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QSAR MODELING FOR INHIBITORY ACTIVITY OF NON-PEPTIDE HIV-1 PROTEASE INHIBITORS: A MLR APPROACH

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ABSTRACT

The multiple linear regression (MLR) methods were used to develop quantitative structure activity relationships (QSAR) models for inhibitory activity of non-peptide HIV-1 protease inhibitors. The results revealed the significant roles of topological, geometrical and substituent electronic descriptor parameters on the inhibitory activity of non-peptide HIV-I protease inhibitors of the studied molecules. The most significant quantitative structure activity relationship model, obtained by MLR could explain and predict 80% of variance in the pIC_{50} data, respectively.

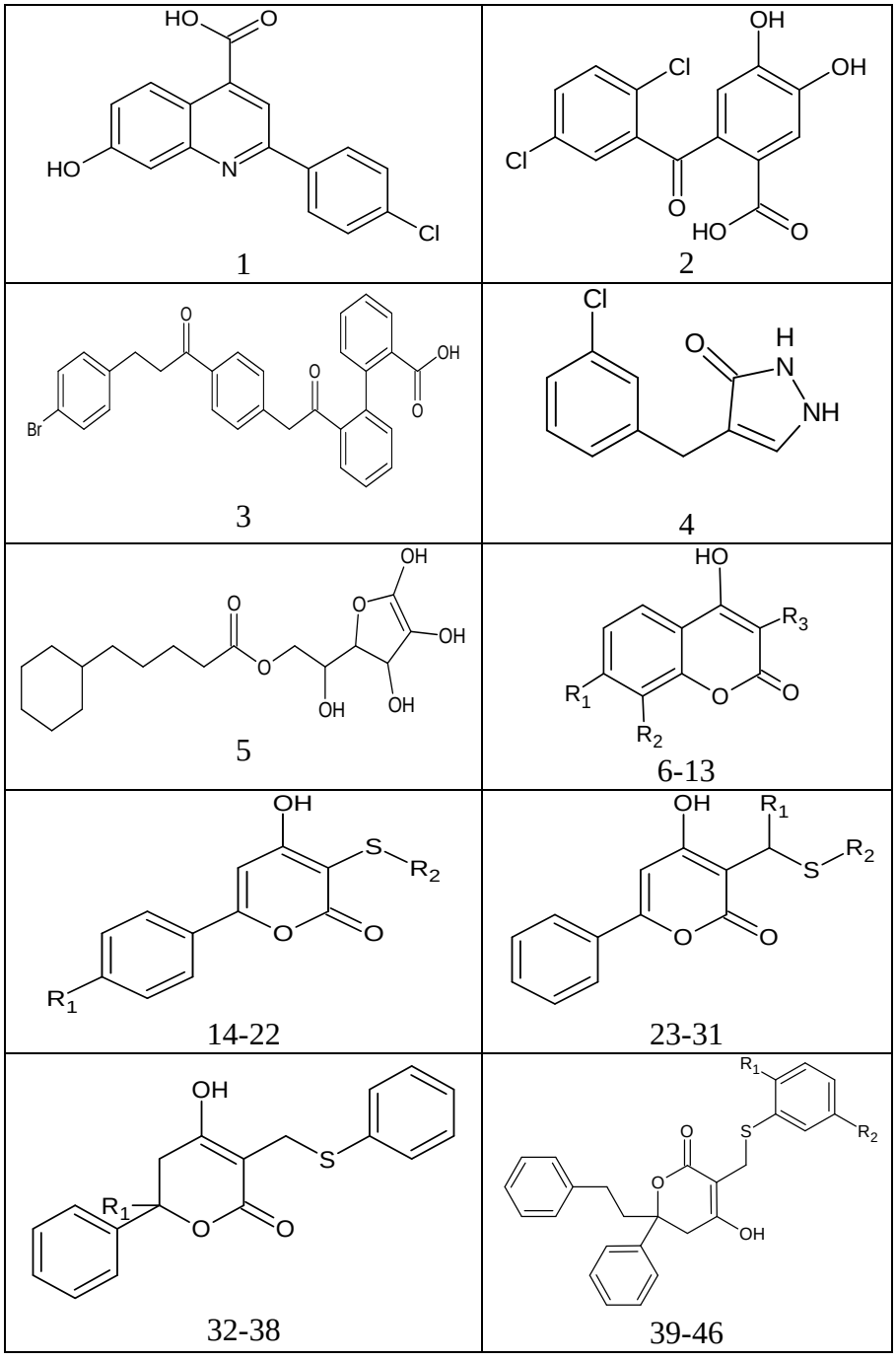
KEYWORDS: QSAR, MLR, pIC_{50}.

