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Qsar studies of substituted diterpenesas selective dehydroandrogr apholide and andrographolide derivatives as anti-hepatitis b virus agents

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ABSTRACT: The anti-HBV (Hepatitis B virus) activity of a series of substituted diterpenes as specific dehydroandrographolide and andrographolide derivatives was investigated using a quantitative structure-activity relationship (QSAR) analysis. The burden eigenvalues and 2D autocorrelation descriptors, among other types of descriptors, were used to establish a quantitative relationship between anti-HBV activity and structural properties. According to a multivariate linear regression study, Eq. 7's penta-parametric model is the best at predicting the logIC50 activity of the current set of compounds. The best QSAR model has the following results: R2 = 0.8612, Q-ratio = 4.867, F-ratio = 40.934 and N = 39. The leave-one-out (LOO) cross validation method using Ridge regression analysis was used in the future to confirm this model.

KEYWORDS: QSAR analysis, anti-Hepatitis B virus activity, 2D QSAR, LOO, Multivariate analysis.

I. INTRODUCTION

Hepatitis B virus (HBV)-related diseases are a severe concern that has afflicted over 2 billion people globally. Cirrhosis and hepatocellular carcinoma affect about 360 million people who are chronically afflicted.[1] Current hepatitis B virus therapies, which also include influenza vaccine, immunomodulators, interferon-a, polyethylene glycol interferon-a, and nucleoside drugs, still are unsatisfying due to high recurrence, drug resistance, as well as inescapable side effects such as influenza-like disease, myalgia, migraine, neutrophilic granulocyte and blood platelet dramatic drop. [2–5]As a result, it's exciting to look into
new medication classes with various antiviral target s and mechanisms for anti HBV goals. **Hao Chen a nd coworkers** have reported on advancements in th e treatment of hepatitis B virus by the use of anti H BV inhibitors. They have synthesized a series of de hydroandrographolide (1a) and andrographolide derivatives with anti-HBV activity.

Natural products have a variety of skeletons and bioactivities, providing promising candidates with new targets and mechanisms for anti-HBV drug development.[6–10] 17 Andrographis paniculata have been a well Chinese medication which appears in every ed ition of the Chinese Pharmacopoeia. It is commonl y used for anti inflammatory, antipyretic, and detox ifying reasons. The primary active ingredients of A ndrographis
paniculata, dehydroandrographolide (1a) and andrographolide (1b, Fig. 1), have a variety of biological actions, comprising antiinflammation, antiviral, anticancer, anti-bacterium, hepatoprotection, and analgesia. [19–27].

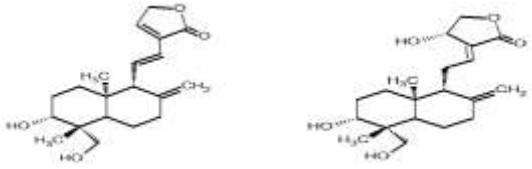

Fig. 1 (1a) (1b)

The quantitative structure-activity relationship technique is now regarded as a scientifically valid strategy for estimating and characterising the biological activities of untested compounds. These have grown inextricably linked to a pharmaceutical sector, from lead finding and refinement through lead generation and computer-aided drug design. An increasing tendency is to employ QSAR initially in the drug development process as a screening and refinement technique to exclude from further development compounds with no drug-like characteristics or molecules expected to provoke a hazardous reaction. The basic

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principle of QSAR is that changes in the biological activity of a group of compounds targeting a common mode of action are linked by changes in their structural, physical, and chemical characteristics.

The current study attempted to model the anti-HBV activity logIC50 of a set of 43 diterpene as selective dehydroandrographolide and andrographolide derivatives these derivatives have wide range of biological activity for hepatitis B virus. The model was created by combining a few Burden eigenvalues, Drug-like indices, 2D autocorrelations descriptors that are easy to calculate and though successful in predicting biological activity. The goal of this research is to use the multivariate regression approach to create QSAR models and investigate the correlations betw een actual anti HBV activity and estimated chemica l descriptors of 43 diterpene as selective dehydroan drographolide and andrographolide derivatives from the hepatitis B virus. In fact 2D autocorrelations and Burden eigenvalues parameters have been very successfully used by us in modeling different activities of drug molecules. A QSAR sequence was established using multiple linear regression (MLR) and cross-validation techniques to predict anti-HBV activity in a series of dehydroandrographolide and andrographolide derivatives as powerful agents against hepatitis B virus.

