Available online at http://jddtonline.info

RESEARCH ARTICLE

2D QSAR STUDIES ON THE DIFFERENTIAL INHIBITION OF ALDOSE REDUCTASE BY FLAVONIODS COMPOUNDS: A COMPARATIVE STUDY

***Mamta Arora, M.N. Noolvi, Harun Patel**

Computer Aided Drug Discovery Department, ASBASJSMCOP, Bela Ropar Punjab,India 140111

**Corresponding Author's Email: mamtaarora.2007@rediffmail.com*

ABSTRACT

A quantitative structure activity relationship study of 66 molecules was performed using MLR(Multiple Linear Regression) and PCR (Principal component Analysis) of aldose reductase by flavonoids compounds.Various descriptors, topological indices were used to characterize flavonoids molecules.In the developed model MLR is giving vary significant results wheras PCR has revealed some important information.

Keywords: Flavonoids, aldose reuctase, QSAR, Multiple Linear Regression, Principle Component Regression

INTRODUCTION

Flavonoids are polyphenol compounds which are phytoconstituents widely distributed in plants.Anumber of biological activities have been reported for flavonoids. Conspicuous among them is as antioxidant.[1] A number of health problems are described due to oxidative stress. Diabetes-related complications are also due to increase of oxidative stress that leads to the progression of polyolpathway[2] POP encompasses two enzymes: aldose reductase (AR) and sorbitol dehydrogenase Aldose Reductase is the first and rate-limiting enzyme of the POP that channels excess glucose to the formation of fructose.[3] This is key rate-limiting enzyme. Aldose reductase inhibitors (ARIs which reduces the accumulation of sorbitol and help to prevent and delay the occurrence and development of diabetic complications.[4] The flux of POP under regular levels of glucose is very small; however, when glucose levels are high, the flux of POP is increased.[5] This results in accumulation of sorbitol, which is not able to cross cell membranes. It leads to an osmotic imbalance and resulting in the progression of diabetic complications.[6]

Experimental studies have confirmed the effectiveness of Aldose Reductase inhibitors when the flux of POP is enhanced and hence wished-for as pharmacotherapeutic agents. Several ARIs such as flavonoids, isoflavone, coumarins, stilbenes, have been reported in the literature.[7] Some are also available in the market but they have suboptimal activities and side effects. Some novel ARIs with enhanced activity and selectivity are desired. In these days Computational models are playing vital role. Computational models can predict the biological activity of compounds .In this Structural properties are powerful tools to design highly active molecules. In this sagacity, quantitative structure–activity relationship (QSAR) studies have been successfully practiced for modeling biological activities of natural as well as synthetic chemicals. Here, we present our observations on the role of different substitutions on the scaffold molecules of flavonoids.

MATERIALS AND METHODS[3,8]

Computational Methods

A] Chemical Data

From the literature a series of 62 molecules belonging to flavonoids derivatives as ARIs inhibitors were taken and used for the present study. Then 2D- QSAR models were generated using 23 molecules as training set. Predictive power of the resulting models was evaluated by a test set of 39 molecules with distributed biological activities

B] Data Set

We used Vlife MDS QSAR plus software developed by Vlife Sciences Technologies Pvt Ltd, Pune, India. computational work was performed on Apple work-station (8-core processor) using windows XP operating system .

Molecules were subjected to energy minimization using MMFF as force field and charge & maximum number of cycles were 1000 , convergence criteria (rms gradient) was 0.01and medium's dielectric constant of 1 by batch energy minimization method. (All the compounds were drawn in Chem DBS using fragment database)

C] Biological Activities

The negative logarithm of the flavonoids was used as dependent variable and taken against ARIs , thus correlating the data linear to the free energy change

as pIC_{50}[$pIC_{50} = -\log (IC_{50}10^{-6})$]

[D] Molecular Descriptors

VlifeMDS software was used to calculate various 2D descriptors like element counts, molecular weight, *topological* index, log *P*, molecular refractivity, Baumann alignment independent, topological descriptors *etc.*, (a total of 202) total 138, 138and 132 descriptors for MLR, PLS and PCR respectively were used for QSAR analysis The preprocessing of the independent variables i.e., descriptors was done by removing invariable i.e.

constant column and cross-correlated descriptors (with r > 0.99)

[E] Selection of Training and Test Set

Spherical exclusion method was used for MLR, PCR model and the dataset of 62 molecules was divided into training and test set . pIC50 activity was taken as as dependent variable and various 2D descriptors *viz chi, chiv, chi*. chain, chiv chain *path count*, chain path count, cluster, kappa, element count, path cluster, estate numbers, estate contribution, information theory, individual and polar surface area as independent variables. These were calculated for the molecules.

