

## QSAR STUDIES ON A SERIES OF SUBSTITUTED FUSED BICYCLIC PYRROLIZINONES USING HANSCH ANALYSIS

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### ABSTRACT

QSAR studies were performed on a series of substituted fused bicyclic pyrrolizinones using Hansch analysis. Substituted fused bicyclic pyrrolizinones derivatives have been analyzed in relation to their physicochemical and molecular properties. The activities of the compounds are found to be significantly correlated with the physicochemical parameters such as MR, MV, MW, Pc, Pz, W, WA,  $^0\chi$ ,  $^1\chi$ ,  $^2\chi$ ,  $^4\chi$ ,  $^5\chi$  Xeq. It was found that the presence of NH<sub>2</sub> group at R<sub>1</sub> position was conducive for the inhibitory activity. The results are critically discussed on the basis of regression data and cross validation techniques.

**KEYWORDS:** QSAR Physicochemical properties regression analysis.

### INTRODUCTION

Akt (Protein kinase B), a serine/threonine kinase that has emerged as a critical enzyme in several signal transduction pathways involved in cell proliferation, apoptosis, angiogenesis and diabetes. Akt directly phosphorylates several proteins that are part of the cell survival machinery.<sup>[1,2]</sup> Akt also plays a key role in regulating cell cycle progression, cell proliferation and cell growth.<sup>[1,2]</sup> Akt is originally identified as a cellular homolog of the viral oncogene *Akt 8*. Akt belongs to the AGC family of kinases and shares high homology with PKA and PKC. The Akt protein plays a critical role in preventing cells from undergoing apoptosis.<sup>[3]</sup> The Akt kinases are central nodes in signal transduction pathways that are important for cellular transformation and tumor progression.

The three isoforms of Akt (Akt1/PKB $\alpha$ , Akt2/PKB $\beta$ , and Akt3/PKB $\gamma$ ) share a high degree of structural similarity and sequence homology, and all possess an amino terminal pleckstrin

homolog (pH) domain and a kinase domain separated by a 39- amino acid hinge region<sup>[2a,b]</sup> It is shown by the common observation that dysregulation of Akt help in the development of human cancer.<sup>[2a-f,4]</sup>

## RESULTS AND DISCUSSION

QSAR was attempted with steric, topological electronic and parameters along with indicator parameter and activity. The correlations were obtained between activity and various structural parameters. The structural parameters such as molar refractivity (MR), molar volume (MV), molar weight (MW), parachor (Pc), polarizability (Pz), were calculated by ACD Lab. Chem. Sketch software.<sup>[5]</sup> Wiener index (W), mean Wiener index (WA),  $\chi^0$ ,  $\chi^1$ ,  $\chi^2$ ,  $\chi^4$ ,  $\chi^5$  were calculated by DRAGON Software.<sup>[6]</sup> These parameters have already been found to be useful in various QSAR studies performed earlier.<sup>[9-20]</sup>

For all the compounds of this series a number of physicochemical parameters are calculated. Autocorrelation matrix showing correlation among all the physicochemical parameters is given in Table-1. Stepwise regression analysis was done by using SPSS 7.5 version. In this series, some significant QSAR models have been obtained which are given below:

$$\text{pIC}_{50} = -0.134 (\pm 0.045) \text{BAC} + 1.486 (\pm 1.554) \text{ID} + 0.246 (\pm 0.809) \text{I}_1 + 0.057 \quad (1)$$

$$n = 17, R = 0.920, R^2 = 0.847, R^2_A = 0.812, SE = 0.358, F_{(3, 13)} = 23.995, P = 1.668, S = 9.234$$

$$\text{pIC}_{50} = -0.142 (\pm 0.042) \text{BAC} - 0.027 (\pm 0.029) \text{MR} + 0.368 (\pm 0.838) \text{I}_1 + 3.656 \quad (2)$$