II. BIOLOGICAL ACTIVITIES

Every one of the compounds have been tested for anti-HBV activity inside a series of diterpene as selective dehydroandrographolide and andrographolide derivatives as potent agents against hepatitis B virus are given in the form of IC_{50}(µM), which was established as first converted to the logarithms of $LogIC_{50}$ value, which is used as dependent variable and directly taken from of the work of Hao Chen and coworkers.[28]

III. PRESENTATION OF DATA

In present study, Table-1 shows the structure with biological activity (anti-HBV) while Table- 2 shows the biological (anti-HBV) activity in the form of $LogIC_{50}$ and calculated molecular descriptors; Burden eigenvalues, Drug-like indices, 2D autocorrelations descriptors and Table-3 shows the correlation matrix between the descriptors which are used in the present study. Table 4 is the regression statistical descriptors while Table-5 is the cross- validated statistical description of developed models. Table-6 shows the predicted and observed biological activity with residuals while Table-7 is the Ridge analysis parameters**.** Fig-2- shows the graph plotted between the observed and calculated biological activity while the Fig-3 is the graph plotted between the observed and residual to illustrate the systemic error and Fig-4 is the graph plotted between VIF and K.

TABLE 1: SUBSTITUTED DITERPENES AS SELECTIVE DEHYDROANDROGRAPHOLIDE AND A NDROGRAPHOLIDE DERIVATIVES

1	2	3
4	5	6
7	8	9

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10	11	12
13	14	15
16	17	18
19	20	21
22	23	24
25	26	27
28	29	30

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31	32	33
34	35	36
37	38	39
40	41	42
43		

TABLE-2 **CALCULATED VALUES OF PARAMETERS ALONG WITH THEIR BIOLOGICAL ACTIVITY**

S.No.	LOGIC50	SpMax3_Bh(s)	SpMin4_Bh(v)	SpMin7_Bh(v)	SpMin1_Bh(s)	SpMax2_Bh(s)	GATS6m	DLS_05
1	1.354108	7.232	0.969	0.506	0.848	7.269	0.952	0.5
2	1.733197	7.235	1.042	0.43	0.844	7.269	0.968	0.5
3	1.164353	7.235	1.344	0.764	0.844	7.432	1.19	0.5
4	1.012837	7.235	1.401	0.929	0.844	7.432	0.981	0.5
5	2.133539	7.235	1.366	0.78	0.844	7.432	0.448	0.5
6	1.344392	7.235	1.26	0.751	0.845	7.431	0.882	0.5
7	0.968483	7.235	1.231	0.779	0.845	7.431	0.949	0.5
8	1.344392	7.235	1.229	0.765	0.845	7.431	0.995	0.5
9	1.563481	7.424	1.396	0.94	0.845	7.432	1.113	0.5
10	1.841985	7.235	1.184	0.53	0.844	7.433	0.934	0.5
11	2.383815	7.431	1.443	0.967	0.857	7.431	0.908	0.5
12	2.267172	7.431	1.436	0.926	0.857	7.431	1.005	0.5
13	2.658011	7.433	1.306	0.745	0.856	7.454	0.888	0.5
14	2.017033	7.437	1.478	1.147	0.858	7.607	0.683	0.5