1. INTRODUCTION

In the study of pharmacodynamic, pharmacokinetic, and toxicological properties of drugs and other chemical agents, a variety of molecular descriptors has been developed and routinely used for describing physicochemical and structural properties of chemical agents. [1-7] These descriptors were initially developed for the construction of quantitative structure-activity relationship (QSAR) and quantitative structure-property relationship (QSPR) of structurally related compounds.[8] Human immunodeficiency virus (HIV), a retrovirus, is the primary cause of acquired immunodeficiency syndrome (AIDS),and one of the main medical and social problems nowadays [9]. An estimated 36 million people worldwide are currently suffering from HIV and some 20 million people having already died, representing a cumulative total number of HIV infections to be 56 million. However, there is still no known

cure or vaccination against it [10]. The human immune deficiency virus type-1 (HIV-1) pandemic has grown to become one of the greatest infectious disease threats to human health and social stability that the world has ever encountered [11-12]. Nearly 40 million persons are living with HIV-1 infection and more than 21 million people have already died from HIV-induced disease.

Fig 1: General structure of non-peptide HIV-1 protease inhibitors



Although effective anti-retroviral therapy has slowed the epidemic in some industrialized countries, worldwide there are still an estimated 15,000 new HIV infections occurring daily. In addition to the vast personal suffering, the loss of young adult parents, caretakers, and wage-earners, HIV has created an unprecedented strain on the social and economic infrastructure of many developing countries, particularly in Sub-Saharan Africa. These facts make it imperative that the epidemic be controlled as rapidly as possible through prevention of new infections. Peptidic and peptidomimetic non-hydrolyzable transition state mimics were rapidly developed as highly potent HIV protease inhibitors. These competitive inhibitors possess optimal interactions in substrate binding pockets with low to sub nanomolar Ki values However, their peptidic nature often makes them poor pharmacological agents, with low bioavailability and rapid clearance. Several peptidic inhibitors are currently under clinical trials and significant efforts to improve their pharmacology continues. In this study, we picked out small non-peptide HIV protease inhibitors with potentially better pharmacological characteristics based on the structural features of peptidic inhibitors bound to the enzyme, and performed quantitative structure activity relationship (QSAR) studies.

Table 1. General Structure of the compounds with their substitutions.

No	R_1	R_2	R_3
1			
2			
3			
4			
5T			
6	H	H	$(CH_2)_3OPh$
7	H	H	CH_2Ph
8	H	H	$CH(Ph)CH_2COCH3$
9	CH_3	CH_3	$CH(Ph)CH_2COCH3$
10	H	H	$(CH2)_3SPh$
11	H	H	$(CH2)_4Ph$
12	H	H	$(CH2)_4Ph(2\text{-}OCH3)$
13	OH	H	$(CH2)_4Ph(2\text{-}OCH3)$
14	H	Ph	
15	H	CH_2Ph	
16	H	CH_2CH_2Ph	
17	4-OH	CH_2CH_2Ph	
18T	$4\text{-}OCH_2CO_2H$	CH_2CH_2Ph	
19	H	Ph(2-Me)	
20	H	Ph(2-iPr)	
21	H	Ph(2-tBu)	
22	3-Me	Ph(2-iPr)	
23	Ph	Ph	

24T	Isobutyl	Ph	
25	Ph	CH_2Ph	
26	Isobutyl	CH_2Ph	
27	CH_2-cyclopropyl	CH_2Ph	
28	CH_2-cyclopropyl	Cyclohexyl	
29	CH_2-cyclopropyl	Cyclopentyl	
30T	Isobutyl	Cyclopentyl	
31	Cyclopentyl	Cyclopentyl	
32	H		
33	$CH_3(CH2)_2$		
34	$CH_3(CH2)_4$		
35T	$(CH_3)_2CH(CH2)_2$		
36	$HO_2C(CH_2)_4$		
37	Ph		
38	$Ph(CH_2)_2$		
39	H	H	
40T	Me	H	
41	Isopropyl	H	
42	Isopropyl	Me	
43	Isopropyl	Me	
44T	Isopropyl	Me	
45	t-Butyl	H	
46	t-Butyl	Me	

