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QSAR STUDIES ON A SERIES OF △9-THC ANALOGUES AS CANNABINOID RECEPTOR MODULATORS

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Abstract

QSAR studies were performed on a series of △9-tetrahydrocannabinol (△9-THC) analogues as cannabinoid receptor modulators. △9-tetrahydrocannabinol (△9-THC) analogues have been analyzed in relation to their physicochemical and molecular properties. The activities of the compounds were found to be significantly correlated with the physicochemical parameters such as index of refraction (Ior) , equalized electro-negativity (Xeq), first, second and third order of connectivity indices ($^1\chi$,$^2\chi$,$^3\chi$) and Mean weiner Index (WA). It was found that the presence of –OH group at R_1 position was conducive for the inhibitory activity. The results are critically discussed on the basis of regression data and cross validation techniques. Poglani factor Q and the results of LOO (leave one out) method confirms the reliability and predictability of the proposed models.

Keywords: QSAR; cannabinoid receptor modulators; physicochemical property; regression analysis, LOO

1. INTRODUCTION

The cannabinoid receptor type 1(CB_1) and cannabinoid receptor type 2 (CB_2) are G-protein coupled receptors.The exact location of CB_1 receptors is on the central and peripheral neurons and that of CB_2 receptors is in the periphery. The cannabinoid receptors are having great therapeutic potential.Treatment of pain,neurodegenerative disease and glaucoma can be done by CB_1 agonists and neuropathic pain,asthma,allergies,rheumatoid arthritis and autoimmune diseases can be done by CB_2 agonists.Currently Nabilone is under clinical trials for neuropathic pain.The current study represents the QSAR analysis of a series of △9-tetrahydrocannabinol (△9-THC) analogues as cannabinoid receptor modulators (Burdick et al., 2010)using a number of structural parameters along with indicator parameter at different substitution sites. The aim of our study was to discover selective CB_2 agonists for treatment of neuropathic pain by making modifications in △9-THC(1) at the C-1 position.

2. EXPERIMENTAL

2.1. Physicochemical Parameters- The physicochemical parameters such as Index of refraction (Ior) used as steric parameter was calculated by ACD Lab Chem Sketch (Acd – Lab Software), first,second and third order of connectivity indices ($^1\chi$,$^2\chi$,$^3\chi$) and Mean weiner Index (WA)(DRAGON Software) are the topological Parameters calculated by DRAGON Software .

(i) Index of refraction (IOR) – The index of refraction (IOR) of a medium is the ratio of the speed of light in vacuum to its velocity in the medium.

(ii) Molecular Connectivity Index (χ) - Molecular connectivity is a method of quantifying the structure of chemical groups, which has found wide application in chemistry (Gutman 1994; Khadikar et al 2003; Randic 1975; Randic 1993) . It is based upon an algorithm to encode the ranking of alkanes relative to the attribution of branching. The term molecular connectivity was adopted by Kier and Hall in 1975, in connectivity with a mathematical algorithm proposed by Randic. This index is one of the most widely used topological indexes in QSPR/QSAR analysis. In its original form, it is defined as below:

$$^1\chi = {}^1\chi(G) = \sum_{ij} \left[\delta_i \delta_j\right]^{-1/2} \quad \text{…….. (1)}$$

Where δ_i is the valence of a vertex i, equal to the number of bonds connected to the atom i, in G, representing the graph of the compound. Meaning of δ_i is analogous.

(iii) The first order Connectivity Index ($^1\chi$) -The First order connectivity index follows from the following expression.

$$^1\chi(G) = {}^1\chi = \sum_{i,j} \left(D_i D_j\right)^{-1/2} \quad \text{…….. (2)}$$

Where D_i and D_j are the valences of a vertex i and j, equal to the number of bonds connected to the atoms i and j, in G.

(iv)The second Order Connectivity Index ($^2\chi$) - The second order connectivity index ($^2\chi_R$) is obtained from the

following equation:

$$^{2}\chi^{v}(G) = {}^{2}\chi^{v} = \sum_{S=1}^{SL}\left(D_i\, D_j\, D_k\right)_S^{-1/2} \qquad \text{…….. (3)}$$

i = j = k

Where S stands for a path of length two while SL is the number of paths of length in G. Each path of length two has in this case a weight D_i, D_j, D_k.

