WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 10, Issue 4, 1184-1190. Research Article ISSN 2277– 7105

QSAR STUDIES OF 2 AMINO-6-ARYLTHIO-9-[2-(PHOSPHONOMETHOXY) ETHYL] PURINE BIS (2'2'2-TRIFLUOROETHYL) ESTERS AS NOVEL HBV -SPECIFIC ANTIVIRAL REAGENTS

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Article Received on
31 January. 2021,

Revised on 21 Feb. 2021,
Accepted on 11 March 2021

DOI: 10.20959/wjpr20214-20031

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ABSTRACT

In this Quantitative structure-activity relationship (QSAR) study 18 derivatives of Esters are taken to correlate and predict the antihepatitis activity against Gram-negative virus. Multiple Linear Regression analysis is used to select the best descriptors and predict the activity of the model selected by cross validation. Our result is based on the correlation between descriptors and experimental inhibitory values. Topological descriptors are used for this analysis. Best model represents higher values of regression coefficient with r^2=0.7946 and r^2adj=0.7314.

KEYWORDS: Antihepatitis, Esters, molecular descriptor, QSAR.

Hepatitis B virus is the Causative agent of both acute and chronic hepatitis B infections. Treatment of HBV infection constitutes one of the current therapeutic challenges in virology. the number of chronic carriers is estimated to be more than 400 million worldwide, with roughly 4 million deaths annually from the resulting cirrhosis and hepatocellular carcinoma. Only a few drugs are currently available for the clinical treatment of hepatitis B. Interferon alfa appears effective but only in 10-30 % of treated patients.[1,2]

Yokota et al have reported that 9-[2-phosphonomethoxy) ethyl] Purine Bis(2,2,2-trifluoroethyl) Esters have a broad spectrum of activity against viruses e.g. HIV,[3] HSV,[4] and HBV activity.[5] Drug designing is a process which is driven by technological

breakthroughs implying advanced experimental and computational methods.[6] Quantitative Structure-activity relationships attempt to correlate chemical structure with activity using statistical approaches.[7] The QSAR models are useful for various purposes including the prediction of activities of untested chemicals.[8,9]

METHODOLOGY

When the synthesis of any compound is difficult then choice or adoption of that path which leads to synthesis of a compound in the direction with higher activity is more fruit-full as selection of compound based on this assumption for synthesis and biological testing proves to be a milestone in the direction of training series fulfilling all requirements to be met for application of extra thermodynamic approach i.e. drug designing, there are two general approaches to drug designing used by industrial scientist, which are; Molecular modification and Rational designing (creating mathematical model)The farmer approach is an older one the fundamental principle of which is the existence of a constellation of essential atoms called a pharmacophore.[10] The second approach namely‘’ Rational design” attempt to create mathematical models of major activity as functional of some molecular attributes.[11] in the present study we have used the second approach for developing the quantitative structure activity relationship, in this study we have used Hansch model with Free and Wilson approach.

Parameters Used

In this study physicochemical and topological parameters are calculated with the help of e-Dragon software. Sum of atomic Vander Waals volumes (Sv), Sum of atomic Sanderson electronegativities (Se),Sum of atomic polarizabilities (Sp), mean atomic Vander waals volume(Mv), mean atomic polarizability(Mp), mean first ionization potential (Mi) are used as physicochemical parameters, while Gutman Molecular Topological Index by valence vertex degrees (GMTIV), Balaban centric index (BAC), lopping centric index(LOC) are topological parameters. IR is indicator parameter the value of which is 1 if methoxy group is present in substituent R other-wise it is 0.

RESULTS AND DISCUSSION

A Set of 18 Esters used as anti-hepatitis agents are given in Table-1. QSAR study of 9- [2-(phosphonomethoxy) ethyl] Purine Bis (2,2,2-trifluoroethyl) Esters were studied earlier by Kourichi Sekiya.[14] and co-workers as the training set of 18 compound. We have used the topological and physiochemical parameters for the QSAR modeling of 9- [2-

(phosphonomethoxy) ethyl] Purine Bis(2,2,2-trifluoroethyl) Esters 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 activity relationship (QSAR) of intercept in pharmacology.[12,13]

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 table 1 here IR indicator parameters. If Methoxy group present it is 1 otherwise it is 0. Independent variables are co-related with anti-hepatitis of a series of 2-Amino -6-arylthio-9- [2-(phosphonomethoxy)ethyl] Purine Bis(2,2,2-trifluoroethyl) Esters results are given in table 2 the regression parameters for a number of correlations along with their qualities are shown in table2 the established activities for the obtained excellent regression are tabulated in table3.

Table 1: General Chemical structure and anti-hepatitis potential of 9- [2-(phosphonomethoxy) ethyl] Purine Bis (2,2,2-trifluoroethyl) Esters.

