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QSAR studies on novel bis (L-amino acid) ester prodrugs of 9-[2-(phosphonomethoxy) ethyl] adenine (PMEA) with improved anti-HBV activity compounds

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ABSTRACT: Quantitative structure-activity relationship (QSAR) study ofadenine derivatives 12 training sets are taken to correlate and predict the antihepatitis activity against Gram-negative virus. MLR is used to select the best descriptors and predict the activity of the model selected by cross validation. Our result is the based on the descriptor correlation between experimental and predicted inhibitory values got by the validation procedure. Using topological descriptors the best model with R^2=0.8060and R^2adj=0.7332 higher values of regression coefficient indicate the validity of model and helpful to synthesize the new potent antihepatitis drugs.

Key words: Antihepatitis, adenine, molecular descriptor, QSAR.

I. INTRODUCTION

Hepatitis B virus infection is a worldwide health problem and may lead to lifelong infection cirrhosis of the liver, livercancer, liver failure, and death[1].Although vaccination programs are implemented in various countries but it is still affecting 350 million to 400million people worldwide[2].There are estimated to be 7-9 million carriers of hepatitis B virus with a carrier rate of 3-5% with infection rate risingsteadily[3].

Only a few drugs are conventional recommendation by the FDA for the treatment of chronic HBV infection. They include lamivudine adefovir dipivoxil and entecavir[4]. In particular it has shown impressive ability to suppress replication of HBV Adefovir dipivoxil an ester prodrug of PMEA has potent in vitro and in vivo activity against HBV[5]. however, dose limiting nephrotoxicity and its potential of releasing toxic formaldehyde and pivalic acid are its primary limitations [6,7]. In order to optimize cellular uptake and antiviral, in order to optimize cellular uptake and antiviral activity and to reduce cytotoxicity of PMEA. Several prodrugs such as bis (SATE)-PMEA [8,9]and Hep-direct prodrug remofovir[10] have been reported.these new prodrugs have improved the pharmacodynamics and pharmacokinetics of PMEA.

QSAR concepts have long been used in the design of medicinal chemistry series[11]. the stepwise exploration of a series according to the physical chemical property that governs the increase or decrease in potency of each new compound[12]. The traditional application of QSAR to a series of congeners requires,that each molecule in the dataset has measurable biological activity that is a quantitative,non zero potency value discriminate analysis or a logistic regression method can be applied,generally to modelling binary or categorical responses [13,14].The support vector machines[15] and Bayesian classifiers [16].Have also been successfully applied.

II. METHODOLOGY

All the activity data has been collected from table- 1The activity is expressed in PIC_{50}.The variation in the activity if any is specified with the respective QSAR All the physicochemical, Topological parameters are loaded table-1, and the QSAR regression analysis in Table 3The parameters selected using each method were used for developing QSAR equation, and the goodness of fit and statistical significance of the models were evaluated, using R^2 (correlation coefficient) F (Fisher coefficient),. The parameters used in this report have been discussed in detail along with their application. In the QSAR equation, n is the number of data points, R^2.is the square of the correlation coefficient, q^2.is the measure of quality. Various Topological parameters and indicator variables were used for the QSAR study of each of the molecules. Their contribution to biological activity was studied using simple linear regression analysis by NCSS 2007 software and, due to the problem of colinearity among parameters, different

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combinations of parameters were subjected to sequential and stepwise multiple regression analysis.

PARAMETERS USED

In this papers we use three type of descriptor namely physicochemical, topological and indicator parameters , physicochemical parameters used in this paperis average molecular weight(AMW),Sum of atomic vander Waals volumes (Sv), Sum of atomic Sanderson electronegativities (Se),mean atomic Sanderson electronegativity(Me), mean atomic polarizability(Mp),mean firstionization potential (Mi),Gutman Molecular Topological Index (GMTI),Balaban centric index (BAC),lopping centric index(LOC),indicator parameters (IR)

III. RESULTS AND DISCUSSION

A Set of 12 adenine used as anti-hepatitis agents are given in Table-1,QSAR studying on novel bis (L-amino acid)ester prodrugsof 9- [2-(phosphonomethoxy)ethyl] adenine (PMEA) were earlier studied by Xiaozhong Fu[17],and co-workers as the training set of 12compound . We have used the topological and physiochemical parameters for the novel bis (L-amino acid)esterprodrugsof 9-[2-(phosphonomethoxy)ethyl] adenine (PMEA) . were earlier anti-hepatitis agents. It has been known for some time that certain invariant of moleculer graphs-usually referred to as topological indices-can be used to establish quantitative structure , relationship (QSAR)of intercept in pharmacology.