2 MATERIALS AND METHODS

2.1 Data Set

The data used in this QSAR study consisted of inhibitory activity data (IC_{50}), which is the half maximal (50%) inhibitory concentration (IC) of a compound, have been reported by Tummino et al. [13]. The activity data [IC_{50} (lM)] for non-peptide HIV-1 protease inhibitors (Table 1) was converted to the logarithmic scale [log IC_{50} (M)] and then used for subsequent QSAR analyses as the response variables. Figure 1 shows the general structure of non-peptide HIV-1 protease inhibitors.

2.2 Calculation of Descriptors

It is important to note that quantum chemical descriptor, Constitutional descriptors and topological descriptors are based solely on chemical structure. The calculated topological indices treat the structure of the compound as a graph, with atoms as vertices and covalent bonds as edges. The number of different descriptors reaches thousand in some leading commercial tools [14-18]. Having at hand powerful methods for automatically selecting the informative features, one may be tempted to leave the descriptor selection process entirely to algorithmic techniques. Quantum-chemical descriptors and molecular modeling techniques

enable the definition of a large number of molecular and local quantities characterizing the reactivity, shape and binding properties of a complete molecule as well as of molecular fragments and substituents. Because of the large well-defined physical information content encoded in many theoretical descriptors, their use in the design of a QSAR study presents two main advantages: (a) the compounds and their various fragments and substituent's can be directly characterized on the basis of their molecular structure only; and (b) the proposed mechanism of action can be directly accounted for in terms of the chemical reactivity of the compounds under study. Constitutional descriptors capture properties of the molecule that are related to elements constituting its structure. These descriptors are fast and easy to compute. The reason is that whereas the conventional physical and geometrical descriptors are structure-related, topological indices are just an algebraic description of the structure itself. Thus, one can go backward and forward between structure and property, predicting properties for molecules and vice versa. The molecular descriptor is the final result of a logic and mathematical procedure which transforms chemical information encoded within a symbolic representation of a molecule into a useful number or the result of some standardized experiment [19-39].

Table 2: Calculated descriptors of non-peptide HIV-1 protease inhibitors.

S. No	pIC_{50}	ZM_1	MSD	Wap	X_3	X_2	X_3^v	IP_1
1	5.161	112	4.794	7247	7.617	9.501	2.711	0
2	5.091	108	4.628	3636	7.536	9.416	2.8	0
3	4.721	180	8.734	39619	12.454	15.143	4.439	0
4	4.538	70	4.031	1354	4.515	6.158	1.493	0
5	4.538	116	7.263	4705	8.176	10.043	2.15	0
6	5.638	112	6.01	8016	7.849	9.233	2.491	0
7	3.921	100	4.574	5636	7.054	8.184	2.373	0
8	4.745	120	4.814	7191	8.075	10.049	2.861	0
9	5.721	132	5.144	9072	9.155	11.082	3.108	0
10	4.585	112	6.01	8016	7.849	9.233	3.104	0
11	3.959	112	6.01	8016	7.849	9.233	2.56	0
12	5.769	122	6.339	10446	8.677	9.942	2.815	0
13	6.284	128	6.56	11723	9.013	10.575	2.873	0
14	5.523	108	5.334	5813	7.458	8.988	3.234	0
15	5.769	112	5.785	6541	7.76	9.329	3.206	0
16	5.886	116	6.247	7319	8.002	9.683	3.178	0
17	6.284	122	6.512	8370	8.413	10.305	3.232	0
18	6.796	140	7.775	13465	9.396	12.037	3.468	0
19	6.377	114	5.438	6696	7.991	9.506	3.513	0
20	7.432	124	5.734	8640	8.526	10.436	3.763	0
21	7.769	132	5.832	9615	8.724	11.501	3.888	0
22	8.155	130	5.928	9871	8.854	11.07	3.839	0

