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ORIGINAL ARTICLE

QSAR Study HIV-1 Protease Reprinted with Permission (RP) Inhibitors of Cycloalkylpyranone derivatives

S.S. Tomer[1], Nadreen Banu [1], Kaleem Ahmad [2]*
[1]Department of chemistry R.S.S (P.G.) College Pilkhuwa, Hapur(U.P.). , India
[2]Department of chemistry Mahila (P.G.) College Bahraich (U.P.). , India
Corresponding author, Tel. /Fax 91-5252-234179, Mob No. +918004180005
E-mail address**: -** drkaleem2012@gmail.com

ABSTRACT
The implications for the ability of quantum chemical descriptors of highest occupied molecular orbital energy, lowest unoccupied molecular orbital energy, electron affinityionization potential absolute hardness, Softness ,Chemical Potential Molar refractivity (MR), Molar Volume (MV)and Parachor (Pc) to describe the biological activities HIV-1 Protease (RP) Inhibitors of Cycloalkylpyranone derivatives arediscussed. The relationships between observed biological activity, log 1/Ki, and the quantum chemical descriptors are established. For this establishment various QSAR models have been developed. The parameter adopted in this calculation is the semi-empirical PM3 based. The QSAR model sixth provides a good arrangement between Obs log 1/c & predicted activity.
Key words: *Absolute hardness; Chemical potential; Electronegativity; Global Softness; refractivity (MR) , Molar Volume (MV), HOMO; LUMO, Parachor (Pc). PM3;*

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INTRODUCTION

The World Health Organization has warned about the danger of AIDS, which has killed more than 2.5 million people world-wide [1, 2]. Hagen and coworkers1 have reported on advancements in the treatment of HIV infection by the use of HIV protease inhibitors. Originally referred to as HTLV-III or LAV, this enveloped single-stranded RNA virus is now called human immunodeficiency virus (HIV) [3, 4] and two genetically distinct subtypes, HIV-1 and HIV-2, have been characterized, [5, 6] of which the former has been found to be prevalent in causing the disease.

In the present study we have taken structures of a set of HIV-1 Protease (RP) Inhibitors of Cycloalkylpyranone derivatives of anti-HIV drugs derivatives and then compared to the numerical values of a biological activity. The challenge here has been to find some numerical information for a molecule. This structure information and the measured property or activities are then converted into a mathematical model of relationship. From a quality model it is possible to predict and to design compounds for synthesis and testing that have a good possibility for activity. In this paper, the multi linear regression analysis has been applied for QSAR study. The relationship has been worked out between the Log1/Ki values of a series of compounds and certain quantum chemical descriptors.

MATERIAL AND METHODS

The compounds taken for study are derivatives of a set of HIV-1 Protease Inhibitors of Cycloalkylpyranone derivatives of anti-HIV drugs shown in Fi g.-1.

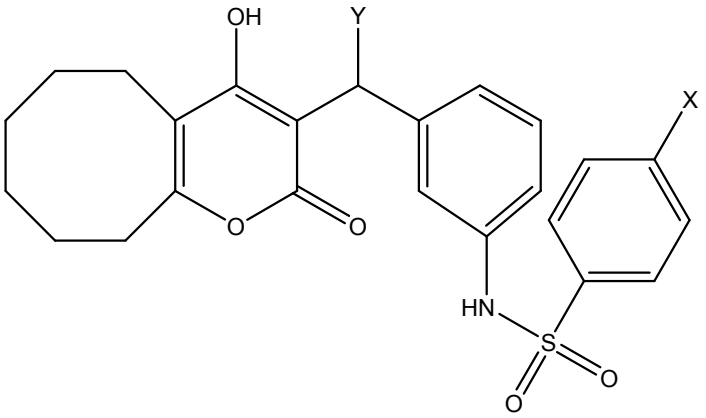


Fig 1: PR Inhibition derivatives of Cycloalkylpyranone

The Quantum Chemical parameter based QSAR study was performed by the following important descriptors like Eigen value of Highest occupied molecular orbital (EHOMO), Eigen value of lowest unoccupied molecular orbital (ELUMO) [7] , Absolute Hardness (η) [8], Chemical Potential (μ) [9] , Global Softness (S) [10], Electronegativity (χ) [11], Molar refractivity (MR) [12], Molar Volume (MV) [13], Parachor (Pc) [14]. The molecules were drawn by spartan06v110, software and the geometries were optimized at PM3 level in conjunction with molecular mechanics. The global hardness and electronegativities were calculated using frontier orbital energies obtained from PM3 results and reported in table 2. The multiple linear regression analysis (MLR) is performed to establish a perfect QSAR model of HIV-1 Protease Inhibitors of Cycloalkylpyranone derivatives. The compounds were taken with their observed activity is shown in table 1.