[F] Model Validation

Validated of the developed QSAR models were done by the cross validation to test the internal stability and predictability. No. of groups for cross validation was 39 and no. of iterations was 100.

[G] Randomization Test

One tail hypothesis test was used. The robustness of the models was examined by comparing these models to those derived for random datasets for training sets. Random sets were generated by rearranging the activities of the molecules in the training set. The statistical model was resulting using a variety of random sets with the selected descriptor and the equivalent q2 were calculated. The significance of the models obtained was derived based on a calculated Z Score.

RESULTS AND DISCUSSION

QSAR by Multiple Linear Regression (MLR) Analysis

Multiple regression is the standard method for multivariate data analysis. It is also known as ordinary least squares regression (OLS). This method of regression estimates the values of the regression coefficients by applying least squares curve fitting method. To get reliable results, dataset having usually 5 times as many data points (molecules) as independent variableis required. The regression equation takes the form

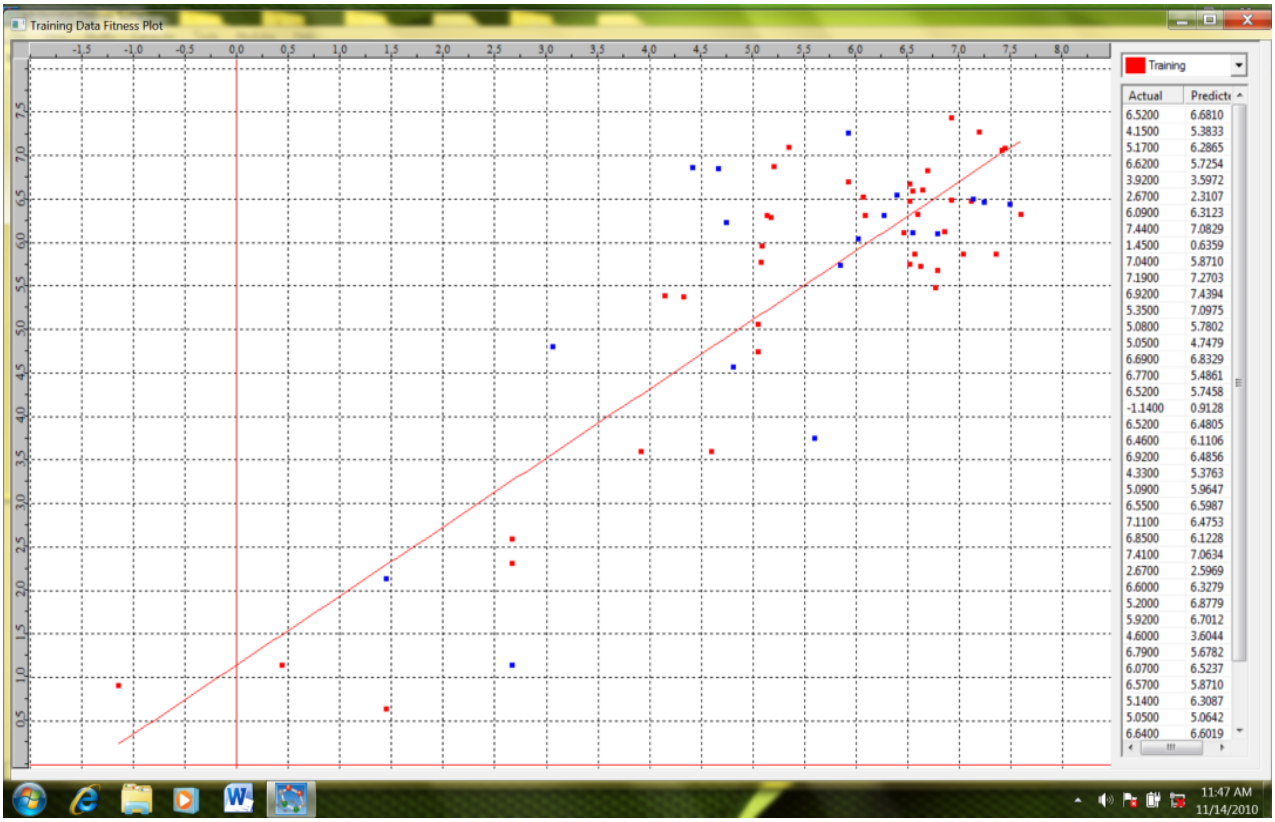
$$Y = b1*x1 + b2*x2 + b3*x3 + c, \quad (4)$$

