e-ISSN: 2248-9126
Vol 6 | Issue 2 | 2016 | 87-93. Print ISSN: 2248-9118

Indian Journal of Pharmaceutical Science & Research

www.ijpsrjournal.com

QSAR STUDY OF SOME ANTI-HEPATITIS B VIRUS AGENTS COMPRISING 4-ARYL-6-CHLORO-QUINOLIN-2-ONES AND 5-ARYL-7-CHLORO-1,4- BENZODIAZEPINES

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ABSTRACT

QSAR analysis on a set of synthesized 4-Aryl-6-chloro-quinolin-2-ones and 5-Aryl-7-Chloro-1, 4-benzodiazepines analogues tested for growth inhibitory antiviral activity was performed by using MLR procedure. The activity contributions of these compounds were determined from regression equation and the validation procedures to analyze the predictive ability of QSAR models were described. The results are discussed on the basis of statistical data. High agreements between experimental and predicted antiviral activity inhibitory values are obtained. The results of this study indicate that the substitution of electron withdrawing group, aromatic ring , polarizability etc. parameters has significant effect on antiviral activity of this class of compounds thus simplifying design of new biological active molecule.

Key Words: QSAR, MLR, Antiviral Activity

INTRODUCTION

Hepatitis B virus (HBV), a member of the hepadnavirus (hepatotropic DNA virus) family, has caused a global health crisis as the ninth leading cause of death in the world by chronically infecting more than 400 million people according to the World Health Organization (WHO).HBV is a fatal disease epidemic in Southeast Asia, Africa and China, where approximately 10% of the populations are chronic carriers. People infected with HBV are at risk of chronic hepatitis, liver failure, cirrhosis, and hepatocellular carcinoma leading to significant mortality and serious long-term morbidity, which are 10 times more numerous than HIV (human immunodeficiency virus) patients. No effective therapy against HBV infection has been fully developed so far and the molecular mechanisms of HBV-mediated hepatocarcinogenesis are still poorly understood. Therefore, continued progress for the effective therapy of chronic HBV infection is still an urgent demand worldwide. Treatment of chronic HBV infection is aimed at suppressing viral replication to the lowest possible level, and thereby to halt the progression of liver disease and prevent the onset of complications. The licensed vaccine against HBV is an effective mean to prevent infection.

A successful example is the national hepatitis B vaccination program in Taiwan of China. But vaccine is not an effective therapeutic strategy to treat established chronic infections when used alone. Two categories of anti-viral drugs have been approved for the treatment of hepatitis B:1,9,12,15 interferon-α (IFN-α) and nucleoside analogues such as lamivudine (3TC), adefovir dipivoxil and entecavir (ETV). However, unresolved critical issues make the current treatment regimens far from satisfactoriness. Relatively low cure rate, dose-dependent side effects and quick accumulation of drug resistant mutants have limited their extensive application.

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The unsatisfactory therapeutic application of current anti-viral drugs has strengthened the urgent demand for novel anti-HBV agents to circumvent the existing therapeutic difficulties. Computational chemistry has developed into an important contributor to rational drug design. The quantitative structure-activity relationship (QSAR) approach pioneered by Hansch and co-workers is a useful tool in correlating the specific biological activity with molecular structural properties of the compounds, which has been proved to be one of the most embraced computational approaches in modern drug discovery. The aim of present work is to derive some statistically significant QSAR models for some anti-hepatitis B virus agents. The results obtained with indispensable structural requirements for bioactivity may contribute to further design of novel anti-HBV agents

MATERIALS AND METHODS

QSAR is the study of the quantitative relationship between the experimental activity of a set of compounds and their physicochemical properties using statistical methods. The experimental information associated with biological activity, which is used as dependent variables in building a QSAR model. In this study, all computational work was performed using E-Dragon software. 2D-QSAR modeling and dataset Apoptosis-inducing activity data EC_{50} (μM) were taken from the published work. The experimental EC_{50} values were evaluated by LI, Zuguang*et al.* in a caspase- based HTS assay in human breast cancer cells ($T_{47}D$). The negative logarithm of the measured EC_{50} (μM) [pEC_{50} = -log (EC_{50})] was used as dependent variable for 2D QSAR analysis and it is listed in Table 1. Since some compounds showed insignificant activity, such compounds were excluded from the dataset. Compounds were sketched using 2D draw application and converted to 3D structures.