23	6.108	146	5.997	11805	10.06	11.963	4.236	1
24	6.387	132	5.904	8136	8.659	11.291	3.645	0
25	6.319	150	6.342	12767	10.362	12.305	4.208	1
26	6.585	136	6.28	8975	8.969	11.633	3.617	0
27	7.076	142	6.28	9988	9.239	11.682	3.742	0
28	6.824	138	5.903	9115	8.929	11.34	3.77	0
29	7.161	134	5.707	7951	8.679	10.987	3.708	0
30	7.236	128	5.708	7016	8.409	10.937	3.583	0
31	6.638	138	5.698	9367	9.56	11.256	4.111	0
32	5.677	112	5.785	6541	7.76	9.329	3.278	0
33	5.292	128	5.901	7748	8.771	10.555	3.635	0
34	7.076	136	6.278	8826	9.301	11.262	3.76	0
35	7.018	138	6.191	8772	9.243	11.738	3.76	0
36	8.301	146	6.746	10076	9.729	12.445	3.862	0
37	6.585	148	6.094	12030	10.335	12.011	4.249	1
38	7.222	156	6.707	14018	10.798	12.848	4.26	0
39	6.886	152	6.306	12742	10.495	12.506	4.44	0
40	7.137	158	6.423	14357	11.029	13.024	4.629	0
41	7.854	168	6.726	17869	11.564	13.955	4.879	0
42	8.137	174	6.846	19518	11.9	14.589	4.941	0
43	6.886	174	6.846	19518	11.9	14.589	4.941	0
44	8.208	174	6.846	19518	11.9	14.589	4.941	0
45	8.444	176	6.839	19628	11.762	15.019	5.004	0
46	8.009	182	6.942	21289	12.097	15.653	5.066	0

IP_1: if ph is present in R_1 it is considered as unity otherwise it is zero

2.3 Statistical Analysis

The data set was analyzed using NCSS statistical software [39]. Stepwise regression analysis was used to determine the most significant descriptors. The regression coefficients were obtained by least-squares regression analysis. For each regression, the following descriptive information is provided: number of observations used in the analysis (n), correlation coefficient (r), cross-validated (**R^{2cv}**), standard error of the estimate (Se), Mean of standard error of estimation (MSe), adjusted regression coefficient (R^2_{adj}), coefficient of variation (CV) and Fisher's criterion (F). Statistical parameters were calculated subsequently for each step in the process, so the significance of the added parameter could be verified. Correspondingly, it represents the part of the variation in the observed (experimental) data that is explained by the model. Y-randomization is a tool used in validation of QSPR/QSAR models, whereby the performance of the original model in data description is compared to that of models built for permuted (randomly shuffled) response, based on the original descriptor pool and the original model building procedure [40]. Theoretical studies indicated that by increasing the number of original descriptors with respect to the number of molecules,

the probability of obtaining chance models is increased, even by using variable selection methods. To decrease the probability of getting chance models, the number of original descriptors, among which the best subset of descriptors are selected, should be kept lower than five times of the number of molecules

2.5 Correlation Analysis

Pearson's correlation coefficients may serve as a preliminary filter for discarding inter-correlated descriptors. This can be done by e.g. creating clusters of descriptors having correlation coefficients higher than certain threshold and retaining only one, randomly chosen member of each cluster.

Table 3: Correlation Matrix of non-peptide HIV-1 protease inhibitors.

	pIC_{50}	**ZM_1**	**MSD**	**Wap**	**X_2**	**X_3^v**	**IP_1**
pIC_{50}	1.0000						
ZM_1	0.6661	1.0000					
MSD	0.3732	0.7244	1.0000				
Wap	0.3389	0.8443	0.7647	1.0000			
X_2	0.6810	0.9941	0.7287	0.8429	1.0000		
X_3^v	0.**7604**	0.9281	0.5579	0.7108	0.9164	1.0000	
IP_1	-0.0106	0.1506	0.0129	0.0582	0.1103	0.1922	1.0000

Table 3. Describe correlation coefficient between the chosen descriptors and inhibitory activity of non-peptide HIV-1 protease inhibitors. Firstly, the descriptors were checked for constant or near constant values and those detected were removed from the original data matrix. Then, the correlation of descriptors with each other's and with the activity data was determined. Among the collinear descriptors detected ($r > 0.8$), one of them that had the highest correlation with activity was retained and the rest were omitted. Recent studies have shown that both yield small prediction error in numerous QSAR applications. Given the complexity of these methods, one may be tempted to treat them as black boxes [41-47].

