WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 7.523
Volume 6, Issue 11, 1068-1079. Research Article ISSN 2277– 7105

# IN SILICO MOLECULAR MODELING AND PREDICTION OF ACTIVITY OF OPTIMIZED PROTEIN KINASE INHIBITORS FOR THE TREATMENT OF RHEUMATOID ARTHRITIS

**Shraddha Srivastava, Neerja Shukla* and A. K. Srivastava***

QSAR Research Laboratory, Department of Chemistry, University of Allahabad, Allahabad, U.P. 211002, India.

Article Received on
08 August 2017,

Revised on 28 August 2017,
Accepted on 18 Sept. 2017

DOI: 10.20959/wjpr201711-9754

***Corresponding Author**
**Neerja Shukla**
QSAR Research Laboratory, Department of Chemistry, University of Allahabad, Allahabad, U. P. 211002, India.

## ABSTRACT

Quantitative structure activity relationship has been performed on a series of thirty compounds of optimized protein kinase inhibitors, using different physicochemical parameters along with appropriate indicator variables. The physicochemical parameters selected for the present series of compounds were used for multiple linear regression analysis (MLRA). Various regression models have been tested and the statitistical data indicate that some of the descriptors provide valuable information to predict activity of these derivatives. The predictive ability of the model was cross-validated by appreciable cross-validated $R^2$ values ($R^2_{cv}$) were obtained and was also tested by leave one out (LOO) technique.

**KEYWORDS:** QSAR, optimized protein kinase, Regression Analysis, MLRA.

## INTRODUCTION

Rheumatoid arthritis is a disease that has direct involvement with the immune system. This disease is considered to be degenerative and currently the only thing that can be done is manage the painful symptoms and suppress the self targeting actions by using immune suppressing drugs. The cause of rheumatoid arthritis is mostly unknown but there is a high amount of evidence that there are genetic predispositions for the disease. This being said however there are also environmental factors to asses these include, bacteria, viruses, fungi and other environmental factors. Doctors primarily use a physical examination to first suspect R.A. then send for blood work to confirm. There are many aspects to this disease and many questions left unanswered, the treatments available now are only temporarily and can in some

cases cause more problems than benefits. Lab experiments and clinical trials are currently showing some great results and could within our lifetimes cure many autoimmune diseases including Rheumatoid arthritis.[1]

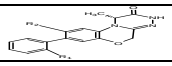
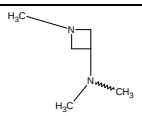
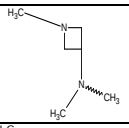
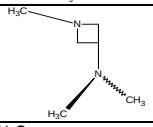
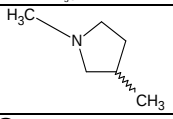
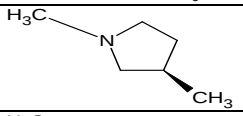
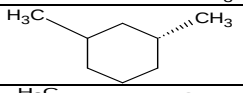
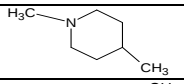
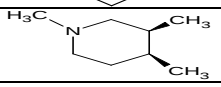
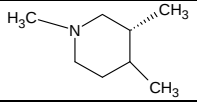
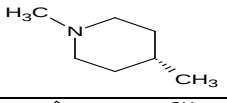
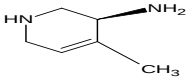
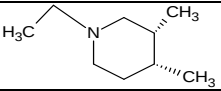
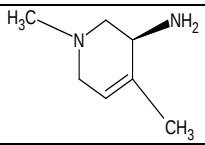
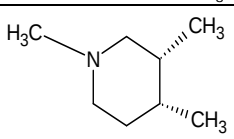
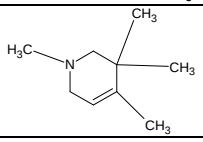
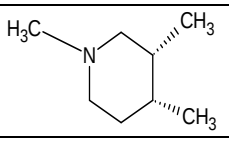
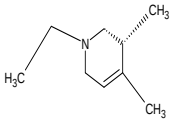
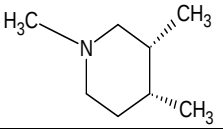
Although much is unknown on the causes of R.A. there are many things we see in correlation with the onset of disease. These include Bacterial, viral, and fungal infections. The mycoplasma bacteria, Epstein-Barr virus, cytomegalovirus, parvovirus and rubella (German measles) virus have all been considered as possible causative factors but conclusive evidence is still lacking. Many times there have only been considerations for infectious bacteria causing this disease but now that idea is being questioned. A study involving mice in bacteria free cages showed that the friendly gut dwelling segmented filamentous bacteria (SFB) can cause onset of R.A. Inhibition of protein kinase Cθ (PKCθ) blocks the activation of cells[2] and thus is hypothesized to ameliorate cell mediated disease states such as rheumatoid arthritis (RA), inflammatory bowel disease (IBD), and psoriasis. Multiple companies have worked to identify suitable chemical matter to inhibit this intriguing target that is predominately expressed in cells.[3]