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15	1.668386	7.235	1.342	0.764	0.845	7.432	1.19	0.5
16	1.348305	7.235	1.4	0.929	0.845	7.432	0.981	0.5
17	1.212188	7.235	1.256	0.752	0.846	7.431	0.882	0.5
18	1.330414	7.235	1.228	0.779	0.846	7.431	0.949	0.5
19	1.371068	7.235	1.226	0.766	0.846	7.431	0.995	0.5
20	1.313867	7.235	1.251	0.751	0.846	7.431	0.882	0.5
21	1.644439	7.235	1.184	0.532	0.845	7.433	0.934	0.5
22	1.841985	7.235	1.195	0.608	0.845	7.432	0.908	0.5
23	1.595496	7.431	1.294	0.98	0.846	7.435	0.802	0.5
24	1.487138	7.265	1.351	0.773	0.85	7.432	1.138	0.5
25	1.725095	7.265	1.4	0.923	0.85	7.432	0.946	0.5
26	1.584331	7.265	1.264	0.772	0.85	7.431	0.812	0.5
27	1.401401	7.265	1.213	0.775	0.85	7.431	0.93	0.5
28	0.908485	7.265	1.209	0.773	0.85	7.431	1.244	0.5
29	1.334454	7.265	1.256	0.771	0.85	7.431	0.792	0.5
30	1.647383	7.265	1.143	0.443	0.85	7.433	0.924	0.5
31	1.843855	7.265	1.158	0.619	0.85	7.432	0.851	0.5
32	1.597695	7.433	1.306	0.742	0.852	7.454	0.888	0.5
33	2.658011	7.432	1.327	0.753	0.852	7.432	0.833	0.5
34	1.677607	7.437	1.393	1.095	0.852	7.608	0.734	0.5
35	1.342423	7.437	1.465	1.144	0.853	7.607	0.683	0.5
36	2.419956	7.423	0.972	0.553	0.859	7.433	0.952	0.5
37	1.127105	7.235	0.971	0.542	0.85	7.433	0.952	0.5
38	2.227887	7.423	1.085	0.473	0.855	7.434	0.952	0.5
39	1.710117	7.423	1.043	0.485	0.855	7.434	0.968	0.5
40	2.187521	7.268	1.249	0.545	0.848	7.277	0.868	0.5
41	2.595496	7.256	1.252	0.549	0.848	7.269	0.896	1
42	1.365488	7.268	0.928	0.544	0.849	7.303	0.931	0.5
43	1.892095	7.232	0.958	0.48	0.876	7.269	1.147	1

Detailed Name of Descriptors

S.No.	Name of Descriptors	Detailed Name of Descriptors[37]
1	SpMax3_Bh(s)	largest eigenvalue n. 3 of Burden matrix weighted by I-stat.
2	SpMin4_Bh(v)	Smallest eigenvalue n. 4 of Burden matrix weighted by van der Waals volume.
3	SpMin7_Bh(v	Smallest eigenvalue n. 7 of Burden matrix weighted by van der Waals volume.
4	SpMin1_Bh(s)	Smallest eigenvalue n. 1 of Burden matrix weighted by I-state.
5	SpMax2_Bh(s)	Largest eigenvalue n. 2 of Burden matrix weighted by I-state.
6	GATS6m	Geary autocorrelation of lag 6 weighted by mass.
7	DLS_05	modified drug-like score from Zheng et al. (2 rules)

IV. RESULTS AND DISCUSSION

In order to understand the experimental biological activity data of 43 substituted diterpenes as selective dehydro andrographolide and andrographolide derivatives on theoretical basics, we
established a QSAR between their in anti HBV acti vity and descriptors coding for moleculardescriptor s; Burden eigenvalues(SpMax3_Bh(s), SpMin4_Bh (v), SpMin7_Bh(v),SpMin1_Bh(s),SpMax2_Bh(s), Drug-like indices(DLS_05), 2D autocorrelations(GATS6m) descriptors of the molecules under consideration using Hansch and Fujita[35-36].

In the present study, a data set of 43 substi tuted diterpenes as selective dehydroandrographoli de and andrographolide derivatives was subjected MLR analysis for model generation. The reference drugs were not included in model development as they belong to different structural series. Inhibitory activity data determined as IC_{50} were first transformed to the logarithms of molar $logIC_{50}$, Table-4.9.2 which was used as a dependent variable in the QSAR study. Different structural molecular descriptors were used as independent variable and were correlated with biological activity.