$$n = 17, R = 0.920, R^2 = 0.846, R^2_A = 0.811, SE = 0.359, F_{(3, 13)} = 23.842, P = 1.677, S = 9.225$$

$$\text{pIC}_{50} = -0.159 (\pm 0.042) \text{BAC} + 0.052 (\pm 0.060) \text{Pz} + 0.370 (\pm 0.861) \text{I}_1 + 4.899 \quad (3)$$

$$n = 17, R = 0.916, R^2 = 0.840, R^2_A = 0.802, SE = 0.366, F_{(3, 13)} = 22.666, P = 1.750, S = 9.152$$

$$\text{pIC}_{50} = -0.138 (\pm 0.047) \text{BAC} + 0.737 (\pm 0.972) \text{WA} + 0.302 (\pm 0.866) \text{I}_1 + 2.161 \quad (4)$$

$$n = 17, R = 0.912, R^2 = 0.832, R^2_A = 0.793, SE = 0.375, F_{(3, 13)} = 21.396, P = 1.836, S = 9.066$$

$$\text{pIC}_{50} = -0.147 (\pm 0.044) \text{BAC} - 0.103 (\pm 0.145) \text{Log P} + 0.358 (\pm 0.899) \text{I}_1 + 8.109 \quad (5)$$

$$n = 17, R = 0.910, R^2 = 0.828, R^2_A = 0.789, SE = 0.379, F_{(3, 13)} = 20.926, P = 1.870, S = 9.031$$

$$\text{pIC}_{50} = -0.145 (\pm 0.047) \text{BAC} + 3.860 (\pm 7.822) \text{IOR} + 0.174 (\pm 0.889) \text{I}_1 + 1.379 \quad (6)$$

$n = 17, R = 0.902, R^2 = 0.813, R^2_A = 0.770, SE = 0.395, F_{(3, 13)} = 18.856, P = 2.037, S = 8.865$

$$pIC_{50} = -0.148 (\pm 0.046) BAC + 2.057 (\pm 4.383) D + 0.074 (\pm 0.904) I_1 + 5.292 \quad (7)$$

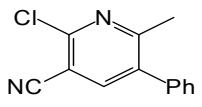
$n = 17, R = 0.901, R^2 = 0.812, R^2_A = 0.768, SE = 0.397, F_{(3, 13)} = 18.678, P = 2.053, S = 8.849$

$$pIC_{50} = -0.136 (\pm 0.040) BAC + 0.270 (\pm 0.217) {}^2\chi + 0.456 (\pm 0.782) I_1 + 3.149 \quad (8)$$

$n = 17, R = 0.932, R^2 = 0.869, R^2_A = 0.839, SE = 0.331, F_{(3, 13)} = 28814, P = 1.425, S = 9477$

In all the QSAR reported here,  $n$  is number of data points,  $R$  is the coefficient of regression or correlation coefficient,  $R^2$  represents coefficient of determination,  $SE$  is the standard error of estimate,  $R^2_A$  is adjusted  $R^2$ ,  $F$  is variance ratio<sup>[21,22]</sup>,  $Q$  is the quality of fit<sup>[23,24]</sup> and data within the parenthesis is confidence interval. The validity of the above QSAR equations was further confirmed, using the cross validation method.

The sign of coefficient of parameters like  $D$ ,  $IOR$ ,  $WA$ ,  $Id$ ,  $Pz$  and  ${}^2\chi$  is positive implying that more denser, larger group having high polarizability and more branching should be preferred for the modeling. The negative sign of coefficient of parameter  $MR$  shows that group having low molar refractivity is beneficial towards the activity. The sign of coefficient of the parameter  $\log P$  is negative but some calculated values of  $\log P$  is also negative so we can say that more hydrophobic group should be preferred for the future drug designing. The negative coefficient of  $BAC$  in all the above models is probably due to its high co-linearity with other parameters.

Positive sign of the coefficient of indicator parameter  $I_1$  indicates that  group is conducive for the activity and should be retained at  $R_1$  position in the future drug modeling.