Selection of training and test set The dataset of 32 molecules was divided into training set (24 compounds) and test set (8 compounds) by Sphere Exclusion (SE) method for multiple linear regression (MLR using pEC50 activity field as dependent variable and various 2D descriptors as independent variables.

QSAR models were generated using pEC_{50} values as the dependent variable and various descriptors values as independent variables. Statistical measures were used for the evaluation of QSAR models were the number of compounds in regression n, regression coefficient r^2, number of descriptors in a model k, F-test (Fisher test value) for statistical significance F.

MLR analysis

MLR is a method used for modeling linear relationship between a dependent variable Y (pEC_{50}) and independent variable X (2D descriptors). MLR is based on least squares: the model is fit such that sum-of-squares of differences of observed and a predicted value is minimized. MLR estimates values of regression coefficients (R^2) by applying least squares curve fitting method. The model creates a relationship in the form of a straight line (linear) that best approximates all the individual data points. In regression analysis, conditional mean of dependant variable (pEC_{50}) Y depends on (descriptors) X. MLR analysis extends this idea to include more than one independent variable. Regression equation takes the form

$$\boldsymbol{Y = b_1 * x_1 + b_2 * x_2 + b_3 * x_3 + c}$$

Where, Y is dependent variable, 'b' s are regression coefficients for corresponding 'x's (independent variable), 'c' is a regression constant or intercept.

Validation of QSAR model

The best way to evaluate quality of regression model is internal validation of QSAR model. Mostly leave-one out (LOO) cross validation, one object (one biological activity value) is eliminated from training set and training dataset is divided into subsets (number of subsets = number of data points) of equal size. Model is build using these subsets and dependent variable value of the data point that was not included in the subset is determined, which is a predicted value. Mean of predicted will be same for R^2 since all the data point will be sequentially considered as predicted in LOO subset. Same procedure is repeated after elimination of another object until all objects have been eliminated once. LOO cross validation resulted in three statistically significant models for each regression method**.**

Definitive validity of model is examined by mean of external validation also, which evaluates how well equation generalizes. Training set is used to derive an adjustment model that is used after to predict activities of test set members.

Molecular modeling

Conformational search was carried out by systemic conformational search method (grid search), which generates all possible conformations, by systematically varying each of the torsion angles of a molecule by some increment, keeping the bond lengths and bond angles fixed and lowest energy conformers were selected.

All the compounds were aligned by template-based method. In template-based alignment method, a template structure was defined and used as a basis for alignment of a set of molecules.

In this study, all the compounds were aligned against minimum energy conformation of most active compound number using quinazoline ring as template.

Descriptors used in generation of 2D-QSAR models are given in Table 3 with detail description. 2D-QSAR study of 4-anilinoquinozaline derivatives resulted in several QSAR models. Statistically significant QSAR models were selected for discussion is given below.

Nearness of experimental to predicted activity reported in Table 1 also adds to this fact. Contribution charts for all the significant models are presented in Figure 2, which gives percentage contribution of descriptors used in deriving the QSAR models.

After 2D QSAR study by Multiple Linear Regression method using forward-backward stepwise variable selection method, the final QSAR equation developed QSAR/QSPR models was as follows. The highest correlation coefficient ($r \geq 0.8$) between the descriptors as illustrated in Table 2.

With reference to table 3 the selected descriptors are used for monoparamatric QSAR model no.1 development which show the importance of topological descriptor X_3 which is directly proportional with the antiviral activity of 4-Aryl-6-chloro-quinolin-2-ones and 5-Aryl-7-chloro-1, 4- benzodiazepines. The under given model enocoded the information about the structural changes which can be applied over the parent structure. The QSAR model no. 1 reveals the relationship between the monoparametric QSAR model No.1 is given below -

pIC_{50}=1.4686+0.2834X3 **Eq.....1**

From QSAR model Equation no. 1 the low statistical results indicates needs for the development of Triparametic or more multiparamteric QSAR models follow by rule of thumb. The QSAR model no.2 has significant importance in which Wap and X_3 has positive contribution with the antiviral activity while the physicochemical descriptor index of refraction show inverse contribution with antiviral activity of 4-Aryl-6-chloro-quinolin-2-ones and 5-Aryl-7-chloro-1,4-benzodiazepines.. The statistical descriptors are given in Table no.3 (Model No.2).

