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Quantum and molecular parameters-based QSAR study on Pyridinone derivatives of Anti-HIV drugs

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A B S T R A C T

Anti-HIV drug discovery has been increasingly focusing on HIV-1-RT (reverse transcriptase) as a potential therapeutic target. Pyridinone derivatives, belongs to non-nucleoside group of reverse transcriptase inhibitors (NNRTIs). A computational chemistry study has been performed on a series of Pyridinone derivatives as HIV-1-NNRT inhibitors. In order to search out a best QSAR model of drug with the help of MLR analysis. physiochemical descriptor Molar refractivity (MR), Molar Volume (MV), Parachor (Pc) and quantum chemical descriptor HOMO energy, LUMO energy, absolute hardness, Softness, Chemical Potential and Electro negativity. The 3D modeling and geometry optimization of the compounds have been done by semiempirical method with SPARTAN software. The study has shown the parameter adopted in this calculation is the semi-empirical PM3 based and made six different models .The QSAR model sixth provides a good arrangement between Obs log 1/c & predicted activity.

Keywords: Absolute hardness, Chemical potential, Electro negativity, Global Softness, refractivity (MR), Molar Volume (MV), HOMO, LUMO, Parachor (Pc). PM3

A R T I C L E I N F O

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1. Introduction

In the present text, acquired immunodeficiency syndrome (AIDS) is the most fatal disorder for which no completely successful chemotherapy has been developed so far. The pandemic spread of this disease has prompted an unprecedented scientific and clinical effort to understand and combat it. The causative agent of AIDS has been identified as a retrovirus of the *Lentiviridae* family. [1, 2] 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 Pyridinone 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/C values of a series of compounds and certain quantum chemical descriptors.

2. Materials and Methods

The compounds taken for studies are the derivatives of Pyridinone of anti-HIV drugs and shown in Fig.-1

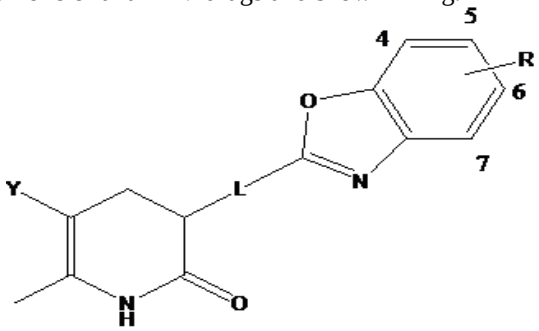

Figure 1: Pyridinone derivatives of anti-HIV drugs

The Quantum Mechanical QSAR

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. Multiple linear regression analysis (MLR) is performed to establish the QSAR. A data set pyridinone derivatives of anti-HIV drugs compounds were taken with their observed activity is shown in table 1.

3. 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/C50 values as the dependent variables. In the statistical analyses, the 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/C is given by-

Obsd log 1/C = 4.56 - 3.13 E LUMO (e.v)……1

S = 0.460565

PRESS = 7.59284

r^2= 78.0%

Second QSAR model

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

Obsd log 1/C = - 23.1 - 3.35 E LUMO (e.v) - 3.13 E HOMO (e.v)……2

S = 0.397290

PRESS = 7.88914

r^2= 84.1%

Third QSAR model

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

Obsd log 1/C = 511 - 35.1 E LUMO (e.v) + 31.0 E HOMO (e.v) - 2068 S.....…...3

S = 0.258217

PRESS = 3.54344

r^2= 93.5%

Fourth QSAR model

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

Obsd log 1/C = 508 - 34.9 E LUMO (e.v) + 30.8 E HOMO (e.v) - 2059 S - 0.0021 MR (cm3/mol)…..……. 4

S = 0.262612

PRESS = 3.75079

r^2= 93.5%

Fifth QSAR model

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

Obsd log 1/C = 469 - 32.5 E LUMO (e.v) + 28.4 E HOMO (e.v) - 1905 S- 0.0114 MR (cm3/mol) + 0.00721 MV (cm3/mol)……..……5