The advantage of topological indices that they may be used directly as simple numerical description QSAR study, these relationship are mathematical models that enable the prediction of activity. Structure of compound anti-hepatitis activity topological parameters are listed in table1 .on novel bis (L-amino acid)ester prodrugsof 9- [2-(phosphonomethoxy)ethyl] adenine (PMEA) were earlier Independent variables are co-related with anti-hepatitis of a series of novel bis (L-amino acid)ester prodrugs of 9- [2-(phosphonomethoxy) ethyl] adenine (PMEA) results are given in table 2 the regression parameters for a number of correlations along with their qualities are shown in table 3 the established activities for the obtained excellent regression are tabulated in table 4.

Table-1- Chemical structure and anti-hepatitis novel bis(L-amino acid) ester prodrugs of 9-[2-(phosphonomethoxy)ethyl]adenine (PMEA) with improved anti-HBV activity compounds

Com	R	X	n
1	Methyl	O	2
2	Isopropyl	O	2
3	2-Methylpropyl	O	2
4	Benzyl	O	2
5	H	S	2
6	Methyl	S	2
7	Isopropyl	S	2
8	2-Methypropyl	S	2
9	Benzyl	S	2
10	Isopropyl	O	1
11	2-Methypropyl	O	1
12	Benzyl	O	1

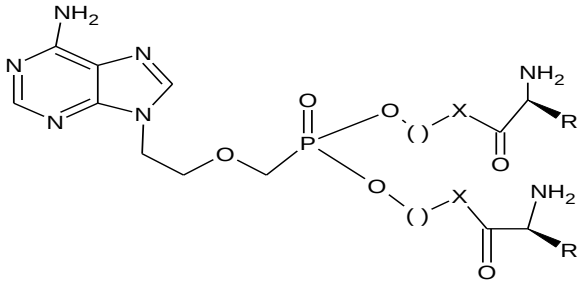

Fig-1

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The first step in multiple regression analysis is to investigate collinearity between molecular descriptor as well as to investigate the correlation of molecular descriptor with the activity from it is clear that there is strong auto correlation exist between LOC and BAC, Mp and Mi, GMTI and Mi,GMTI and BAC .It can be seen That the activity (IC_{50}) shows a mark of relationship with BAC, IR other parameters give significant correlation with activity.

During the process of successive regression analysis we observed that individually all topological parameters Show poor correlation with anti-hepatitis activity. Physiochemical parameters shows the poor correlation individually with activity Me and Mi represents poor correlation with activity analysis of results obtained from biparametric correlation shows that these results are slightly better than monoparametric correlation

Table2- Calculated, topological descriptors of novel bis(L-amino acid) ester prodrugs of 9-[2-(phosphonomethoxy)ethyl]adenine (PMEA) with improved anti-HBV activity compounds

No.	log	AMW	Sv	Se	Me	Mp	Mi	GMTI	BAC	LOC	IR
1	1.0969	13.918	30.212	37.655	1.107	0.826	1.107	16904	94	2.832	0
2	0.1172	13.717	34.212	41.655	1.096	0.844	1.096	22844	134	2.9	0
3	-1.021	13.918	30.212	37.655	1.107	0.826	1.107	16904	94	2.832	1
4	-0.507	13.42	42.212	49.655	1.079	0.871	1.079	44098	37	0.503	0
5	1.0086	14.216	29.683	37.037	1.089	0.859	1.102	14390	66	2.89	0
6	0.1931	14.864	31.156	37.153	1.093	0.896	1.09	16904	94	2.832	0
7	-0.124	14.563	35.156	41.153	1.083	0.907	1.081	22844	134	2.9	0
8	-0.676	14.864	31.156	37.153	1.093	0.896	1.09	16904	94	2.832	1
9	-0.682	14.119	43.156	49.153	1.069	0.923	1.067	44098	37	0.503	0
10	-0.517	13.812	32.212	39.655	1.102	0.835	1.101	19066	130	2.765	0
11	-0.467	14.038	28.212	35.655	1.114	0.815	1.114	13926	90	2.688	1
12	-0.181	13.485	40.212	47.655	1.083	0.865	1.083	37848	37	0.516	0

Further step wise multiple regression is carried out for the data set of 12 adenine as anti-hepatitis agents.

