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Research Article

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QSAR study of anti-HIV drugs of 1-2-[(hydroxyethoxy) methyl]-6-(phenylthio) thymine (HEPT) derivatives by using quantum descriptors

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ABSTRACT

The various QSAR models have been developed to predict the activities in terms of log 1/C for 34 HEPT (1-[(2-hydroxyethoxy) methyl]-6-(phenylthio)-thymine) derivatives anti-HIV compounds with the help of physiochemical descriptor Molar refractivity (MR), Molar Volume (MV), Parachor (Pc) and quantum chemical descriptor HOMO energy, LUMO energy, absolute hardness, Softness, Chemical Potential and Electronegativity. 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;

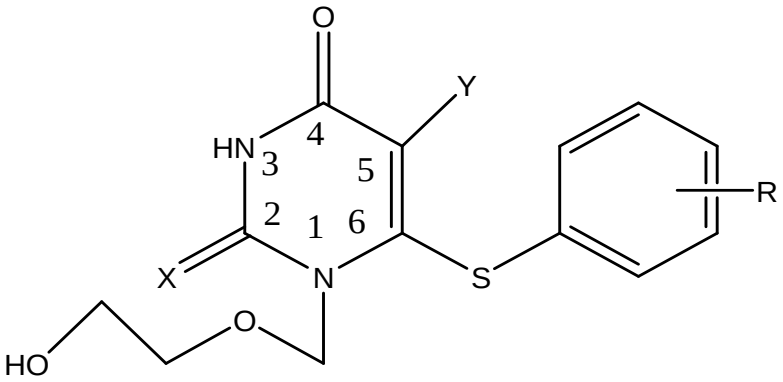
INTRODUCTION

In the present era, 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 HEPT (1-[(2-hydroxyethoxy) methyl]-6-(phenylthio)-thymine) 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.

EXPERIMENTAL SECTION

The compounds taken for study are derivatives of HEPT (1-[(2-hydroxyethoxy) methyl]-6-(phenylthio)-thymine) of anti-HIV drugs and shown in Fig.-1.



HEPT (1-[(2-hydroxyethoxy) methyl]-6-(phenylthio)-thymine) derivatives

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 of HEPT (1-[(2-hydroxyethoxy) methyl]-6-(phenylthio)-thymine) derivatives 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/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 = 0.217 - 5.16 E LUMO (e.v)
S = 0.523851
PRESS = 9.81955
r^2= 86.2%

Second QSAR model

MLR equation of this QSAR model P log 1/C is given by-
Obsd log 1/C = 7.16 - 4.87 E LUMO (e.v) + 0.706 E HOMO (e.v)
S = 0.506241PRESS = 10.2998r^2= 87.5%

Third QSAR model

MLR equation of this QSAR model P log 1/C is given by-
Obsd log 1/C = 34.1 - 6.51 E LUMO (e.v) + 2.36 E HOMO (e.v) - 218 S
S = 0.511107
PRESS = 9.3908
1r^2= 87.7%

Fourth QSAR model
MLR equation of this QSAR model P log 1/C is given by-
Obsd log 1/C = 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/C is given by-
Obsd log 1/C = 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/C is given by-
Obsd log 1/C = 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%

CONCLUSION

Values of the descriptors of the HEPT (1-[(2-hydroxyethoxy) methyl]-6-(phenylthio)-thymine) 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 = 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%

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) is **0.437862** 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.

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

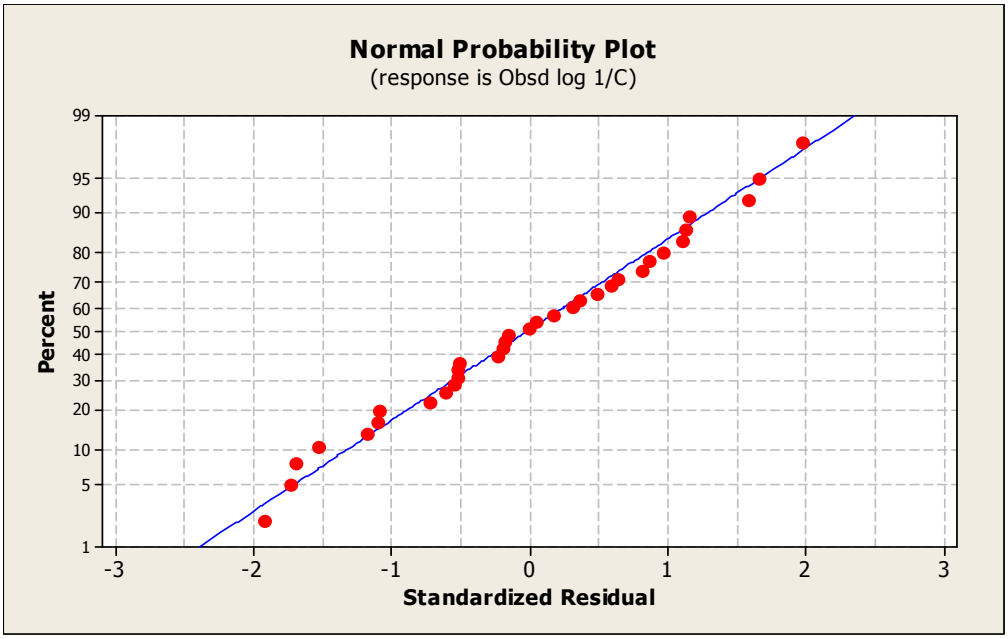


Table 1. Structural detail and biological activity for the compounds used in the present study