S = 0.254918

PRESS = 3.94834

r^2= 94.1%

Sixth QSAR model

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

Obsd log 1/C = 698 - 46.8 E LUMO (e.v) + 42.7 E HOMO (e.v) - 2810 S - 0.0934 MR (cm3/mol) - 0.0109 MV (cm3/mol) + 0.0150 Parachor (cm3/mol) ……

…6

S = 0.147543

PRESS = 0.915736

r^2= 98.1%

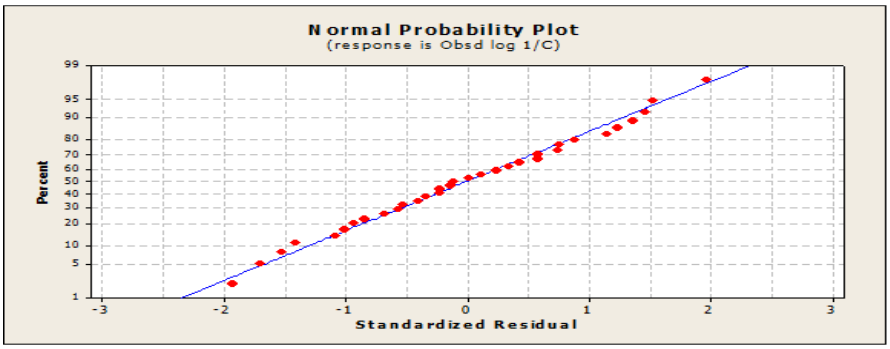

Figure 2: Correlation between observed and estimated log 1/C -using model 6

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

Comp.No.	R	X	L	Obsd log 1/C
1	H	S	CH_2CH_2	7.620
2	4,7-di-Me	S	CH_2CH_2	7.280
3	4,7-di-Cl	S	CH_2CH_2	7.520
4	4,7-di-F	S	CH_2CH_2	7.820
5	4-F	S	CH_2CH_2	7.890
6	7-F	S	CH_2CH_2	7.370
7	4-Cl	S	CH_2CH_2	7.520
8	7-Cl	S	CH_2CH_2	7.540
9	H	O	CH_2CH_2	7.640
10	4-Me	O	CH_2CH_2	7.480
11	4-Cl	O	CH_2CH_2	7.210
12	4-F	O	CH_2CH_2	7.820
13	7-Me	O	CH_2CH_2	7.400
14	7-Cl	O	CH_2CH_2	7.410
15	7-F	O	CH_2CH_2	7.430
16	4,7-di-Me	O	CH_2CH_2	7.550
17	4,7-di-Cl	O	CH_2CH_2	7.850
18	4,7-di-F	O	CH_2CH_2	7.850
19	6-Me	O	CH_2CH_2	6.760
20	6-F	O	CH_2CH_2	6.350
21	5-F	O	CH_2CH_2	5.770
22	H	O	OCH_2	6.720
23	4,7-di-Cl	O	OCH_2	7.060
24	4,7-di-Cl	O	SCH_2	7.960
25	4,7-di-Cl	O	$S(O)CH_2$	5.850
26	4,7-di-Cl	O	SO_2CH_2	6.690
27	H	O	$NHCH_2$	6.680
28	4,7-di-Cl	O	$NHCH_2$	7.700
29	H	O	$NHCH_2$	5.900
30	H	O	CH=CH (*trans*)	5.230
31	H	O	CH=CH (*cis*)	5.520
32	H	O	CH_2	4.350
33	H	O	$(CH_2)_3$	4.800