3. RESULTS AND DISCUSSION

First, separate stepwise selection-based MLR analyses were performed using different types of descriptors, and then, an MLR equation was obtained utilizing the pool of all calculated descriptors. The results are summarized in Tables 4 for training set of molecules and in Table 6 for whole studied molecules. After this, the molecules were classified into two groups and for each set of compounds separate QSAR models were obtained. Then attempts were made to obtain a unified QSAR model for a whole set of molecules.

From table 3 the correlation matrix between the descriptors and antiviral activity was obtained. The correlation coefficient between the pIC_{50} and X_3^V (r = 0.76) was significant and used for the model development. MLR models for subsets of molecules Table: 3 provide the obtained equations for training set series of 39 compounds**.** In this series, the geometrical parameters did not represent a significant impact on the biological activity. The topological parameters had a moderate impact on the inhibitory activity of non-peptide HIV-1 protease inhibitors according to a medium R^2 for the corresponding QSAR model. The equations obtained from topological and indicator descriptors were predictive. This three-parametric model can explain and predict 70% of variances in the biological activity of molecules of training set series.

Table 4: Developed QSAR models a set of non-peptide HIV-1ProtraseInhibitor with Statistical and Cross Validated statistical descriptors.

Eq. No	QSAR/QSPR Models	N	R^2	R^2adj	MSE	PRESS	R^2cv	CV	F Ratio
1	$pIC_{50} = 2.3336 + 1.1136X_3^V$	46	0.58	0.57	0.52	29.91	0.54	0.04	60.34
2	$pIC_{50}=1.6431-7.8714*10^{-5}Wap + 1.5378X_3^V$	46	0.66	0.64	0.52	29.71	0.55	0.11	41.82
3	$pIC_{50} = 1.4489-8.479*10^{-5}Wap + 1.6265X_3^V - .9591IP_1$	46	0.70	0.68	0.47	26.71	0.59	0.10	32.35
4	$pIC_{50} =-.18327-1.327*10^{-4} Wap+.3913X_2+1.0044\ X_3^V-.8417\ IP_1$	46	0.73	0.71	0.42	22.12	0.66	0.07	28.26
5	$pIC_{50} = 6.3382*10^{-2}-1.2634*10^{-4} Wap+.3029\ X_2+1.1757X_3^V -8225\ IP_1$	42	0.80	0.78	0.30	20.29	0.75	0.06	37.87

The **QSAR model-1** shows that topological descriptor X_3^V is well directly proportional with the antifungal activity and the correlation co-efficient **(0.76)** which is not sufficient to overcome this problem the stepwise multiple regression is progressed whose positive results are displayed in Table-4 with non-cross-validated and cross validated descriptors.

For inhibitory activity of non-peptide HIV-1 protease inhibitors, the **QSAR model-2** show statistically more significant important with comparison previous one. According to this QSAR model-2, Wap is negatively while X_3^V are positively correlated with the inhibitory activity, resulting we means that our research are move in a positive direction it is because there is appropriate enhancing of correlation coefficient (**R^2=0.66)** with other statistical descriptors but it not reached their goal indicating the addition of well-known indicator descriptor IP_1 which play a very important role in computational world especially in QSAR/QSPR world launch **QSAR model-3** with magnificent statistical compositions which produce a lot of information regarding the development of antiviral drugs The generation of

QSAR model-4 (training set) is the result of addition of connectivity index X_2 to get statistically significant result. The regression coefficient of QSAR **model-4 (R^2 = 0.73)** which is good developed QSAR models On further regression analysis dramatic change is observed when compound no.13,22,33 and 36 are considered as outlier. The activity of these compounds is abnormally high or low in their corresponding structure. The statistics is changed with a value of 80% variance in place of 73%.