Compound no.	R	Compound no.	R
1	SPh	10	SPh(3-OMe)
2	SPh(4-Me)	11	SPh(2-OMe)
3	SPh(3-Me)	12	SPh(4-OEt)
4	SPh(2-Me)	13	SPh(4-O-nPr)
5	SPh(4-Et)	14	SPh(4-O-iPr)
6	SPh(4-iPr)	15	SPh(4-O-nBu)
7	SPh(4-No_2)	16	SPh(4-O-iBu)
8	SPh(4-Cl)	17	SPh(4-O-CF_3)
9	SPh(4-OMe)	18	S-(2-naphthyl)

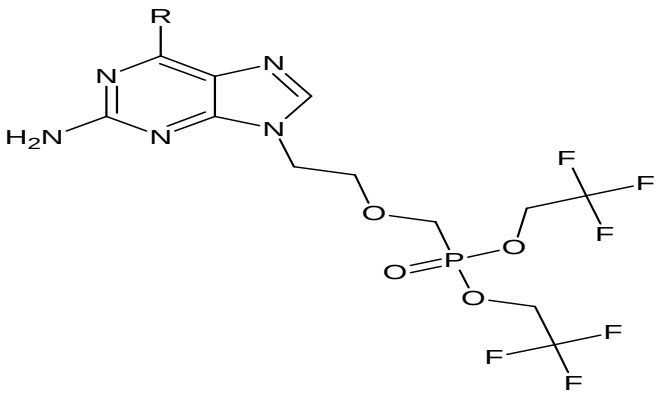

Fig. 1:

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 table- 2 it is clear that there is strong auto correlation exist between Se and Sv, SP and Sv, Sp and Se, GMTV and BAC, GMTV and LOC, BAC and LOC. It can be seen from Table 2 That the activity (IC50) shows a mark of relationship with Se, Sv 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 Structure of compound anti-hepatitis activity topological parameters are listed in table 1 here IR poor correlation individually with activity Mp, MV, and Mi represents poor correlation with activity analysis of results obtained from biparametric correlation shows that these results are slightly better than monoparametric correlation e.g. further step wise multiple regression is carried out for the data set of 18 Esters as anti-hepatitis agents.

Activity (IC50) = -5.8089+ 0.2038SP 1

N=18, R2=0.5211, MSE=0.2588, R2A = 0.4912, F-Ratio=17.411

Activity = 29.8749-26.9301MI+0.0125BAC 2

N=18, R2=0.6550, MSE=0.2269, R2A=0.6090, F-Ratio=14.242

Activity=31.6133+0.0141BAC-28.8947Me 3

N=18, R2=0.6166, MSE=0.2392, R2A=0.5655, F-Ratio=12.061

Eq. 3 needs Further classificated so in an attempt to obtain still better regression expression we tried for several biparametric correlation which are statistically significant than earlier correlation and that the one involving BAC,Mp. The regression expression for this correlation is found as under. than trivarient correlation such as:

Activity= -10.2069+3.1852LOC-0.2534IR+0.1292SP 4

N=18, R2=0.7190, MSE=0.212, R2A=0.6588, F-Ratio= 11. 941

Activity=28.482-25.6129MI+0.0118BAC-0.2262IR 5

N=18, R2=0.7103, MSE=0.2152, R2A=0.6482, F-Ratio=11.443

Table 2: Calculated, topological descriptors of 2 Amino-6-arylthio-9-[2-(phosphonomethoxy) ethyl] purine Bis (2'2'2-trifluoroethyl) Esters.

No.	log	Sv	Se	Sp	Mv	Mp	Mi	GMTIV	BAC	LOC	IR
1	0.05	30.618	40.156	28.017	0.875	0.8	1.161	109520	99	2.091	0
2	0.06	31.618	41.156	29.017	0.878	0.806	1.157	116472	118	2.07	0
3	0.09	31.618	41.156	29.017	0.878	0.806	1.157	117032	118	2.07	0
4	0.08	31.618	41.156	29.017	0.878	0.806	1.157	116424	118	2.07	0
5	0.4	32.618	42.156	30.017	0.882	0.811	1.152	124144	123	2.104	0
6	0.98	33.618	43.156	31.017	0.885	0.816	1.148	131848	144	2.083	0
7	0.52	32.806	43.971	29.551	0.863	0.778	1.167	141310	144	2.083	0
8	0.12	31.709	41.422	29.256	0.881	0.813	1.161	121686	118	2.07	0
9	0.03	32.333	42.484	29.471	0.874	0.797	1.158	127628	123	2.104	1
10	0.04	32.333	42.484	29.471	0.874	0.797	1.158	129028	123	2.104	1
11	0.08	32.333	42.484	29.471	0.874	0.797	1.158	127508	123	2.104	1
12	0.64	33.333	43.484	30.471	0.877	0.802	1.154	136052	128	2.137	0
13	0.87	34.333	44.484	31.471	0.88	0.807	1.15	145236	133	2.171	0
14	0.29	34.333	44.484	31.471	0.88	0.807	1.15	144508	149	2.117	0
15	1	35.333	45.484	32.471	0.883	0.812	1.146	155196	136	2.222	0
16	0.84	35.333	45.484	32.471	0.883	0.812	1.146	154452	154	2.151	0
17	0.06	34.273	46.847	30.426	0.857	0.761	1.187	172148	172	2.096	0
18	0.09	33.904	42.829	31.562	0.892	0.831	1.143	124214	82	1.973	0