Developing a QSAR model requires a diverse set of a data and there by a large number of descriptors have to be considered descriptors are numerical values that encode different structural features of the molecules selection of a set of

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appropriate descriptors from a large number of them requires a method, which is able to discriminate between the parameters. Pearson's correlation matrix has been performed on all descriptors by using NCSS statistical Software[31]. The analysis of the matrix revealed seven descriptors for the development of MLR model. The value of descriptors selected for MLR model are presented in Table 2 these parameters are calculated using the software dragon supplied by Vcc lab[30].

The dissert molecular descriptors independe nt variables like molecular descriptors; Burden eige nvalues, Drug like indices,2D autocorrelations desc riptors are calculated for substituted diterpenes as s elective dehydroandrographolide and andrographoli de derivatives presented in Table 3.

Table 3 CORRELATION MATRIX

	LogIC50	SpMax3_Bh(s)	SpMin4_Bh(v)	SpMin7_Bh(v)	SpMin1_Bh(s)	SpMax2_Bh(s)	GATS6m	DLS_05
LOGIC50	1							
SpMax3_Bh(s)	0.50394	1						
SpMin4_Bh(v)	0.071853	0.295292	1					
SpMin7_Bh(v)	-0.14036	0.392619	**0.849212**	1				
SpMin1_Bh(s)	0.43184	0.459088	-0.187904	**-0.042688**	1			
SpMax2_Bh(s)	-0.10921	0.46984	0.581174	0.699945	**0.009511**	1		
GATS6m	-0.2814	-0.247336	-0.228809	-0.26076	0.048858	-0.342622	1	
DLS_05	0.280382	-0.148207	-0.208473	-0.259488	0.462745	-0.459492	0.147917	1

Preliminary analysis was carried out in terms of correlation analysis (Table-4.9.3). A correlation matrix constructed for biological activity is presented in Table 3. The correlations of different descriptors with biological activity are presented in Table-3. In general, high collinearity interrelationship is observed between SpMin4_Bh(v) and SpMin7_Bh(v) (r=**0.849212)** and low interrelationship is observed between SpMin1_Bh(s) and SpMax2_Bh(s)(r=**0.009511).** The correlation matrix indicated the predominance of molecular parameters in describing the biological activity of synthesized compounds. The data presented in Table-3 demonstrated the low co-linearity between the parameters (r<8) indicated that these parameters could be combined to get multiples regression (MLR) models.

Validation is a crucial aspect of any QSAR analysis. The statistical quality of the resulting models as depicted in Table-4.9.4 are determined by R^2= regression coefficient, MSE= means standard error of estimations, F-ratio Fisher's ratio and Q=√R/MSE, Quality factor. After performing regression analysis, we have adopted maximum R^2 method and followed stepwise regression analysis. The result have show that for the set of 43 compounds mono-parametric regression start giving statistically significant model. The best models are given below.

The data on Burden eigenvalues, drug-like indices, and 2D autocorrelation descriptors was analysed using regression (Table-4.9.4), and the best mono-parametric model with Burden eigenvalues (SpMax3_Bh(s)) descriptor is as follows.

The regression analysis gave mono parametric models. Out of which one contain SpMax3_Bh(s) was found to give good results, the model obtained is as follows

$LogIC_{50}$=-17.6976+2.6527 (±0.7101)SpMax3_Bh(s)

N=43, $\mathbf{R^2}$=0.254, $\mathbf{AR^2}$=0.2358, MSE=0.1593,F-ratio=13.957, Q-value=1.262 ……Eq-1

Here N is the number of compounds, MSE is the means square error of estimation, R2 is the regression coefficient, AR2 is adjusted Regression coefficient, F-ratio and Q=$\sqrt{R2}$/MSE; Pogliani' s Quality factor.

However to have better model we carried out several multi parametric correlation and those which are statistically significant are presented in Table 4.9.4.