Data of predicted and residual values for model no. 1 are given in Table - 2. The calculated  $F$  value is greater than  $F$  theoretical value [ $F_{(3, 13)} = 3.41$ ] for all the significant equation. The plot of observed  $pIC_{50}$  versus predicted  $pIC_{50}$  based on the equation 1 is shown in graph (fig. 1).

### Cross Validation

The cross validation analysis was performed using leave one out (LOO) method<sup>[25,26]</sup>, in which one compound is removed from the data set and the activity is correlated using the rest

of the data set. The cross-validated  $R^2$  in each case was found to be very close to the value of  $R^2$  for the entire data set and hence these models can be termed as statistically significant.

Cross validation provides the values of PRESS, SSY and  $R^2_{cv}$  and PSE from which we can test the predictive power of the proposed model. It is argued that PRESS, is a good estimate of the real predictive error of the model and if it is smaller than SSY the model predicts better than chance and can be considered statistically significant. Furthermore, the ratio PRESS/SSY can be used to calculate approximate confidence intervals of prediction of new compound. To be a reasonable QSAR model PRESS/SSY should be smaller than 0.4. Also, if PRESS value is transformed in a dimension less term by relating it to the initial sum of squares, we obtain  $R^2_{cv}$  i.e. The complement to the traces on of unexplained variance over the total variance. The PRESS and  $R^2_{cv}$  have good properties. However, for practical purposes of end users the use of square root of PRESS/N, which is called predictive square error (PSE), is more directly related to the uncertainty of the predictions. The PSE values also support our results. The calculated cross-validated parameters confirm the validity of the models. All the requirements for an ideal model have been fulfilled by model no. 1 (table 3), that's why, we have considered as the best model.

$R^2_A$  takes into account the adjustment of  $R^2$ .  $R^2_A$  is a measure of the percentage explained variation in the dependent variable that takes into account the relationship between the number of cases and the number of independent variables in the regression model, whereas  $R^2$  will always increase when an independent variable is added.  $R^2_A$  will decrease if the added variable doesn't reduce the unexplained variable enough to offset the loss of decrease of freedom.

#### **Predictive error of coefficient of correlation (PE)**

The predictive error of coefficient of correlation (PE)<sup>[27]</sup> is yet another parameter used to decide the predictive power of the proposed models. We have calculated PE value of all the proposed models and they are reported in Table 4. It is argued that of

- (i)  $R < PE$ , then correlation is not significant;
- (ii)  $R > PE$ ; several times (at least three times), then correlation is indicated; and if
- (iii)  $R > 6PE$ , then the correlation is definitely good.

For all the models developed the condition  $R > 6PE$  is satisfied and hence they can be said to have a good predictive power.

Table 1: Correlation matrix.

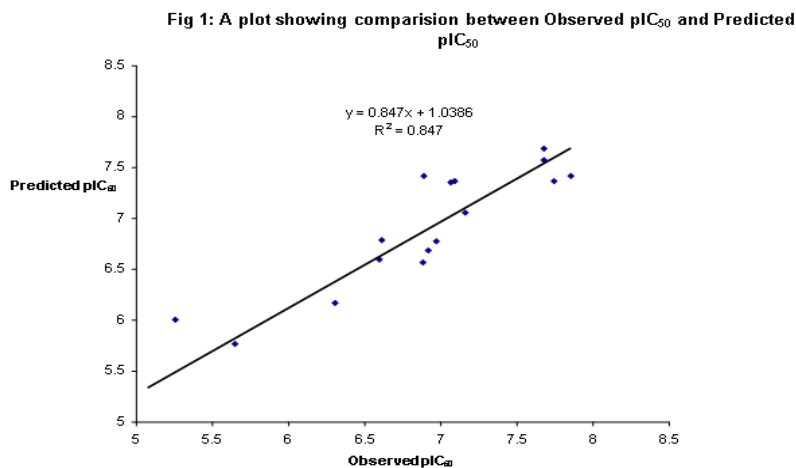
	pIC <sub>50</sub>	MR	MV	MW	PC	PZ	W	WA	X0	X1	X2	X4	X5	XEQ
<b>A3</b>	1.000													
<b>MR</b>	.326	1.000												
<b>MV</b>	.337	.997	1.000											
<b>MW</b>	.269	.996	.992	1.000										
<b>PC</b>	.317	.999	.998	.997	1.000									
<b>PZ</b>	.326	1.000	.997	.996	.999	1.000								
<b>W</b>	.295	.992	.988	.996	.995	.992	1.000							
<b>WA</b>	.305	.984	.977	.989	.986	.984	.997	1.000						
<b>X0</b>	.277	.995	.996	.998	.998	.995	.994	.984	1.000					
<b>X1</b>	.272	.994	.984	.997	.993	.994	.994	.990	.991	1.000				
<b>X2</b>	.261	.984	.991	.987	.987	.984	.974	.960	.993	.973	1.000			
<b>X4</b>	.256	.988	.982	.986	.986	.988	.976	.963	.983	.986	.975	1.000		
<b>X5</b>	.245	.982	.983	.980	.982	.982	.967	.946	.983	.972	.984	.994	1.000	
<b>XEQ</b>	-.531	-.873	-.898	-.837	-.871	-.873	-.827	-.800	-.858	-.815	-.880	-.846	-.871	1.000