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

Compd No.	Obsd log 1/C	E LUMO (e.v)	E HOMO (e.v)	μ	η	S	χ	MR (cm3/mol)	MV (cm3/mol)	Parachor (cm3/mol)
1	7.620	-1.072	-8.716	-4.894	3.822	0.131	4.894	89.040	250.500	683.500
2	7.280	-1.066	-8.710	-4.888	3.822	0.131	4.888	98.290	282.000	760.000
3	7.520	-1.109	-8.748	-4.929	3.820	0.131	4.929	98.700	272.300	757.700
4	7.820	-1.143	-8.783	-4.963	3.820	0.131	4.963	89.270	259.600	698.200
5	7.890	-1.118	-8.761	-4.940	3.822	0.131	4.940	89.160	255.000	690.800
6	7.370	-1.093	-8.740	-4.917	3.824	0.131	4.917	89.160	255.000	690.800
7	7.520	-1.098	-8.741	-4.920	3.822	0.131	4.920	93.870	261.400	720.600
8	7.540	-1.086	-8.727	-4.907	3.821	0.131	4.907	93.870	261.400	720.600
9	7.640	-0.821	-8.802	-4.812	3.991	0.125	4.812	82.210	254.200	642.000
10	7.480	-0.854	-8.796	-4.825	3.971	0.126	4.825	87.040	270.500	680.300
11	7.210	-0.721	-8.827	-4.774	4.053	0.123	4.774	87.110	266.100	679.100
12	7.820	-0.854	-8.838	-4.846	3.992	0.125	4.846	82.200	258.400	649.300
13	7.400	-0.845	-8.807	-4.826	3.981	0.126	4.826	87.040	270.500	680.300
14	7.410	-0.754	-8.797	-4.776	4.022	0.124	4.776	87.110	266.100	679.100
15	7.430	-0.850	-8.815	-4.833	3.983	0.126	4.833	82.200	258.400	649.300
16	7.550	-0.812	-8.798	-4.805	3.993	0.125	4.805	91.860	286.700	718.500
17	7.850	-0.958	-8.831	-4.895	3.937	0.127	4.895	92.000	278.100	716.300
18	7.850	-0.880	-8.854	-4.867	3.987	0.125	4.867	82.200	262.600	656.700
19	6.760	-0.652	-8.784	-4.718	4.066	0.123	4.718	87.040	270.500	680.300
20	6.350	-0.543	-8.844	-4.694	4.151	0.120	4.694	82.200	258.400	649.300
21	5.770	-0.428	-8.856	-4.642	4.214	0.119	4.642	82.200	258.400	649.300
22	6.720	-0.546	-8.821	-4.684	4.138	0.121	4.684	79.160	232.200	622.300
23	7.060	-0.625	-8.843	-4.734	4.109	0.122	4.734	88.810	254.000	696.500
24	7.960	-0.972	-8.905	-4.939	3.967	0.126	4.939	95.080	261.800	728.600
25	5.850	-0.452	-8.880	-4.666	4.214	0.119	4.666	95.940	258.000	749.200
26	6.690	-0.812	-8.456	-4.634	3.822	0.131	4.634	95.890	267.100	755.900
27	6.680	-0.621	-8.864	-4.743	4.122	0.121	4.743	81.070	233.700	630.200
28	7.700	-0.745	-8.900	-4.823	4.078	0.123	4.823	90.720	255.500	704.400
29	5.900	-0.426	-8.775	-4.600	4.175	0.120	4.600	82.270	240.800	630.200
30	5.230	-0.415	-8.764	-4.590	4.175	0.120	4.590	85.650	234.000	629.600
31	5.520	-0.435	-8.764	-4.600	4.165	0.120	4.600	85.650	234.000	629.600
32	4.350	-0.265	-8.832	-4.549	4.283	0.117	4.549	77.560	234.200	601.900
33	4.800	-0.141	-8.759	-4.450	4.309	0.116	4.450	82.200	258.400	728.600

4. Conclusion

Values of the descriptors of the pyridinone derivatives of anti-HIV drugs 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/C is given by-

Obsd log 1/C = 698-46.8 E LUMO (e.v) + 42.7 E HOMO (e.v)-2810 S

0.0934 MR (cm3/mol) -0.0109 MV (cm3/mol) + 0.0150 Parachor (cm3/mol) 6

S = 0.147543

PRESS =0.915736

r^2= 98.1%

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 98.1% (PRESS) is 0.915736 regression (S) is 0.147543 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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