RESULTS AND DISCUSSION

Multiple Linear Regression (MLR) analysis

MLR analyses were performed using Minitab 16 software. The quantum mechanical descriptors were used as independent variables and the Obsd log1/Ki values as the dependent variables. In the statistical analyses, a systematic search was performed to determine the significant descriptors. The correlation matrix was developed to minimize the effect of co-linearity and to avoid dependencies between subsets of the variables and multi-co-linearity (high multiple correlations between subsets of the variables). The MLR equations of different QSAR models are as fallows-

First QSAR model

MLR equation of this QSAR model P log 1/Ki is given by-

Obsd log 1/Ki = 5.89 - 1.96 E LUMO (e.v) S = 0.523851

S = 0.162964

PRESS = 0.465827

r^2= 79.4%

Second QSAR model

MLR equation of this QSAR model P log 1/Ki is given by-

Obsd log 1/Ki = 7.16 - 4.87 E LUMO (e.v) + 0.706 E HOMO (e.v)

S = 0.506241

PRESS = 10.2998

r^2= 87.5%

Third QSAR model

MLR equation of this QSAR model P log 1/Ki is given by-

Obsd log 1/Ki = 34.1 - 6.51 E LUMO (e.v) + 2.36 E HOMO (e.v) - 218 S

S = 0.511107

PRESS = 9.39081

r^2= 87.7%

Fourth QSAR model

MLR equation of this QSAR model P log 1/Ki is given by-

Obsd log 1/Ki = 65.1 - 8.47 E LUMO (e.v) + 4.26 E HOMO (e.v) - 539 S+ 0.0445 MR (cm3/mol)

S = 0.487954

PRESS = 8.71520

r^2= 89.2%

Fifth QSAR model
MLR equation of this QSAR model P log 1/Ki is given by-
Obsd log 1/Ki = 67.5 - 8.32 E LUMO (e.v) + 4.54 E HOMO (e.v) - 525 S
- 0.0216 MR (cm3/mol) + 0.0212 MV (cm3/mol)
S = 0.472278
PRESS = 8.68476
r^2= 90.2%
Sixth QSAR model
MLR equation of this QSAR model P log 1/Ki is given by-
Obsd log 1/Ki = 15.0 - 5.43 E LUMO (e.v) + 1.03 E HOMO (e.v) - 127 S
+ 0.183 MR (cm3/mol) + 0.0505 MV (cm3/mol) - 0.0379 Parachor (cm3/mol)
S = 0.437862
PRESS = 8.72525
r^2= 91.9%

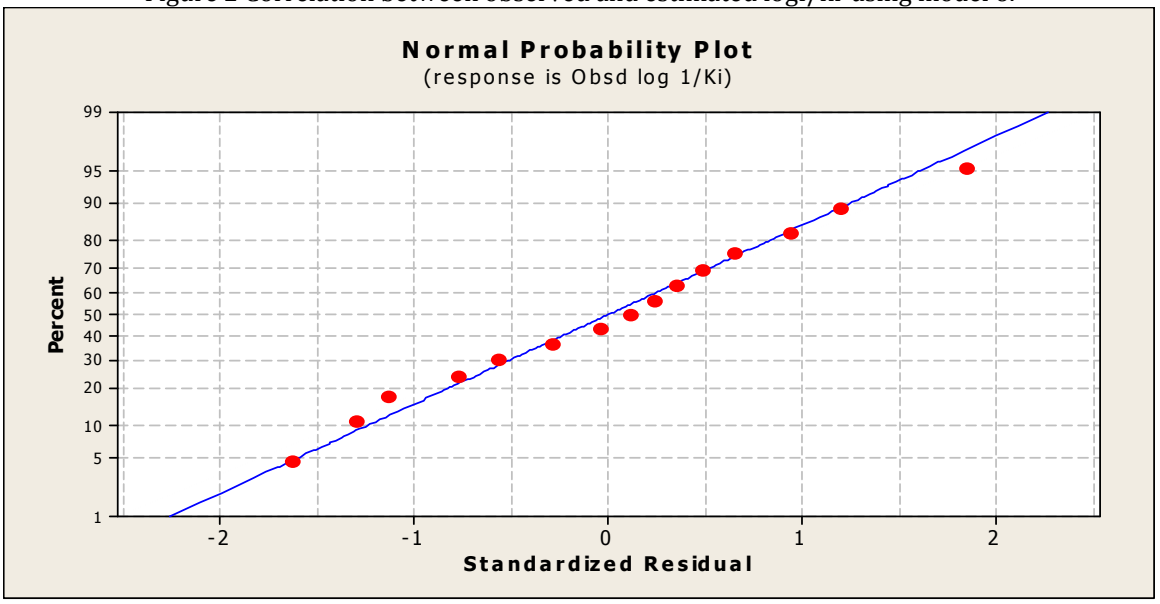
Table 1. Structural detail and biological activity for the compounds used in the present study

