEP} = 0.291$. The

predicted activity shows linear relationship with observed activity.

The negative contribution of LUMO on the biological activity showed that the increase in electron withdrawing groups leads to loss of fit of molecules with the enzyme binding site resulting decrease in HIV–1 RT binding affinities. The positive coefficient of $I_{NH}$ showed that the 3rd position carbon atom of benzoxazinone has been replaced by NH is conducive for the inhibitory activity. The positive coefficient of $I_{CP}$ indicated that the cyclopropyl group at $R^1$ position is most favorable for HIV–1 RT inhibitory activity. These studies are promising for the development of novel compounds, which may have potent HIV–1 RT inhibitory activity.

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