Activity(IC_{50}) = -0.5759+0.1908LOC

N=12, R^2=0.0930, ,R^2A=0.0023 ,F-Ratio=1.025 1

Activity=-32.9056 -1.1931IR+30.2422Mi

N=12, R^2=0.5979, R^2A=0.5086,F-Ratio=6.691 2

Activity = 3.3360-1.2780IR-0.0931Sv

N=12, R^2=0.6831, R^2A=0.6126, F-Ratio=9.698 3

Eq. 3 needs Further classified so in an attempt to obtain still better regression expression we tried for several triparametric correlation which are statistically significant than earlier correlation and that the one involving Sv,IR. The regression expression for this correlation is found as under.

Activity = 2.6151-1.3614IR-0.0001GMTI-0.0104BAC

N =12,R^2 =0.7970, R^2A =0.7208, F-Ratio =10.468 4

Activity=5.4291-1.4345IR-0.1330Sv-0.0080BAC

N=12, R^2=0.8007,R^2A=0.7260, F-Ratio=10.713 5

Activity= -0.2211+0.8853LOC-1.2516IR-0.0185BAC

N=12, R^2=0.8060, R^2A=0.7332, F-Ratio= 11.078 6

From these results it is established that BAC is an important Parameters for all the best statistically significant expression in this study. In view of above equation(6) LOC,IR,and BAC, is found to be best correlation among eq.-4, 5, and 6. Although eq - 6 has higher R^2 Value but lower F-Ratio. So eq.-6 is more significant among this equation.

Final evidence of our result is obtained by plotting the estimated anti –hepatitis such plots are shown in fig 2, Fig 3 Represent probability distribution ofobservedand predicted inhibitory activity and this

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confirms over 92 % of confidence value in this Analysis.

Table 3- Best models for anti-hepatitis potential of novel bis(L-amino acid) ester prodrugs of 9-[2-(phosphonomethoxy)ethyl]adenine.

Model. No.	Parameter	Ai =1,2,3	Intercept	MSE	R2	AR2	F-Ratio	R	Qvalue
1	IR	-0.7664	0.045	0.5871	0.2771	0.2048	3.833	0.5264	0.8966
2	GMTI	0	0.2926	0.6548	0.1007	0.0108	1.12	0.3173	0.4846
3	LOC	0.1908	-0.5759	0.6577	0.093	0.0023	1.025	0.3049	0.4636
4	Sv	-0.0388	1.1735	0.6579	0.0922	0.0014	1.016	0.3036	0.4615
5	IR Sv	-1.278 -0.0931	3.336	0.4098	0.6831	0.6126	9.698	0.8264	2.0168
6	IR Se	-1.2702 -0.0918	3.93	0.4246	0.6597	0.5841	8.724	0.8122	1.9129
7	IR GMTI	-1.1722 0	1.0574	0.4411	0.6327	0.5511	7.752	0.7954	1.8032
8	IR Mi	-1.1931 30.2422	-32.9056	0.4615	0.5979	0.5086	6.691	0.7732	1.6754
9	LOC IR BAC	0.8853 -1.2516 -0.0185	-0.2211	0.34	0.806	0.7332	11.078	0.8977	2.6405
10	IR Sv BAC	-1.4345 -0.133 -0.008	5.4291	0.34469	0.8007	0.726	10.713	0.8948	2.596
11	IR GMTI BAC	-1.3614 -0.0001 -0.0104	2.6151	0.3478	0.797	0.7208	10.468	0.8927	2.5668
12	IR Se BAC	-1.4435 -0.1354 -0.0084	6.483	0.3602	0.7823	0.7007	9.584	0.8844	2.4555

F = F-Ratio, Se=Square Root of Mean square
R^2A =Adjusted R^2 , R^2= Multiple Correlation coefficient,