2 $LogIC_{50}$=-5.6801+3.7507 (±0.7257) SpMax3_Bh(s) -2.6989 (±0.8380) SpMax2_Bh(s)

N=43, R2=0.4076, AR2= 0.3779, MSE=0.1297, F-ratio=13.759, Q-value=1.772 …Eq-2

3 $LogIC_{50}$= -26.1911+3.6642 (±0.6112) SpMax3_Bh(s)+ 2.4273 (±0.6291) SpMin4_Bh(v) -2.5969 (± 0.5069) SpMin7_Bh(v)

N=43, R^2=0.5579, AR^2=0.5239, MSE=0.09927, F-ratio=16.408, Q-value=2.3706 …Eq-3

4 $LogIC_{50}$=-27.5191+3.7445 (± 0.5637) SpMax3_Bh(s) + 2.3958 (±0.5795) SpMin4_Bh(v) -2.4108 (±0.4715) SpMin7_Bh(v)+ 1.2305 (±0.4359) DLS_05

N=43, R2=0.6346, AR2= 0.5961, MSE= 0.08422, F-ratio=16.498, Q-value=2.745 …Eq-4

5 $LogIC_{50}$=-40.1045+2.3691 (±0.6248) SpMax3_Bh(s)+ 2.9174 (±0.5609) SpMin4_Bh(v) -

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2.8243 (± 0.4362) SpMin7_Bh(v)+ 27.9563 (±8.5945) SpMin1_Bh(s) -0.8908 (±0.3084) GATS6m
N=43, R2= 0.6946, AR2= 0.6533, MSE= 0.072302, F-ratio=16.828, Q-value=3.0995…….Eq-5
For biological activity (anti-HBV) against Hepatitis B virus (HBV), the developed QSAR model Eq-2 to Eq-5 describes the importance of SpMax3_Bh(s), SpMax2_Bh(s), SpMin4_Bh(v), SpMin7_Bh(v), DLS_05, SpMin1_Bh(s), and GATS6m. In these case, the positive correlation was observed between SpMax3_Bh(s), SpMin4_Bh(v), SpMin4_Bh(v), DLS_05 SpMin1_Bh(s) and biological activity (anti-HBV) against Hepatitis B virus (HBV), while negative correlation is observed between SpMin7_Bh(v) and GATS6m with biological activity. The regression coefficient between the Burden eigenvalues, Drug-like indices, 2D autocorrelations descriptors and the biological activity in Eq-2 to Eq-5(R^2=0.4076, R^2=0.5579,R^2=0.6346 and R^2= 0.6946) with the variance of Eq-2 to Eq-5 (40.76%,55.79%,63.46% and 69.46%) which is good but not best. So further addition of descriptor take place for getting statistically significant models.
$LogIC_{50}$=-26.797+2.8086 (± 0.6062)SpMax3_Bh(s)+ 2.8530 (±0.5229) SpMin4_Bh(v) -2.3359 (±0.4481) SpMin7_Bh(v)+ 25.7828 (±8.0475) SpMin1_Bh(s) -1.9967 (±0.7733) SpMax2_Bh(s) -1.0265 (±0.2920) GATS6m
N=43, **R^2=0.7423**, AR^2=0.6993, MSE= 0.06269 F-ratio=17.283, Q-value=3.441 ……..Eq-6
For biological activity (anti-HBV) against Hepatitis B virus (HBV), the developed QSAR model Eq-6 describes the importance of SpMax3_Bh(s), SpMax2_Bh(s), SpMin4_Bh(v), SpMin7_Bh(v), DLS_05, SpMin1_Bh(s), and GATS6m. In these case, the positive correlation was observed between SpMax3_Bh(s), SpMin4_Bh(v), SpMin4_Bh(v), DLS_05 SpMin1_Bh(s) and biological activity (anti-HBV) against Hepatitis B virus (HBV), while negative correlation is observed between SpMin7_Bh(v) and GATS6m with biological activity. It is important to note that Eq-1 To Eq-6 was derived using the entire data set as four serious outliers in the data set and after the removing these outliers the QSAR model no -7 is developed which is statistically significant.
After deletion of Outlier Compounds no.
$LogIC_{50}$=-46.9561+3.4498 (± 0.4868) SpMax3_Bh(s)+ 3.2101 (±0.4113) SpMin4_Bh(v) -3.3224 (±0.3416) SpMin7_Bh(v)+ 26.9233 (±6.1305) SpMin1_Bh(s) -0.9921 (±0.2233) GATS6m
N=39, **R^2=0.8612**, AR^2=0.8401, MSE=0.03635, **F-ratio=40.934**, **Q-ratio=4.867 ……..Eq-7**
The developed QSAR model Eq-7 is statistically significant with high regression coefficient between the descriptors and biological activity. In developed model Eq-7 as the positive coefficient value of SpMax3_Bh(s), SpMin4_Bh(v), SpMin1_Bh(s) increases the biological activity increases while as the negative coefficient value of SpMin7_Bh(v) and GATS6m decreases the biological activity becomes increases. Initial regression analysis indicated that of seven molecular descriptors used, in combination with other molecular descriptors. SpMin4_Bh(v) plays a dominant role in shaping biological activity (the greatest value of regression coefficient). The positive coefficient of SpMin4_Bh(v) indicates that the biological activity increase as the magnitude of those descriptors increases(Eq-3 to Eq-7).
Finally , in order to confirm which out of the proposed models is the most appropriated for modeling the biological activity (anti-HBV) we calculated the pogliani' s quality factor Q which is ratio of R2 and MSE. These Q value for aforementioned correlation are found (Eq.1 to Eq-7) as 1.262, 1.772, 2.3706, 2.745, 3.0995, 3.441 and 4.867 respectively. The highest value in case of **penta parametric model** expressed by Eq.7 as 4.867. So **Eq-7** is the best model for modeling anti-Hepatitis B virus (HBV) activity with Burden eigenvalues, 2D autocorrelations descriptors.