(v) Mean Wiener Index (WA) -It is interesting to note that the number of element in a triangular of diagonal sub matrix is equal to -

1/2 N (N-1) …….. (4)

Where, N is the number of vertices in Graph G. In terms of this, the mean wiener index (WA) (Weiner 1947; Weiner 1947) is defined as -

WA (G) = 2 W/N (N-1) …….. (5)

(vi) Equalized electronegativity (Xeq)[18] **-** Electronegativity was first defined by Pauling (1939) as the power of an atom in a molecule to attract electrons to it. He found an empirical relation between the energy of a bond the electronegativities of the bonded and from this relation he estimated the electronegativity of several atoms.

Xeq is an electronic parameter and is based upon Sanderson's Principle. It was calculated using the following formula:

$$\text{Xeq} = \frac{\text{N}}{\sum(\text{V}\,|\,\text{X})}$$

Where N is the total number of atom and V is the particular number of atom and X is the electronegativity of that element.

(vii) Indicator Variables – Indicator variables (parameters), sometimes called dummy variables, are used in multiple linear regression analysis to account for certain features which cannot be described by continuous variables. The indicator parameters (variables) are generally assigned only two values zero and one. It is taken as 1 (one) for that particular group or substituent and at a specific site in the molecule and 0 (zero) for all such cases where that group or substituent is absent(Recantint et al., 1986).

2.2. Regression Analysis- The regression analysis is done using SPSS 7.5 version software.

3. RESULTS AND DISCUSSION

The success of QSAR studies mainly depends whether or not the molecular descriptors chosen are appropriate to explain the biological activity(pKi).The present work deals with the QSAR studies on a series of 23 compounds of △9-tetrahydrocannabinol (△9-THC) analogues with steric and topological parameters along with indicator parameter and activity. It is envisioned that this study will produce models that can be used for future designing of new analogues with higher potency..Here the biological activity (pKi) is a measure of inhibitory activity. In an attempt to determine the role of structural features, which appears to influence the observed activity of reported compounds, QSAR studies were undertaken using linear free energy relationship (LFER) model of Hansch and Fujita(Hanch et al., 1964) The multiparametric regression analysis used to derive the correlation was executed with the SPSS (7.5) programme. For QSAR studies, different analogues of parent structure and values of biological activity (pKi) along with, calculated physicochemical parameters are reported in Table-1. The autocorrelation between all the structural parameters and biological activity (pKi) is shown in Table-2. A close study of this table makes it clear that those parameters, which are orthogonal, can be used together in multiparametric regression studies. These parameters have already been found to be useful in various QSAR studies performed earlier (Srivastava et al., 2011-2007; Chaurasia et al., 2007; Agarwal et al., 2006, Agarwal et al., 2005, Agarwal et al., 2003 ;Khadikar et al.,2005, Khadikar et al.,2003, Khadikar et al.,2002; Jaiswal et al., 2004; Thakur et al., 2004).

The aim of current study is mainly to study the different physicochemical parameters linear models and their stepwise regression analysis by using indicator variable and different parameters (According to correlation matrix). In this series, some significant QSAR models have been obtained which are given below:

pIC50 = −0.482 (±0.202) Log P − 0.069 (±0.051) St − 0.833 (±0.917) I_1 + 0.636 (±0.731) I_2 + 12.959 **------ (1)**

n = 24, R = 0.884, R^2 = 0.782, R^2_A = 0.736, SE = 0.426, $F_{(4, 19)}$ = 17.007, Q = 2.364

pIC50 = −0.519 (±0.204) Log P − 2.826 (±2.313) J − 0.830 (±0.941) I_1 + 0.555 (±0.752) I_2 + 5.828 **------ (2)**

n = 24, R = 0.878, R^2 = 0.770, R^2_A = 0.722, SE = 0.437, $F_{(4, 19)}$ = 15.925, Q = 2.364

pIC50 = −0.509 (±0.205) Log P − 8.301 (±6.874) Ior − 0.833 (±0.943) I_1 + 0.681 (±0.755) I_2 + 23.621 **------ (3)**