pIC_{50}= pIC_{50} = -.9103-1.5838E-04*Wap + 0.7576*X3 **Eq……2**

The QSAR model no.3 show their significant statistical importance with quadratic parametric model in which IR and X_0 are directly proportional with the anticancer activity while X_2 are inversely proportional with the anticancer activity.

pIC_{50}=-15.1304+ 11.0610*IR + 1.1888X0 -1.8377X2 **Eq……. 3**

The above described all models are not statistically excellent indicates the deletion of outliers compound whose activity are not uniform and After deleting Comp No.22 and 23 resulting the development of high statistically significant QSAR model no.6 indicates that the IR, MAXDM. Wap and X_0 a major role in the antiviral activity of 4-Aryl-6-chloro-quinolin-2-ones and 5-Aryl-7-chloro-1,4- benzodiazepines..

pIC_{50}=-18.5025+ 16.2255IR + 1.1760MAXDN + 3.9348E-04*Wap + 2.4587X0 -5.0652X2 **Eq……4**

Eq…… 1

The randomization test suggests that the developed model have a probability of less than 1% that the model is generated by chance. Statistical data is shown in Table 3. The observed and predicted pIC_{50} along with residual values are shown in Table 4. The plot of observed vs. predicted activity is shown in Fig. (2). From the plot it can be seen that MLR model is able to predict the activity of training set quite well (all points are close to regression line) as well as external.

Table 1. Experimental and calculated topological descriptors of 4-anilinoquinozaline derivatives

Compound	R_1	pIC_{50}	IR	X_0	X_2	X_3	Wap	MAXDN
1a	H	3.314	1.641	12.535	7.981	6.495	5052	2.163
1b	2-F	2.547	1.624	13.405	8.508	6.968	5883	2.39
1c	2-Cl	3.124	1.647	13.405	8.508	6.968	5883	2.208
2a	H	3.523	1.599	14.82	8.983	7.521	6961	2.313
2b	2-F	3.728	1.587	15.69	9.511	7.999	8008	2.503
2c	2-Cl	4.131	1.606	15.69	9.511	7.999	8008	2.358
3a	H	3.593	1.66	13.242	8.322	6.813	5886	2.277
3b	2-F	3.532	1.647	14.113	8.85	7.286	6815	2.415
3c	2-Cl	4.119	1.673	14.113	8.85	7.286	6815	2.312
4a	H	3.535	1.644	16.397	10.242	7.944	8726	3.116
4b	2-F	3.793	1.634	17.267	10.77	8.416	9957	3.205
4c	2-Cl	3.777	1.656	17.267	10.77	8.416	9957	3.144

5a	H	3.138	1.723	13.742	9.21	7.699	10056	2.345
5b	2-F	3.71	1.703	14.613	9.743	8.136	11517	2.73
5c	2-Cl	3.45	1.729	14.613	9.743	8.136	11517	2.487
6a	H	4.174	1.658	13.405	8.39	7.178	5615	2.437
6b	2-F	4.252	1.641	14.276	8.917	7.656	6512	2.589
6c	2-Cl	3.467	1.664	14.276	8.917	7.656	6512	2.481
7a	H	3.682	1.668	15.69	9.824	7.642	7673	2.937
7b	2-F	3.851	1.653	16.56	10.351	8.12	8798	3.057
7c	2-Cl	3.889	1.675	16.56	10.351	8.12	8798	2.978

Table 2. Correlation matrix between calculated topological descriptors and antiviral activity

	pIC_{50}	**IR**	**X_0**	**X_2**	**X_3**	**Wap**	**MAXDN**
pIC_{50}	1.0000						
IR	-0.0765	1.0000					
X_0	0.3815	-0.1522	1.0000				
X_2	0.2888	0.1133	0.9553	1.0000			
X_3	0.3835	0.1342	0.8716	0.9247	1.0000		
Wap	0.1036	0.4987	0.5988	0.7845	0.8432	1.0000	
MAXDN	0.2874	0.0707	0.8797	0.9042	0.7542	0.5659	1.0000