TABLE 4 REGRESSION PARAMETERS AND QUALITY OF CORRELATIONS

Model No.	parameter	Ai,i=1,2,3….	Intercept	MSE	AR2	R2	F-Ratio	Q-Value=√R2/MSE
1	SpMax3_Bh(s)	A1=2.6527 (±0.7101)	-17.6976	0.1593	0.2358	0.254	13.957	1.262
3	SpMax3_Bh(s) SpMax2_Bh(s)	A1=3.7507 (±0.7257) A2=-2.6989	-5.6801	0.1297	0.3779	0.4076	13.759	1.772

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		(±0.8380)						
5	SpMax3_Bh(s) SpMin4_Bh(v) SpMin7_Bh(v)	A1=3.6642 (±0.6112) A2=2.4273 (±0.6291) A3=-2.5969 (± 0.5069)	-26.1911	0.0992	0.5239	0.5579	16.408	2.3706
8	SpMax3_Bh(s) SpMin4_Bh(v) SpMin7_Bh(v) DLS_05	A1=3.7445 (± 0.5637) A2=2.3958 (±0.5795) A3=-2.4108 (±0.4715) A4=1.2305 (±0.4359)	-27.5191	0.0842	0.5961	0.6346	16.498	2.745
12	SpMax3_Bh(s) SpMin4_Bh(v) SpMin7_Bh(v) SpMin1_Bh(s) GATS6m	A1=2.3691 (±0.6248) A2=2.9174 (±0.5609) A3=-2.8243 (± 0.4362) A4=27.9563 (±8.5945) A5=-0.8908 (±0.3084)	-40.1045	0.07230	0.6533	0.6946	16.828	3.0995
16	SpMax3_Bh(s) SpMin4_Bh(v) SpMin7_Bh(v) SpMin1_Bh(s) SpMax2_Bh(s) GATS6m	A1=2.8086 (± 0.6062) A2=2.8530 (±0.5229) A3=-2.3359 (±0.4481) A4=25.7828 (±8.0475) A5=-1.9967 (±0.7733) A6=-1.0265 (±0.2920)	-26.797	0.06269	0.6993	0.7423	17.283	3.441
19	SpMax3_Bh(s) SpMin4_Bh(v) SpMin7_Bh(v) SpMin1_Bh(s) GATS6m	A1=3.4498 (± 0.4868) A2=3.2101 (±0.4113) A3=-3.3224 (±0.3416) A4=26.9233 (±6.1305) A5=-0.9921 (±0.2233)	-46.9561	0.03635	0.8401	0.8612	40.934	4.867

In order to obtain further support in favor of our result we have also used the cross-validation process. We have undertaken a cross validation methodology for deciding the predictive power of the proposed model. It is necessary for a best model to have good statistics but this is not sufficient for good predictive potential.