Comp.No.	X	Y	Obsd log 1/Ki
1	4-Cl	Cy-C_3H_5	8.600
2	4-Cl	C_2H_5	8.460
3	4-Cl	C_3H_7	8.400
4	4-Cl	$CHMe_2$	7.750
5	4-CN	Cy-C_2H_5	9.100
6	4-CN	C_2H_5	8.510
7	4-CN	C_3H_7	8.850
8	4-CN	C_4H_9	8.680
9	4-CN	$CHMe_2$	8.230
10	4-CN	CH_2CHMe_2	8.820
11	4-F	Cy-C_3H_5	8.510
12	4-F	C_3H_7	8.680
13	4-F	C_4H_9	8.220
14	4-F	$CHMe_2$	7.960
15	4-F	CH_2CHMe_2	8.550

Table 2. Calculated values of quantum and physiochemical indices for the set of compounds used in the present study

Compd No.	Obsd log 1/Ki	E LUMO (e.v)	E HOMO (e.v)	μ	η	S	χ	MR (cm3/mol)	MV (cm3/mol)	Parachor (cm3/mol)
1	8.600	-1.325	-9.021	-5.173	3.848	0.130	5.173	134.340	362.400	1032.000
2	8.460	-1.236	-8.964	-5.100	3.864	0.129	5.100	131.780	364.500	1023.500
3	8.400	-1.256	-9.011	-5.134	3.878	0.129	5.134	136.410	380.500	1063.600
4	7.750	-1.066	-8.960	-5.013	3.947	0.127	5.013	136.380	381.200	1061.500
5	9.100	-1.601	-8.999	-5.300	3.699	0.135	5.300	134.080	360.700	1042.600
6	8.510	-1.370	-9.053	-5.212	3.842	0.130	5.212	131.520	362.800	1034.000
7	8.850	-1.530	-9.105	-5.318	3.788	0.132	5.318	136.150	378.900	1074.100
8	8.680	-1.463	-9.106	-5.285	3.822	0.131	5.285	140.780	395.000	1114.200
9	8.230	-1.310	-9.070	-5.190	3.880	0.129	5.190	136.120	379.500	1072.000
10	8.820	-1.455	-8.858	-5.157	3.702	0.135	5.157	140.750	395.600	1112.100
11	8.510	-1.455	-9.214	-5.335	3.880	0.129	5.335	134.080	360.700	1042.600
12	8.680	-1.336	-9.065	-5.201	3.865	0.129	5.201	129.630	356.000	1002.300
13	8.220	-1.113	-8.811	-4.962	3.849	0.130	4.962	136.320	390.300	1073.800
14	7.960	-1.125	-9.020	-5.073	3.948	0.127	5.073	131.670	374.800	1031.700
15	8.550	-1.235	-8.899	-5.067	3.832	0.130	5.067	136.300	390.900	1071.800

Figure 2 Correlation between observed and estimated logI/ki-using model 6.



CONCLUSIONS

Values of the descriptors of QSAR of HIV-1 Protease (RP) Inhibitors of Cycloalkylpyranone derivatives have been calculated using PM3 method and are given in table-2. With the help of these values of descriptors, six QSAR models have been developed using MLR analysis in different combinations of descriptors. The Chemical Potential (μ) and Absolute Hardness (η) descriptors have no predicting power and hence not included in the models. Best QSAR models is the model sixth listed below-

Sixth QSAR model

MLR equation of this QSAR model P log 1/Ki is given by-

Obsd log 1/Ki = 15.0 - 5.43 E LUMO (e.v) + 1.03 E HOMO (e.v) - 127 S
+ 0.183 M**R** (cm3/mol) + 0.0505 MV (cm3/mol) - 0.0379 Parachor (cm3/mol)

S = 0.437862

PRESS = 8.72525

r^2= 91.9%

This is one of the best QSAR model in all the six models and has been developed using E LUMO, E HOMO, Global Softness (S), Molar refractivity (MR), Molar Volume (MV), Parachor (Pc). This MLR equation is given by Value of regression coefficient is 91.9% Prediction sum of squares coefficient (PRESS) is 8.72525 and Standard error of the regression (S) is0.437862 which indicate the ability of predictive power of this QSAR model. QSAR model sixth can efficiently be used for the prediction of activity of any derivative of compound. The normal probability plot of responses is obsd log 1/C is shown in fig-2, which is clearly illustrates the high predictive power of the QSAR model six.

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