Table 3. Results of regression analysis

Eq. No.	**QSAR/QSPR Models**	**N**	**R^2**	**R^2adj**	**MSE**	**PRESS**	**R^2cv**	**CV**	**F**
1	pIC_{50} = 1.4686+0 .2834X3	21	0.1471	0.1022	0.1443	3.3036	0.0000	0.1045	3.277
2	pIC_{50} = -.9103-1.5838E-04*Wap + 0.7576*X3	21	0.3147	0.2382	0.1225	2.9180	0.0928	0.0963	4.126
3	pIC_{50} = -15.1304+ 11.0610*IR + 1.1888X0 -1.8377X2	21	0.4149	0.3116	0.1107	3.0604	0.0485	0.0915	4.018
4	pIC_{50} =-17.0172+ 11.3743*IR + 1.2500X0 -2.3668X2 +0.7075X3	21	0.5449	0.4324	0.0091	2.7935	0.1315	0.0831	4.809
5	pIC_{50} = -14.9845+ 14.4636IR + 1.5072MAXDN + 4.3314E-04*Wap + 2.4093X0 -5.1760X2	21	0.6102	0.4803	0.0083	2.4396	0.2415	0.0795	4.697
After deletion of compound no. 17 and 18 as outlier									
6	pIC_{50} = -18.5025+ 16.2255IR + 1.1760MAXDN + 3.9348E-04*Wap + 2.4587X0 -5.0652X2	19	0.7309	0.6274	0.0578	1.9136	0.3157	0.0666	7.061

Table 4. Experimental pEC_{50} and predicted pEC_{50} activity of 4-anilinoquinozaline derivatives after deletion of outliers compound no. 7, 15, 31 and 32

Compound number	Actual pIC_{50}	Predicted pIC_{50}	Residual
1	3.314	3.049	0.265
2	2.547	2.837	-0.29
3	3.124	2.996	0.128
4	3.523	3.838	-0.315
5	3.728	3.743	-0.015
6	4.131	3.881	0.25
7	3.593	3.831	-0.238
8	3.532	3.615	-0.083
9	4.119	3.915	0.204
10	3.535	3.707	-0.172
11	3.793	3.599	0.194
12	3.777	3.884	-0.107
13	3.138	3.305	-0.167
14	3.71	3.45	0.26
15	3.45	3.586	-0.136
16	4.174	3.936	0.238
17	3.682	3.851	-0.169
18	3.851	3.661	0.19
19	3.889	3.925	-0.036