The **QSAR model-5** show the importance of all used topological in which only Wap show negative correlation coefficient while X_3^V show positive coefficient. The regression coefficient value is higher and cross- validated descriptor shows the validation of developed

QSAR model-5

For inhibitory activity of non-peptide HIV-1 protease inhibitors the developed **QSAR model-5** describes the importance of topological descriptors and indicator descriptors .We observes that third order connectivity index has mostly affected the antiviral activity which encode for the branching of compounds, while IP_1 and Wap show negative coefficient with the antiviral activity. The correlation coefficient is quite significant between the used independent descriptors and antiviral property in the QSAR model-5. Generated **QSAR model-5** is statistically sounded model which demonstrate the importance of different variable in the generation of inhibitory activity of non-peptide HIV-1 protease inhibitors.

Table 5: The actual observed and predicted inhibitory activity of non-peptide HIV-1 protease inhibitors observed from eq. no .04

Compound. NO	Observed pIC_{50}	From eq. 4		From eq. 5	
		Predicted pIC_{50}	Residual	Predicted pIC_{50}	Residual
1	5.161	5.296	-0.135	5.213	-0.052
2	5.091	5.831	-0.740	5.749	-0.658
3	4.721	4.943	-0.222	4.864	-0.143
4	4.538	3.546	0.992	3.513	1.025
5	4.538	5.282	-0.744	5.039	-0.501
6	5.638	4.868	0.770	4.776	0.862
7	3.921	4.655	-0.734	4.621	-0.700
8	4.745	5.668	-0.923	5.563	-0.818
9	5.721	6.071	-0.350	5.929	-0.208
10	4.585	5.483	-0.898	5.497	-0.912
11	3.959	4.937	-0.978	4.858	-0.899
12	5.769	5.148	0.621	5.065	0.704
13	6.284	5.285	0.999	-	-

14	5.523	5.810	-0.287	5.854	-0.331
15	5.769	5.819	-0.050	5.832	-0.063
16	5.886	5.826	0.060	5.809	0.077
17	6.284	5.984	0.300	5.928	0.356
18	6.796	6.223	0.573	6.086	0.710
19	6.377	6.176	0.201	6.227	0.150
20	7.432	6.533	0.899	6.558	0.874
21	7.769	6.946	0.823	6.904	0.865
22	8.155	6.694	1.461	-	-
23	6.108	6.344	-0.236	6.354	-0.246
24	6.387	6.816	-0.429	6.741	-0.354
25	6.319	6.322	-0.003	6.303	0.016
26	6.585	6.810	-0.225	6.706	-0.121
27	7.076	6.821	0.255	6.740	0.336
28	6.824	6.831	-0.007	6.780	0.044
29	7.161	6.785	0.376	6.747	0.414
30	7.236	6.764	0.472	6.703	0.533
31	6.638	7.107	-0.469	7.123	-0.485
32	5.677	5.891	-0.214	5.917	-0.240
33	5.292	6.570	-1.278	-	-
34	7.076	6.829	0.247	6.781	0.295
35	7.018	7.022	-0.004	6.932	0.086
36	8.301	7.228	1.073	-	-
37	6.585	6.346	0.239	6.355	0.230
38	7.222	7.262	-0.040	7.193	0.029
39	6.886	7.479	-0.593	7.462	-0.576
40	7.137	7.657	-0.520	7.637	-0.500
41	7.854	7.806	0.048	7.770	0.084
42	8.137	7.898	0.239	7.826	0.311
43	6.886	7.898	-1.012	7.826	-0.940
44	8.208	7.898	0.310	7.826	0.382
45	8.444	8.115	0.329	8.017	0.427
46	8.009	8.205	-0.196	8.072	-0.063

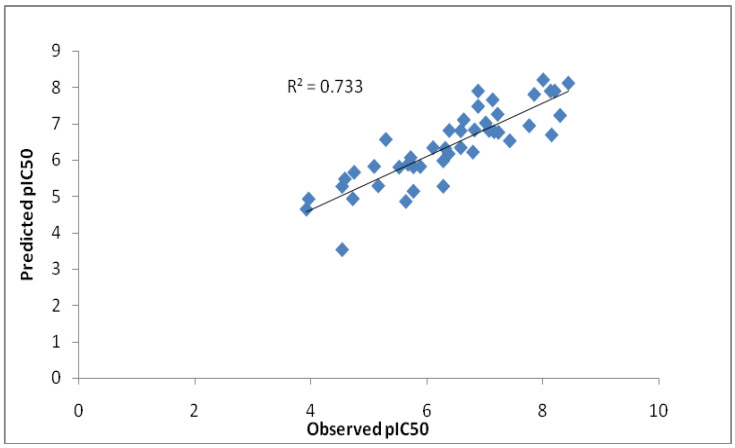


Fig 1: Graph plotted between observed pIC_{50} and predicted pIC_{50} inhibitory activity of non-peptide HIV-1 protease inhibitors by equation no. 04.