Where Y is the dependent variable, the 'b's are regression coefficients for corresponding 'x's is independent variable, 'c' is a regression constant . In the present study QSAR model was developed using multiple regression by forward-backward variable selection method with pIC50 activity field as dependent variable and 140 physico-chemical descriptors as independent variable having cross-correlation limit of 1. Selection of test and training set was done by sphere exclusion method.Final MLR equation developed was as follows:

P IC 50 = 0.9644 (SaasCcount) +0.6318 (XlogP) - 0.2824 (SsCH3E-index)-2.3759

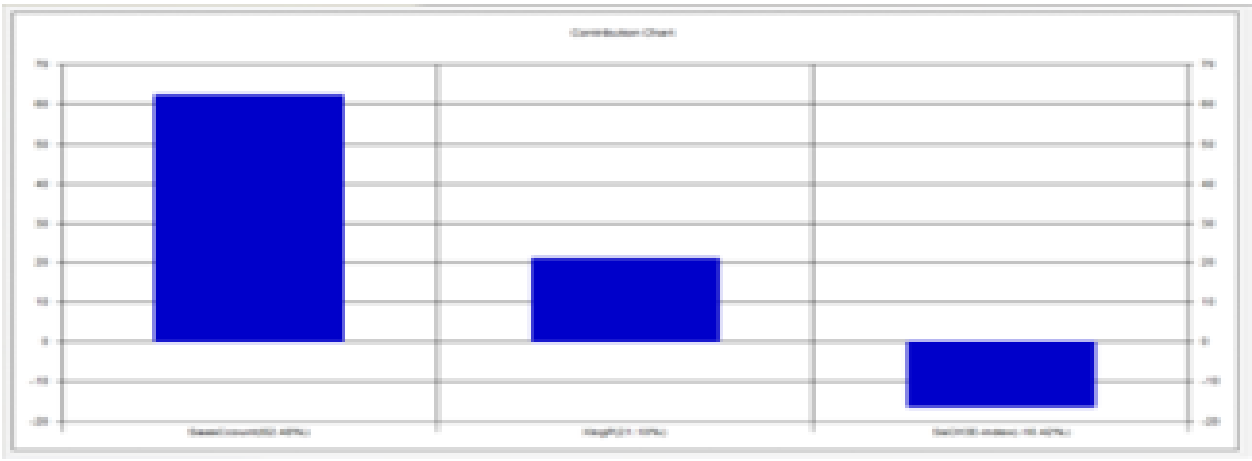
Graph of Actual vs. Predicted activities for training and test set

(x-axis Actual activity ,Yaxis predicted activity)



 ISSN: 2250-1177 CODEN (USA): JDDTAO

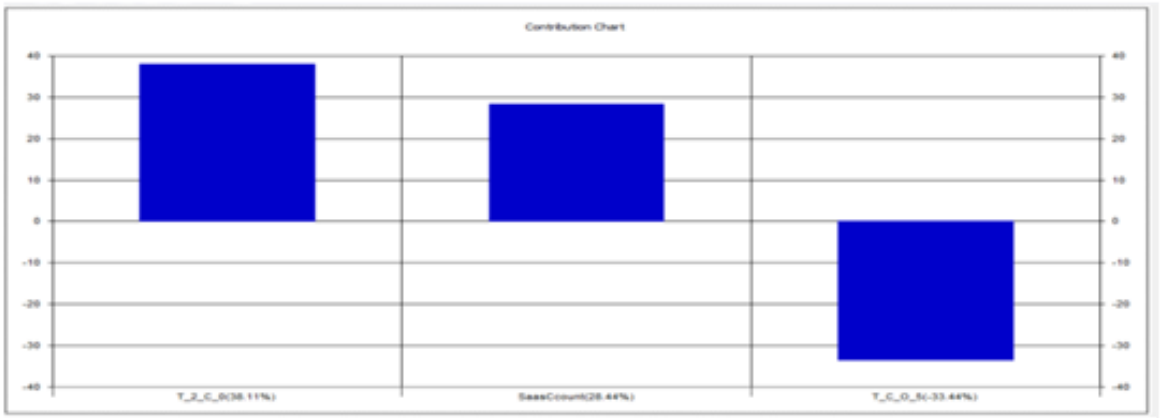
TABLE a) Experimental Graph of al and Predicted AR Inhibitory Activities of flavonoids used in thecurrent study