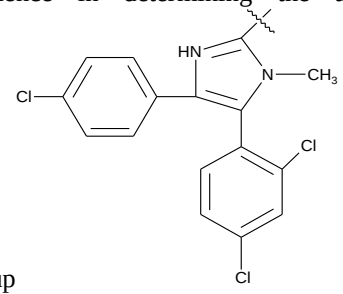
n = 24, R = 0.877, R^2 = 0.769, R^2_A = 0.720, SE = 0.438, $F_{(4, 19)}$ = 15.803, Q = 2.364

pIC50 = −0.446 (±0.234) Log P − 3.538 (±3.754) D − 0.887 (±0.991) I_1 + 0.568 (±0.793) I_2 + 14.349 **------ (4)**

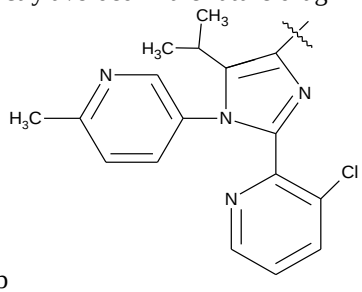
n = 24, R = 0.862, R^2 = 0.744, R^2_A = 0.690, SE = 0.461, $F_{(4, 19)}$ = 13.784, Q = 2.364

Here and hereafter n is the number of compounds, R is the correlation coefficient, R^2 is the coefficient of determination, R^2_A is the adjusted R^2, F is the Fischer statistics (Diudea ,2000; Bikash et al., 2003) S.E. is the standard error of estimate and Q is the quality of fit (Pogliani,1994; Pogliani,1996)

The resulting models are not statistically good, they are not sufficient for QSAR modeling, for further improvement in statistical terms we must go through stepwise regression analysis. In above shown models the negative sign of coefficient of St, Ior, D, LogP indicate that less bulkier, less denser and lesser hydrophobic groups are preferable for the activity. The coefficient of J was found to be positive which clearly indicates that this parameter has positive influence in determining the activity. The negative sign of coefficient of I_1 makes it that the



group at R_1 position should be strictly avoided in the future drug



modeling while positive coefficient of I_2 explains that the group at R_1 position. is beneficial for the activity. In order to examine the relative potential of models, predictive correlation coefficient (R^2Pred) were estimated by plotting graphs between observed and calculated pIC50 values obtained with the help of model no. 1. The comparison between observed and calculated activities is listed in Table-3. Such correlations are shown in figure 1. From the figure 1 R^2Pred values obtained for equation 1 is 0.782 and this is fairly high indicating the quality of the models. The calculated F value for these models is greater than F theoretical value [$F_{(4, 19)}$ = 2.90] for all the models and this fact also indicates towards significant correlation level.

Predictive ability was also evaluated by the LOO (Leave one out) (Cramer et al., 1988;Podlgar et al., 2000) cross-validation procedure. This method systematically removes one data point at a time, a model is constructed on the basis of this reduce data set and is subsequently used to predict the removed sample. This procedure was repeated for all the points until complete set of predicted values were obtained. Various cross-validation parameters calculated for the proposed models are presented in Table- 4.

3.1. Cross Validation

The cross validation analysis was performed using leave one out (LOO) method ((Cramer etal., 1988; Podlgar et al., 2000)) 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, 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.

3.2. Predictive error of coefficient of correlation (PE)

The predictive error of coefficient of correlation (PE) (Chattergee et al., 2000) 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 if

(i) if R < PE, then correlation is not significant;

(ii) if R > PE; several times (at least three times), then correlation is indicated; and if

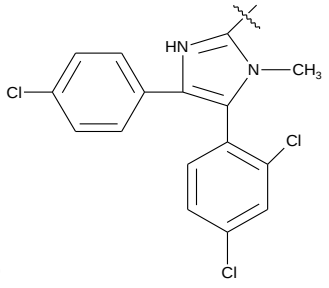
(iii) if R > 6PE, then the correlation is definitely good.