The most significant model in the study is obtained as:

Activity = 112.5458-13.7424SV+15.4457SP+275.9520MV-457.2497MP 6

N =18, R2 =0.7946, MSE=0.188, R2A =0.7314 F –Ratio =12.574

From these results it is established that LOC is an important Parameters for all the best statistically significant expression in this study. In view of above equation (6) SV ,SP, MV, and MP is found to be best correlation among eq.-4, 5 , and 6 Although eq. -6 has higher R2 Value but lower MSE valueSS. So eq.-6 is more significant among these equations.

Final evidence of our result is obtained by plotting the estimated anti –hepatitis such plots are shown in Fig.2 Represent probability distribution of IC_{50} with their residual Value and this confirms over 97% of confidence value in this Analysis.

Table 3: Obtained Predicted (pre.) log IC_{50} and Residual Value with Observed (obs.) log IC_{50}.

Compd. No.	Obs. log IC_{50}	Pred. log IC_{50}	Residual	Compd. No.	Obs. log IC_{50}	Pred. log IC_{50}	Residual
1	0.05	0.18	-0.13	10	0.04	0.166	-0.126
2	0.06	-0.032	0.092	11	0.08	0.166	-0.086
3	0.09	-0.032	0.122	12	0.64	0.411	0.229
4	0.08	-0.032	0.112	13	0.87	0.656	0.214
5	0.4	0.489	-0.089	14	0.29	0.656	-0.366
6	0.98	0.734	0.246	15	1	0.901	0.099
7	0.52	0.554	-0.034	16	0.84	0.901	-0.061
8	0.12	0.036	0.084	17	0.06	0.026	0.034
9	0.03	0.166	-0.136	18	0.09	0.294	-0.204

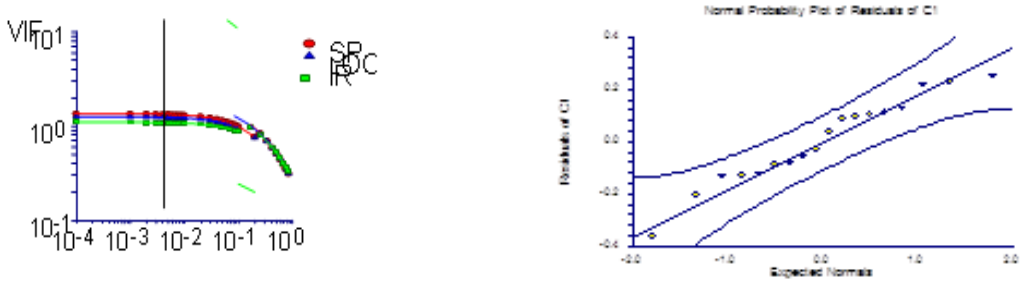

Fig. 2: Variance Inflation Factor Plot.

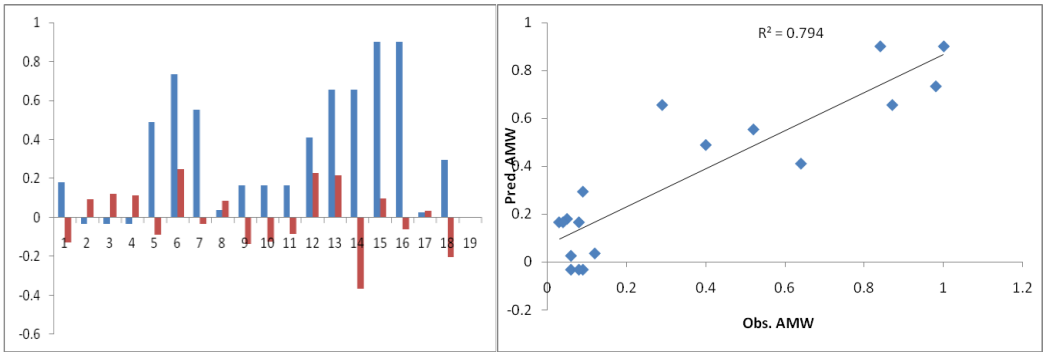

Fig. 3: Plot of the cross validation predicted activities against the corresponding experimental values for the different employed regression model

CONCLUSION

The result and discussion of above analysis leads to the conclusion that topological index LOC play an important role in this modeling. Presence of Methoxy group has also played an important role in this modelling.

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