PRINCIPLE COMPONENT REGRESSION

PCR

Principal components analysis rotates the data into a new set of axes such that the first few axes reflect most of the variations within the data. We can plot the data on these axes, and can locate major underlying structures automatically. When rotated to a given axis the value of each point is called principal component value. Principal Component Analysis selects a new set of axes for the data. These are selected in declining order of variance within the data .and are perpendicular to each other. Hence the principal components are not correlated. Some components may be constant but these will be amongst the last selected. The probability noted with MLR was that correlated variables cause instability. So, how about calculating these principal components, discarding the ones which only appear to contribute noise or constants and using MLR on these? This process gives the modeling method known as Principal Components Regression. Instead of forming a single model, as with MLR, a model can be formed using 1, 2… components and a judgment can be made as to how many components are best possible. If the original variables contained collinearity, then several components will contribute only noise. As long as these are dropped, the models can be guarantee that our model



Plot of percentage contribution of each descriptor in developed MLR model

(Graph of Actual vs. predicted activity)

INTREPRETATIONS

MLR

SaaScount-This descriptor defines the total no. of carbon atom with one single bond along with two aromatic bonds.It means that presence of COOH,COCH3goup over coumarin nucleus favours the activity as in case of compound 38,48 and 62.

XlogP-This descriptor is directly contributing to the activity and explain the role of lipophilic substituents over coumarin ring such as OH,OCH3

Ssch3-Index

Electropologica lindices for no.of CH3 grup connected with one single bond. Negative contributors of this descriptor shows that electron donating group decrease the activity.

PCR

T-2-C-0-

This is the count group of double bonded atoms separated from carbons by 0 bond.It explain thatoxy group present at c-2 position of coumarin C,d is very significant for activity.

T-C-0-5-

This is the count no. of carbon atoms single,double or triple bonded atom seprated from oxygen atom by 5 bond.

The negative contributions of this descriptor shows that OH,OCH3 group should be directly attached with coumarin nucleus for better inhibitory activity.

CONCLUSION

In the model developed to predict the structural features of coumarines derivatives as ARIs ,reveal useful information about the structural features requirements for the molecule.In above 2 optimised model MLR method is giving very significant results and reveal that

- ❖ Presence of –COOH,COCH3 gp. On coumarine nucleus favours the activity.
- ❖ Presence of Xlog P descriptor signifies the role of lyophilic substratees on coumarine derivatives enhanceARIs.
- ❖ Presence o electron donating group decrease the activity.

PCR This method also reveals some important information like

- For inhibition AR OH,OCH3gp. It should be directly attached with coumarine nucleus for better activity
- The descriptor T-2=C-O reveals that presence of any gp. Is essential for ARI activity at position C-2 on coumarine ring.

The current study provides better insight into designing of more potent ARIs in the future before synthesis.

REFERENCES

1. Orsolya F, Judit J , Héberger K, Quantitative Structure - Antioxidant Activity Relationships of Flavonoid Compounds Molecules, 2004, 9, 1079-1088
2. Chung SS, Ho EC, Lam KS, Chung SK, Contribution of polyol pathway to diabetes-induced oxidative stress, Journal of American Society, Nephrology, 2003, 14, 233–236.
3. Noolvi MN, Patel HM, Bhardwaj V, 2D QSAR studies on a series of 4-Anilino Quinazoline derivatives as Tyrosine Kinase (Egfr) Inhibitor: An approach to design anticancer agents, Digest Journal of Nano materials and Bio structures, 2010, 5(2), 387 – 401.
4. Hotta N, Akanuma Y, Kawamori R, Matsuoka K, Oka Y, Shichiri M , Long- term clinical effects of epalrestat, analdose reductase inhibitor, on diabetic peripheral neuropathy, Diabetes Care,2006, 29, 1538–1544.
5. Fernandez M, Caballero J, Helguera AM, Castro EA, González Quantitative structure–activity relationship to predict differential inhibition of aldose reductase by flavonoid compounds, Bioorganic & Medicinal Chemistry,2005, 13 (9), 3269–3277.
6. Matsuda H, Morikawa T, Toguchida I, Yoshikawa M, Structural requirements of flavonoids and related compounds for aldose reductase inhibitory activity, Chememical and Pharmaceutical .Bulletein, 2002,50,788–795.
7. Koukoulitsa C, Bailly F, Pegklidou K, Demopoulos VJ, Cotelle P, Evaluation of aldose reductase inhibition and docking studies of 6-nitro and6,6- dinitroro smarinic acids, European Journal of .Medicinal Chemistry, 2010, 45, 1663–1666.
8. Noolvi MN, Patel HM, A comparative QSAR analysis and molecular docking studies of quinazoline derivatives as tyrosine kinase (EGFR) inhibitors: A rational approach to anticancer drug design, Journal of Saudi Chemical Society, 2013, 17(4), 361–379.

 ISSN: 2250-1177 CODEN (USA): JDDTAO