Figure 1. Structure of compounds

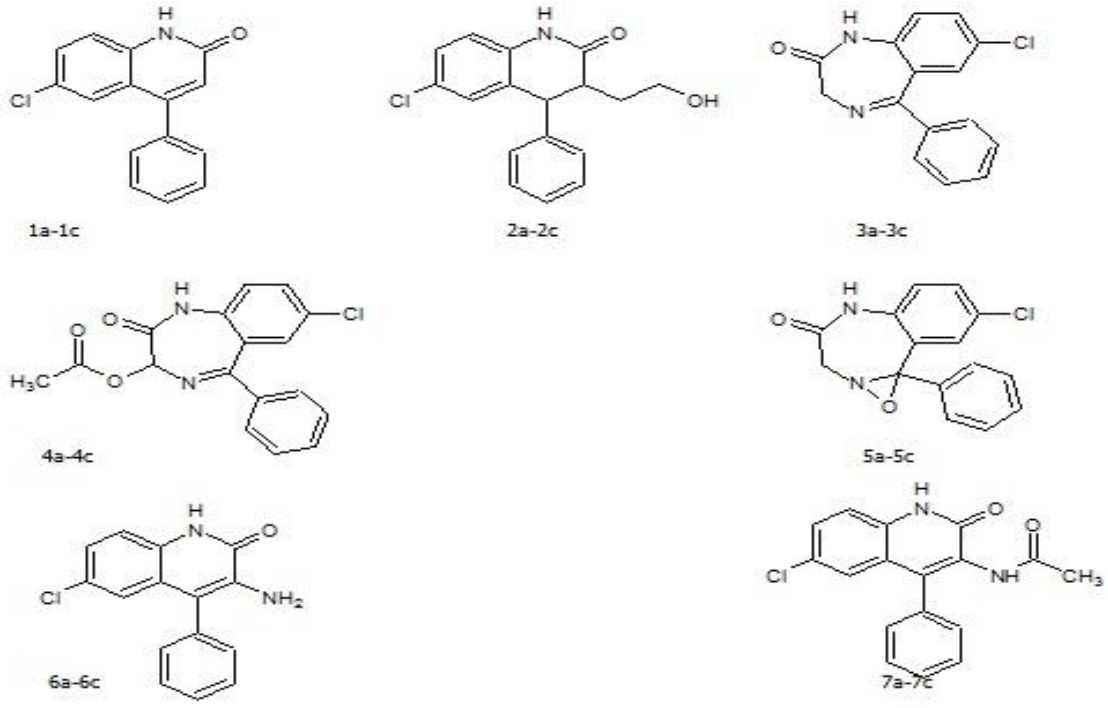


Figure 2. Graph plotted between actual EC_{50} and predicted EC_{50}

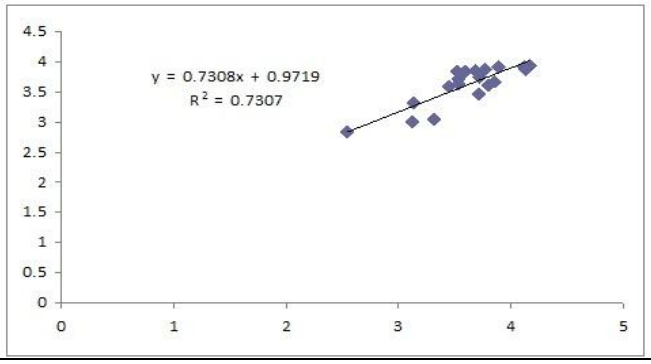


Figure 3. Graph plotted between k and Standardized beats of used descriptors in QSAR modeling

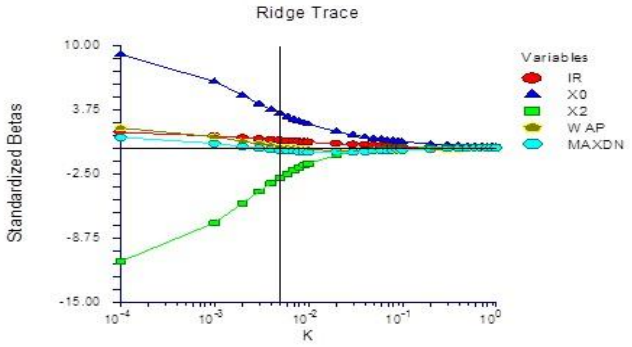
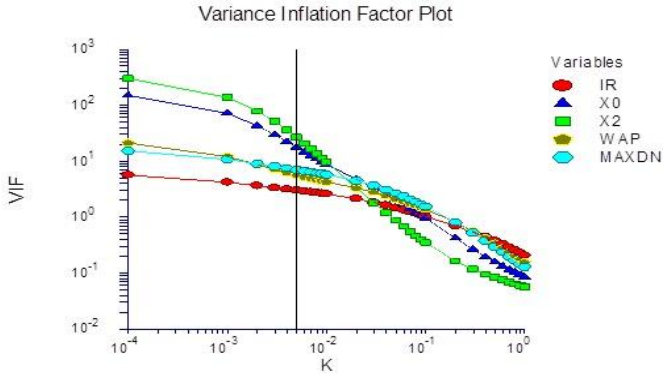


Figure 4. Graph plotted between VIF and K of used descriptors in QSAR/QSPR modeling



CONCLUSION

The results reveals that the cyclization and branching inhibit the antiviral activity of 4-Aryl-6-chloro-quinolin-2-ones and 5-Aryl-7-chloro-1,4- benzodiazepines.

ACKNOWLEDGEMENT: Authors are thankful to Dr. V.K. Agrawal, A.P.S. University Rewa for giving necessary suggestions and to principal Govt. M. S. Golvalkar College Rewa for providing computer facility this QSAR study.

CONFLICT OF INTEREST:

The authors declare that they have no conflict of interest.

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