The various cross validation parameters, calculated for the proposed models, are presented on Table-4.9.5 and are discussed below.

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TABLE-5 CROSS VALIDATION STATISTICAL PARAMETERS

MODEL NO	N	PRESS	SSY	PRESS/SSY	R^2	Adj R^2	R2CV	PSE	SPRESS
3	43	3.871832	4.886933	0.7922	0.5579	0.5239	0.2078	0.30007	0.315
4	43	3.20062	5.558145	0.5758	0.6346	0.5961	0.4242	0.2728	0.2902
5	43	2.675202	6.083563	0.4397	0.6946	0.6533	0.5603	0.2494	0.2688
6	43	2.257138	6.501627	0.3472	0.7423	0.6993	0.6528	0.2291	0.2503
7	**39**	**1.199588**	**7.440053**	**0.1612**	**0.8612**	**0.8401**	**0.8388**	**0.1753**	**0.1906**

QSAR should be evaluated according to its ability to predict the activity of molecules, which were not used in the original QSAR table, which contains the data, the dependent activity and the independent variables. Such an evaluation can be done by cross-validation method, which is based on 'leave-n-out 'concept. In each step 'N' molecules are randomly or on turn excluded from the QSAR table. The QSAR equation is then calculated and used to predict the activity of these n molecules. The methodology yields cross-validated parameters, PRESS (predictive residual sum of squares), SSY (sum of the square of the response value), R^2 (regression coefficient), R^2_{cv} (overall predictive ability), R^2_A (adjustable $-R^2$) S_{PRESS} (uncertainty of predictive), and PSE(predictive square error). These parameters obtained for the model discussed above is calculated as given in Table4.6.5.

A perusal of Table 4.9.5 shows that in each case PRESS<<SSY and also that PRESS/SSY <0.4 and the value of these ratio lower than 0.1 indicates an excellent model. The PRESS/SSY value for the model- 7, that is, 0.1612 indicates to the best model. The R^2_{cv} values also support these findings. The cross-validated parameters S_{PRESS} is not useful as it similar to the MSE. The other cross-validated parameters viz., PSE is, therefore, used to estimate uncertainty of prediction, the lowest value of PSE for the model-7 establishes it to be the model with best statistics and the best predictive power.

The high R^2_{cv} is indicative of its reliability in predicting the biological activity (anti-HBV). But, the only way to estimate the true predictive power of a model is to test their ability to predict accurately the biological activities of compounds.

Based on the magnitude of residue a close agreement between the observed and calculated anti HBVactivity against Hepatitis B virus (HBV),i s found. Future, the plot of Predicted LogIC_{50}values against Observed LogIC_{50} values also proves the superiority of the model expressed by Eq. No.-7 the results of biological studies of substituted diterpenes as selective dehydroandrographolide and andrographolide derivatives as anti-hepatitis B virus agents are summarized in given below table.

TABLE-6:- RESIDUAL REPORT (FROM EQ.-7)

Comp.no	Obs.	Prd.	Residual
1	1.354	1.309	0.045
2	1.733	1.682	0.051
3	1.164	1.322	-0.157
4	1.013	1.164	-0.151
5	2.134	2.075	0.058
6	1.344	1.428	-0.083
7	0.968	1.175	-0.207
8	1.344	1.17	0.175
9	1.563	1.659	-0.096
10	1.842	1.84	0.002
11	2.384	2.271	0.113
12	2.267	2.289	-0.021
13	2.658	2.569	0.089
14	2.017	2.056	-0.039
15	1.668	1.342	0.326
16	1.348	1.188	0.161
17	1.212	1.439	-0.226

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18	1.33	1.193	0.138
19	1.371	1.184	0.187
20	1.314	1.426	-0.112
21	1.644	1.86	-0.215
22	1.842	1.668	0.174
23	1.595	1.559	0.037
24	1.487	1.631	-0.144
25	1.725	1.48	0.245
26	1.584	1.678	-0.094
27	1.401	1.388	0.014
28	0.908	1.07	-0.161
29	1.334	1.676	-0.341
30	1.844	1.808	0.036
31	2.658	2.553	0.105
32	1.678	1.744	-0.066
33	2.42	2.117	0.303
34	1.127	1.26	-0.133
35	2.228	2.638	-0.41
36	2.188	2.285	-0.098
37	2.595	2.213	0.383
38	1.365	1.223	0.143
39	1.892	1.92	-0.028

Finally, we have plotted a graph between observed $LogIC_{50}$ and predicted in the anti-HBV activity against Hepatitis B virus (HBV). From the best model no. (7) And equations no (Eq-7) to establish the importance of best model of this study.