TABLE 2: Predicted and residual values for model no. 1.

S.No.	Observed	Predicted	Residual
1.	6.596	6.596	0.000
2.	6.305	6.169	0.135
3.	5.648	5.768	-0.120
4.	5.072	4.831	0.241
5.	5.255	6.005	-0.749
6.	7.065	7.354	-0.289
7.	6.917	6.685	0.231
8.	6.882	6.567	0.315
9.	7.677	7.686	-0.008
10.	6.612	6.786	-0.173
11.	6.970	6.775	0.195
12.	7.091	7.366	-0.274
13.	6.889	7.416	-0.527
14.	7.161	7.056	0.104
15.	7.744	7.366	0.378
16.	7.677	7.573	0.104
17.	7.853	7.416	0.436

Table 3: Cross validated parameters and predictive error of coefficient of correlation (PE) for the proposed models.

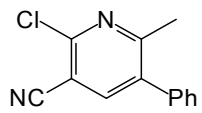
Eq.no.	N	Parameter used	PRESS	SSY	PRESS/SSY	R <sup>2</sup> <sub>cv</sub>	PSE	R	1-R <sup>2</sup>	PE	6PE
1.	17	BAC+Id+I <sub>1</sub>	1.668	9.234	0.180	0.820	0.313	0.920	0.153	0.024	0.144
2.	17	BAC+MR+I <sub>1</sub>	1.677	9.225	0.181	0.819	0.313	0.920	0.153	0.024	0.144
3.	17	BAC+Pz+I <sub>1</sub>	1.750	9.152	0.191	0.809	0.320	0.916	0.160	0.025	0.150
4.	17	BAC+WA+I <sub>1</sub>	1.836	9.066	0.202	0.798	0.328	0.912	0.168	0.027	0.162
5.	17	BAC+logP+I <sub>1</sub>	1.870	9.031	0.207	0.793	0.331	0.910	0.171	0.027	0.162
6.	17	BAC+IOR+I <sub>1</sub>	2.037	8.865	0.229	0.771	0.346	0.902	0.186	0.030	0.180
7.	17	BAC+D+I <sub>1</sub>	2.053	8.849	0.232	0.768	0.347	0.901	0.188	0.030	0.180
8.	17	BAC+ $\chi$ +I <sub>1</sub>	1.425	9.477	0.150	0.850	0.289	0.932	0.131	0.021	0.126



## CONCLUSION

On the basis of the above discussions some general conclusions can be drawn:

1. Denser, more bulky, having high polarizability and low molar refractivity groups should be used in the future drug modeling.
2. More hydrophobic group is beneficial towards the activity in future drug designing.



3. The indicator  $I_1$  for group at  $R_1$  site is preferentially favorable.

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