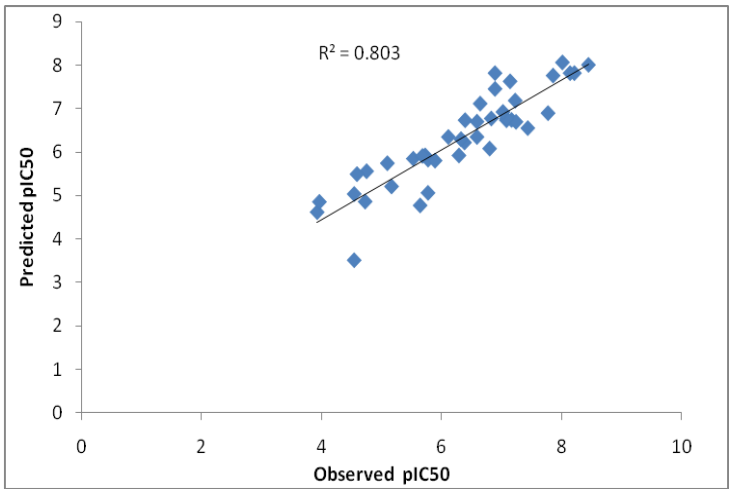


Fig 2: Graph plotted between observed pIC_{50} and predicted pIC_{50} inhibitory activity of non-peptide HIV-1 protease inhibitors by equation no. 05.

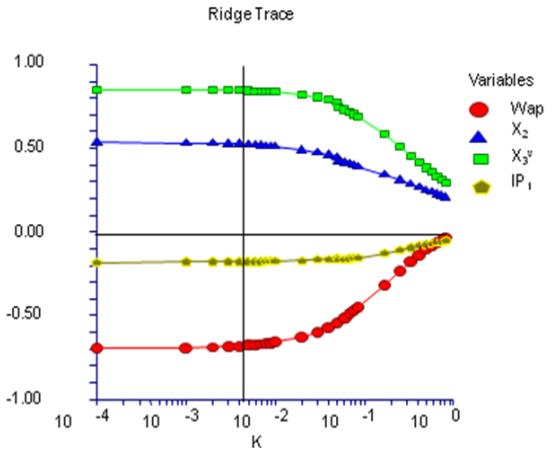


Fig 3: Graph plotted between VIF and K of used descriptors in QSAR modeling by equation no .04, Ridge regression.

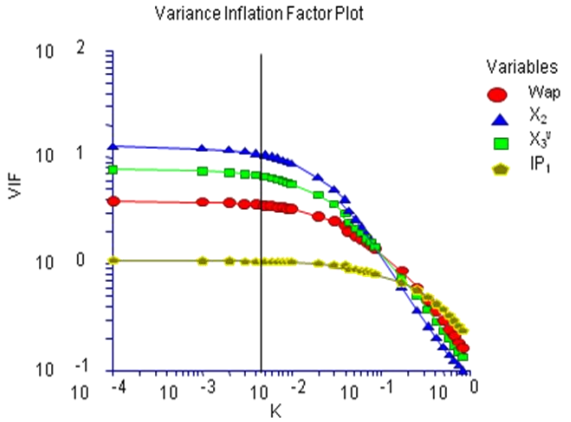


Fig 4: Graph plotted between VIF and K of used descriptors in QSAR modeling by equation no .05, Ridge regression.

CONCLUSION

Quantitative relationships between molecular structure and inhibitory activity of non-peptide HIV-1 protease inhibitors were discovered by chemometric methods i.e. MLR applied on two series of descriptors: those calculated from whole molecular structure. Significant QSAR equations were obtained from topological and indicator descriptors. This implies that the inhibitory activity of non-peptide HIV-1 protease inhibitors of the studied molecules can be accounted by the topological features of the substituents. By combining both types of descriptors, QSAR models with high prediction ability were obtained. Finally, MLR regression resulted in more appropriate QSAR model.

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