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

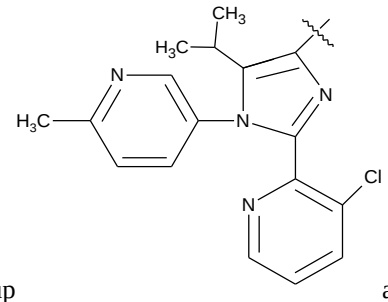
4. CONCLUSIONS

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

1. Less denser, less bulkier and lesser hydrophobic groups should be used in the future drug modeling.



2. The indicator I_1 for group at R_1 position should be avoided.

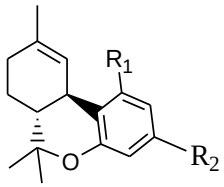


3. The group at R_1 position is preferentially favorable.

5. REFERENCES

1. Burdick D.,DeOrazio R.,Guzzo P.,Habershaw A.,Helle M.,Paul B.,Wolf M., 2010,Synthesis and structure-activity relationship of substitutions at the C-1 position of Δ9-tetrahydrocannabinol ,*Bioorganic and Medicinal Chemistry Letters* , 20 , 1424-1426.
2. Gutman I, 1994, *Graph Theory Notes,* New York, 27, 9, (b) Khadikar P. V., Lukvits I., Agrawal V. K., Gutman S., Karmakar S. and Srivastava A., 2003,*Ind. J. Chem.*, 42(A), 1436.
3. Randic M, 1975,*J. Am. Chem. Soc*. ,97, p. 6609-6615.
4. Randic M., 1993,Novel molecular descriptors in structure property studies, chem. Phys. Lett**. 211**, p 478-483.
5. Weiner H., *Amer. Chem. Soc.*, 1947, **69,** 17; (b) Weiner H., *J. Amer. Chem. Soc.*, 1947, **69**, 2636.
6. Pauling L., *The Nature of Chemical Bond* Chap-2, Cornell University Press, Itacha, New York, 1939.
7. Acd-Lab software for calculating the referred physicochemical parameters.Chemsketch.<www.acdlabs.com/acdlabs-rss-feed.xml >.
8. DRAGON Software for calculation of topological indices.< www.disat unimib. It>.
9. Chaurasia S., Srivastava A. K., Nath A., Srivastava M. K., Pandey A., 2007.Quantitative Structure Activity Relationship Studies on a Series of Tetrahydroquinoline-based Farnesyltransferase Inhibitors. *Oxidation Communication (Bulgaria)* 30, 778-787.
10. Recanatini M., Klein T., Yang C. Z., McClarin J., Langridge R., Mol. Pharmacol.,1986, 29, 436.
11. Hanch C., Fujita T., 1964.p-σ-π Analysis. A method for the correlation of biological activity and chemical structure. *J Am Chem Soc*, 86, 1616-1626.
12. Srivastava A. K.,Pandey A.,Srivastava A.,Shukla N., 2011.QSAR Based modeling of hepatitis C virus NS5B inhibitors..*J Saudi Chemical Society*,15,25-28.
13. Srivastava A. K., Jaiswal M., Archana, Pathak V. K., 2009.Molecular modeling of anti-HIV activity of bifunctional betulinic acid derivative with physicochemical parameters. *Oxidation Communications*, 32 (2), 455-462**.**
14. Srivastava A. K., Jaiswal M., Archana, Srivastava A., 2009.QSAR modeling of selective cc chemokine receptor 3 (CCR3) antagonists using physicochemical parameters. *Oxidation Communications*, 32(1), 55-61**.**
15. Srivastava A. K., Archana, Jaiswal M., 2008.A series of p- Arylthio cinnamides as QSAR studies on antagonists of Biochemical ICAM-1 / LFA-1 Interaction in Relation to anti-inflammatory activity. *Oxidation Communications*, 31(1), 44-51**.**
16. Srivastava A. K., Jaiswal M., Archana, Chaurasia S., 2008.QSAR of substituted N-benzyl piperidines in the GBR series. *J Indian Chem Soc*, 85, 842-848.
17. Srivastava A. K., Pathak V. K., Archana, Jaiswal M., 2008. QSAR based modeling of a new class of RNA polymerase inhibitors. *J Indian Chem. Soc*, 85, 627-631.