Comp. No.	R	Y	X	Obsd log 1/C
1	2-Me	Me	O	4.15
2	2-NO_2	Me	O	3.85
3	2-OMe	Me	O	4.72
4	3-Me	Me	O	5.59
5	3-C_2H_5	Me	O	5.57
6	3-CMe_3	Me	O	4.92
7	3-CF_3	Me	O	4.35
8	3-F	Me	O	5.48
9	3-Cl	Me	O	4.89
10	3-Br	Me	O	5.24
11	3-I	Me	O	5.00
12	3-NO_2	Me	O	4.47
13	3-OH	Me	O	4.09
14	3-OMe	Me	O	4.66
15	4-Me	Me	O	3.66
16	3,5-di-Me	Me	O	6.59
17	3,5-di-Cl	Me	O	5.89
18	3,5-di-Me	Me	S	6.66
19	3-CO_2Me	Me	O	5.10
20	3-COMe	Me	O	5.14
21	3-CN	-Me	O	5.00
22	H	$CH_2CH=CH_2$	O	5.60
23	H	C_2H_5	S	6.96
24	H	C_3H_7	S	5.00
25	H	$CHMe_2$	S	7.23
26	3,5-di-Me	C_2H_5	S	8.11
27	3,5-di-Me	$CHMe_2$	S	8.30
28	3,5-di-Cl	C_2H_5	S	7.37
29	H	C_2H_5	O	6.92
30	H	C_3H_7	O	5.47
31	H	$CHMe_2$	O	7.20
32	3,5-di-Me	C_2H_5	O	7.89
33	3,5-di-Me	$CHMe_2$	O	8.57
34	3,5-di-Cl	C_2H_5	O	7.85

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	4.150	-0.860	-9.394	-5.127	4.267	0.059	5.127	85.380	245.400	683.500
2	3.850	-0.852	-9.521	-5.187	4.335	0.058	5.187	86.790	240.900	702.300
3	4.720	-0.800	-9.240	-5.020	4.220	0.059	5.020	87.130	251.500	703.900
4	5.590	-0.870	-9.520	-5.195	4.325	0.058	5.195	85.380	245.400	683.500
5	5.570	-0.880	-9.540	-5.210	4.330	0.058	5.210	90.010	261.600	723.600
6	4.920	-0.890	-9.500	-5.195	4.305	0.058	5.195	99.280	294.400	800.000
7	4.350	-0.876	-9.700	-5.288	4.412	0.057	5.288	85.750	260.800	707.200
8	5.480	-0.990	-9.520	-5.255	4.265	0.059	5.255	80.870	234.200	652.600
9	4.890	-0.940	-9.470	-5.205	4.265	0.059	5.205	85.590	240.500	682.400
10	5.240	-0.980	-9.530	-5.255	4.275	0.058	5.255	88.480	242.400	696.300
11	5.000	-0.940	-9.310	-5.125	4.185	0.060	5.125	93.680	249.000	719.200
12	4.470	-0.814	-9.830	-5.322	4.508	0.055	5.322	86.790	240.900	702.300
13	4.090	-0.940	-9.500	-5.220	4.280	0.058	5.220	82.290	226.500	660.500
14	4.660	-0.904	-9.506	-5.205	4.301	0.058	5.205	87.130	251.500	703.900
15	3.660	-0.701	-9.528	-5.115	4.413	0.057	5.115	85.380	245.400	683.500
16	6.590	-1.456	-9.427	-5.442	3.986	0.063	5.442	90.010	261.200	721.800
17	5.890	-1.075	-9.382	-5.229	4.154	0.060	5.229	90.420	251.400	719.500
18	6.660	-1.253	-8.939	-5.096	3.843	0.065	5.096	97.000	269.300	763.300
19	5.100	-1.051	-9.593	-5.322	4.271	0.059	5.322	91.870	264.600	749.100
20	5.140	-1.010	-9.550	-5.280	4.270	0.059	5.280	90.130	258.500	728.800
21	5.000	-1.125	-9.660	-5.393	4.268	0.059	5.393	85.330	239.000	692.900
22	5.600	-0.880	-9.499	-5.190	4.310	0.058	5.190	89.790	257.400	714.500
23	6.960	-1.292	-8.967	-5.130	3.838	0.065	5.130	92.390	254.000	726.800
24	5.000	-0.823	-8.969	-4.896	4.073	0.061	4.896	97.020	270.200	766.900
25	7.230	-1.274	-8.949	-5.112	3.838	0.065	5.112	97.000	270.800	764.800
26	8.110	-1.458	-8.939	-5.199	3.741	0.067	5.199	101.640	285.500	803.300
27	8.300	-1.546	-8.901	-5.224	3.678	0.068	5.224	106.240	302.300	841.400
28	7.370	-1.458	-9.035	-5.247	3.789	0.066	5.247	102.040	275.800	801.100
29	6.920	-1.340	-9.498	-5.419	4.079	0.061	5.419	85.390	245.900	685.300
30	5.470	-0.857	-9.467	-5.162	4.305	0.058	5.162	90.020	262.100	725.400
31	7.200	-1.235	-9.537	-5.386	4.151	0.060	5.386	90.000	262.700	723.300
32	7.890	-1.540	-9.402	-5.471	3.931	0.064	5.471	94.640	277.400	761.900
33	8.570	-1.584	-9.498	-5.541	3.957	0.063	5.541	99.250	294.200	799.900
34	7.850	-1.354	-9.547	-5.451	4.097	0.061	5.451	95.050	267.600	759.600

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