Table 4- Observed(obs.), Predicted (pre.)Residual Value Obtained using Eq.6

	Actual	**Predicted**	
Compd	**log Ic**	**log IC**	**Residual**
1	1.097	0.548	0.549
2	0.117	-0.131	0.249
3	-1.021	-0.704	-0.318
4	-0.507	-0.46	-0.047
5	1.009	1.117	-0.109

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6	0.193	0.548	-0.355
7	-0.124	-0.131	0.008
8	-0.676	-0.704	0.028
9	-0.682	-0.46	-0.222
10	-0.517	-0.177	-0.34
11	-0.467	-0.757	0.29
12	-0.181	-0.448	0.267

Res. = Residual = difference between observed and predicted inhibitory activity.

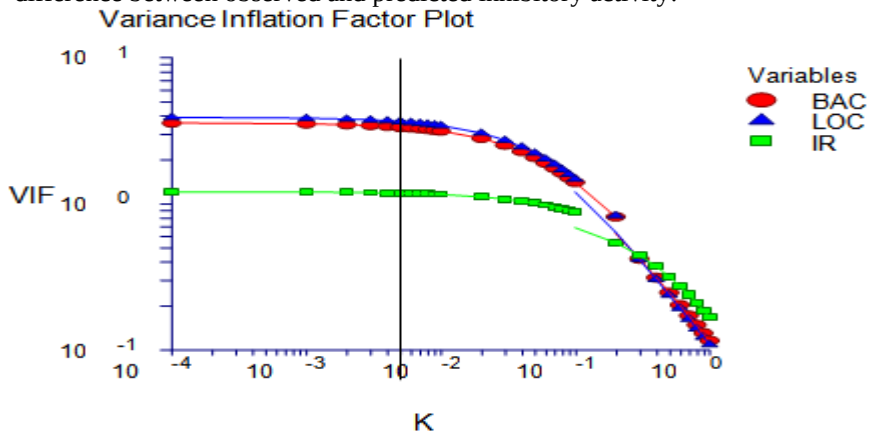

Fig.2- Ridge Regression Report

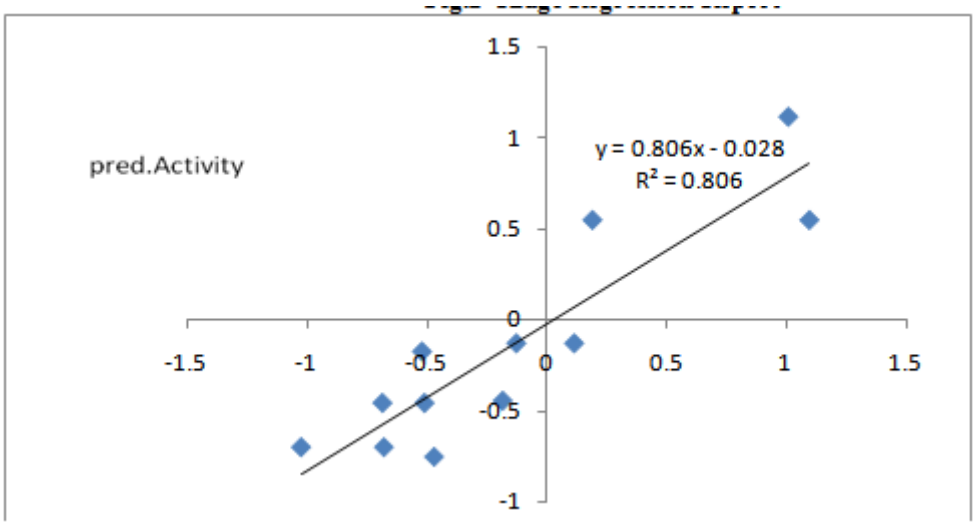

Fig.3- Graph between observed.and predicted inhibitory activity

IV. CONCLUSION

The result and discussion of above analysis leads to the conclusion that topological index BAC play importent role in this modelling. Presence methoxy group and ethyl group also play an important role in this modelling.The results of these QSAR study give raise a QSAR models with good predictive ability for anti-hepatitis activity of theprodrugs of adenineanti-hepatitis B.

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