18. Agarwal V. K., Singh J., Louis B., Khadikar P. V., 2006.The topology of molecule and its lipophilicity. Current Computer Aided Design, 2, 369-403.
19. Agarwal V. K., Gupta M., Singh J., Khadikar P. V., 2005.*A* novel method of estimation of lipophilicity using distance based topological indices:dominating role of equalized electronegativity. *Bioorg Med Chem*, 13(6),2109-2120.
20. Agarwal V. K., Bano S., Khadikar P. V., 2003.Topological approach to quantifying molecular lipophilicity of heterogenous set of organic compounds. *Bioorg Med Chem*, 11(18), 4039-4047.
21. Khadikar P. V., Jaiswal M., Gupta M., Mandolai D., Sisodia R. S., 2005.QSAR studies on 1,2-dithiol-3-thiones :modeling of lipophilicity, quinone reductase specific activity and production of growth hormone. *Bioorg Med Chem Lett* , 15(4),1249-1255.
22. Khadikar P. V., Sharma V., Verma R. G., 2005.Novel estimation of lipophilicity using 13C NMR chemical shifts as molecular descriptor. *Bioorg Med Chem Lett*, **15**(2), 421- 425.
23. Khadikar P. V., Singh S., Mandoloi D., Joshi, S., Bajaj A. V., 2003.QSAR study on bioconcentration factor (BCF) of polyhaloginated biphenlys using the PI index. *Bioorg Med Chem*, 11(23), 5045-5050.
24. **.**Khadikar P. V., Mandoloi D., Bajaj A .V., Joshi S., 2003.QSAR study on solubility of alkanes in water and their partition coefficient in different solvent system using PI index. *Bioorg Med Chem Lett*, 13(3),419-422.
25. Khadikar P. V., Singh S., Srivastava A., 2002.Novel estimation of lipophilic behavioural polychlorinated biphenys. *Bioorg Med Chem Lett*, 12(7), 1125-1128.
26. Jaiswal M., Khadikar P. V., Supuran C. T., 2004. Topological modeling of lipophilicity, diuretic activity, and carbonic inhibition activity of benzene sulphonamides:a molecular connectivity approach. *Bioorg Med Chem Lett*, 14(22), 5661-5666.
27. Thakur M., Agarwal A., Thakur A., Khadikar P. V., 2004.QSAR study on phenolic activity: need of positive hydrophobic term (logP) in QSAR. *Bioorg Med Chem*, 12, 2287-2293.
28. Bikash D., Shovanlal G., Subrata B., Soma S., Jha T., 2003.QSAR study on some pyridoacridine ascididamine analogues as anti-tumor agents. *J Bioorg Med Chem* , 11(24),5493-5499.
29. Diudea M. V., 2000.QSPR/QSAR studies for molecular descriptors Ed Nova Science Hunting don, NewYork.
30. Pogliani L., 1994.Structural property relationships of amine acids and some Peptides. Aminoacids, 6**,** 141.
31. Pogliani L., 1996.Modeling with special descriptors derived from a medium size set of connectivity indices. *J Phys Chem*, 100, 1806.
32. Cramer R. D. III, Bunce J. D., Patterson D. E., 1988.Cross validation, Bootstrapping, and partial least squares compared with multiple regression in conventional QSAR studies. *Quant Struct Act Relat*, 7, 18.
33. Podlgar B. L., Ferguson D. M., 2000.QSAR and CoMFA: a perspective on the practical application to drug discovery. *Drug Des Discov*, 7(1), 4-12.
34. Chattergee S., Hadi A. S., 2000.Price B Regression analysis by example 3rd Edn Willey Vch New York.