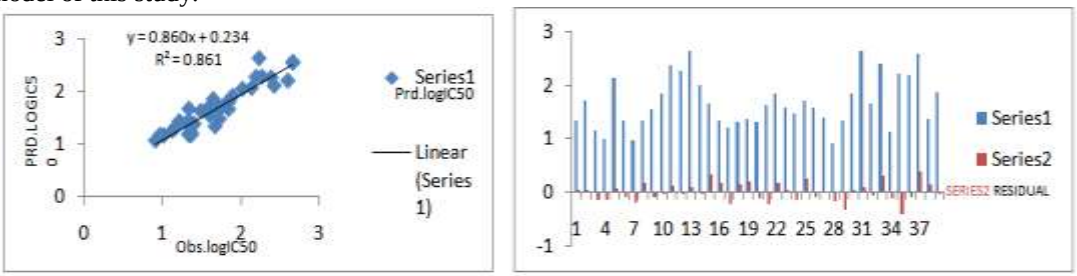

Fig- Graph between predicted and observed LogIC50 values of substituted diterpenesas derivatives (from Eq-7)

Fig2- Plot of the residual values again the experimental observed LogIC50 values

To demonstrate that the suggested models are free of collinearity, we calculated the VIF (variance inflation factor), Eigen values, I condition number (k), and tolerance (T) for all of the independent parameters utilised in the proposed models, and the results are shown in Table 7. Co linearity will be seen for parameters with a VIF value larger than 10. A review of this table reveals that in certain cases, VIF is less than 10, indicating that all of the developed models given to us would be free of co - linearity. Likewise, when I (Eigen value) is greater than 5, the model could suffer from co - linearity. Table 7 demonstrates that I is smaller than 5 for all parameters. As a result, from this perspective, the presented models are likewise free of the problem of collinearity.

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Table- 7 RIDGE ANALYSIS PARAMETERS

Model No.	Parameters used	VIF	Tolerance	Eigenvalue	Condition no.
	SpMax3_Bh(s)	1.7031	0.5872	2.17358	1
7	SpMin4_Bh(v)	3.7322	0.2679	1.375351	1.58
	SpMin7_Bh(v)	3.8173	0.262	0.932393	2.33
	SpMin1_Bh(s)	1.494	0.6694	0.373711	5.82
	GATS6m	1.0871	0.9199	0.144966	14.99

Figure- 4.9.4: plot between VIF and K

V. CONCLUSIONS

From the result and discussion made above, we conclude that the selective dehydroandrographolide and andrographolide derivatives were more active against hepatitis b virus agents.The results of the QSAR study give rise to QSAR models with good predictive ability for biological activity of selective dehydroandrographolide and andrographolide derivatives . Liner regression for the total data set of 43 compounds in the present study with biological activity(anti-HBV) demonstrated that the SpMax3_Bh(s), SpMin4_Bh(v), and SpMin7_Bh(v), SpMin1_Bh(s),GATS6m molecular descriptors appears to be governing factors for the biological potency of synthesized of substituted diterpenesas selective dehydroandrographolide and andrographolide derivatives .

The following conclusions are obtained from this analysis

1. The positive coefficient of SpMax3_Bh(s), SpMin4_Bh(v), SpMin1_Bh(s) suggest that these parameters plays a dominating role in deciding the activity of present set of compounds.
2. The negative coefficient of SpMin7_Bh(v) and GATS6m, suggest that the low or negative value of SpMin7_Bh(v) and GATS6m will favors the biological activity(anti-HBV).

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