Table-1 Biological activities and physicochemical parameters of



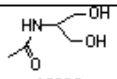
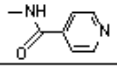
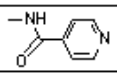
S. No.	R_1	R_2	Ior	Xeq	$^1\chi$	$^2\chi$	$^3\chi$	WA	I	Observed pKi
1.	-OH	$-C_5H_{11}$	1.528	2.279	10.920	10.529	8.207	4.545	1	7.444
2.	$-CONH_2$	$-C_5H_{11}$	1.533	2.289	11.831	11.460	8.801	4.653	0	5.660
3.	$-CONHCH_3$	$-C_5H_{11}$	1.521	2.282	12.369	11.601	9.319	4.754	0	5.900
4.	$-CON(CH_3)_2$	$-C_5H_{11}$	1.523	2.282	12.741	12.319	9.671	4.832	0	5.917
5.		$-C_5H_{11}$	1.549	2.307	13.817	12.651	10.412	5.064	0	5.699
6.	-NH2	$-C_5H_{11}$	1.536	2.271	10.920	10.529	8.207	4.545	0	6.668
7.	-CN	$-C_5H_{11}$	1.550	2.282	11.458	10.720	8.549	4.609	0	6.412
8.	$-NHCO_2CH_3$	$-C_5H_{11}$	1.537	2.298	12.852	12.061	9.427	4.957	0	5.854
9.	$-NHSO_2CH_3$	$-C_5H_{11}$	1.541	2.301	12.604	13.077	8.900	4.889	0	5.764
10.	$-NHCONHCH_3$	$-C_5H_{11}$	1.543	2.291	12.852	12.061	9.427	4.957	0	5.688
11.	$-NHCONH_3$	$-C_5H_{11}$	1.538	2.285	12.314	11.942	8.799	4.818	0	5.854
12.		$-C_5H_{11}$	1.572	2.303	14.886	13.923	11.154	5.501	0	5.752
13.	$-CH_2NHCONH_2$	$-C_5H_{11}$	1.536	2.291	12.814	12.283	9.140	5.020	0	6.107
14.	$-CH_2NHCOCH_3$	$-C_5H_{11}$	1.519	2.282	12.814	12.283	9.140	5.020	0	5.824
15.	$-SCH_3$	$-C_5H_{11}$	1.561	2.265	11.458	10.720	8.549	4.609	0	6.329
16.	$-SOCH_3$	$-C_5H_{11}$	1.574	2.279	11.831	11.460	8.801	4.653	0	5.714
17.	-OH		1.515	2.267	12.654	12.664	9.673	5.202	1	9.699
18.	-CN		1.538	2.270	13.192	12.855	10.016	5.241	0	8.276
19.	$-NH_2$		1.521	2.261	12.654	12.664	9.673	5.202	0	8.538
20.	$-NHCOCH_3$		1.524	2.274	14.048	14.076	10.265	5.400	0	6.666
21.	$-NHCONHCH_3$		1.529	2.279	14.586	14.195	10.893	5.514	0	6.590
22.			1.554	2.289	16.620	16.057	12.620	5.987	0	5.963
23.	$-NHSO_2CH_3$		1.528	2.285	14.338	15.211	10.366	5.454	0	6.593

Table-2 Correlation matrix showing correlation among various physico-chemical parameters and inhibitory activity

	pKi	Ior	Xeq	$^1\chi$	$^2\chi$	$^3\chi$	WA	I
pKi	1.000							
Ior	-0.444	1.000						
Xeq	-0.688	0.348	1.000					
$^1\chi$	-0.109	0.112	0.346	1.000				
$^2\chi$	0.014	-0.024	0.231	0.949	1.000			
$^3\chi$	-0.004	0.119	0.252	0.976	0.905	1.000		
WA	0.154	-0.018	0.131	0.956	0.953	0.945	1.000	
I	0.625	-0.319	-0.263	-0.259	-0.196	-0.189	-0.122	1.000

TABLE- 3 Comparisons between Observed and Predicted Activities and Their Residual Values

S. No.	Observed	Predicted	Residual
1.	7.444	7.972	-0.528
2.	5.660	5.763	-0.103
3.	5.900	6.259	-0.359
4.	5.917	6.311	-0.394
5.	5.699	5.110	0.589
6.	6.668	6.550	0.118
7.	6.412	5.977	0.435
8.	5.854	5.539	0.315
9.	5.764	5.312	0.452
10.	5.688	5.851	-0.163
11.	5.854	6.065	-0.211
12.	5.752	5.529	0.223
13.	6.107	5.942	0.165
14.	5.824	6.485	-0.661
15.	6.329	6.756	-0.427
16.	5.714	6.024	-0.310
17.	9.699	9.171	0.528
18.	8.276	7.149	1.127
19.	8.538	7.661	0.877
20.	6.666	7.159	-0.493
21.	6.590	6.975	-0.385
22.	5.963	6.717	-0.754
23.	6.593	6.635	-0.042

Table-4 Cross-validated parameters and predictive error of coefficient of correlation (PE) for the proposed model

Eq. no.	n	Parameter Used	PRESS	SSY	PRESS/SSY	R^2_{cv}	PSE	R	$1-R^2$	PE	6PE
1.	23	Xeq +Ior +WA+ I	5.571	19.116	0.291	0.709	0.492	0.880	0.226	0.031	0.186
2.	23	Xeq +Ior + $^1\chi$ + I	6.124	18.563	0.330	0.670	0.516	0.867	0.248	0.034	0.204
3.	23	Xeq +Ior + $^2\chi$ + I	6.171	18.516	0.333	0.667	0.518	0.866	0.250	0.034	0.204
4.	23	Xeq +Ior + $^3\chi$ + I	6.306	18.381	0.343	0.657	0.524	0.863	0.255	0.035	0.210

Figure 1. A plot showing comparison between observed pKi and predicted pKi values using model 1