**Experimental Section**

**METHODOLOGY**

Inhibitory activity as reported by George et al. as $IC_{50}$ were converted into their log units (log $IC_{50}$) and used in the present investigation. An attempt has been made to correlate the activity of these compounds with various physicochemical parameters[5] such as surface tension (St), wiener index (W), mean wiener index (WA), molecular weight (MW) and molecular connectivity and have been used to study the relationship between parameters and properties. St and MW were calculated by ACD Lab Chem. Sketch Software version[5] 12 whereas W, WA, were evaluated by E-Dragon Software[5] as given in Table 1.

**Table 1: Structural detail and Biological activity for series of Optimized Protein Kinase Cθ (PKCθ) Inhibitors with indicator parameter.**

| Comp. No. | R1 | R2 | $I_6$ | $I_7$ | $I_8$ | $I_{11}$ | $I_{14}$ | $I_{17}$ | $IC_{50}$ |
|---|---|---|---|---|---|---|---|---|---|
| 1 |  | H | 0 | 0 | 0 | 0 | 0 | 0 | 7.64 |
| 2 | CF3 | H | 0 | 0 | 0 | 0 | 0 | 0 | 7.64 |
| 3 | CF3 | Me | 0 | 0 | 0 | 0 | 0 | 0 | 7.23 |
| 4 | CF3 | H | 0 | 0 | 0 | 0 | 0 | 0 | 7.24 |
| 5 | CF3 | Me | 0 | 0 | 0 | 0 | 0 | 0 | 6.15 |
| 6 | Ph | H | 0 | 0 | 0 | 0 | 0 | 0 | 7.28 |
| 7 | Ph | Me | 0 | 0 | 0 | 0 | 0 | 0 | 8.39 |
| 8 | 2-F-Ph | Me | 0 | 0 | 0 | 0 | 0 | 0 | 8.39 |
| 9 | H |  | 0 | 0 | 0 | 0 | 0 | 0 | 8.39 |
| 10 | F |  | 0 | 0 | 0 | 0 | 0 | 0 | 8.39 |
| 11 | F |  | 0 | 0 | 0 | 0 | 0 | 0 | 8.52 |
| 12 | F |  | 0 | 0 | 0 | 0 | 0 | 0 | 7.37 |
| 13 | F |  | 0 | 0 | 0 | 0 | 0 | 0 | 7.39 |
| 14 | F |  | 0 | 0 | 0 | 0 | 0 | 0 | 7.37 |
| 15 |  |  | 1 | 0 | 0 | 0 | 0 | 0 | 7.37 |
| 16 |  |  | 0 | 1 | 0 | 0 | 0 | 0 | 8.52 |
| 17 |  |  | 0 | 0 | 1 | 0 | 0 | 0 | 8.39 |
| 18 |  |  | 0 | 0 | 0 | 0 | 0 | 0 | 7.80 |
| 19 |  |  | 0 | 0 | 0 | 0 | 0 | 0 | 8.52 |
| 20 |  |  | 0 | 0 | 0 | 1 | 0 | 0 | 8.30 |

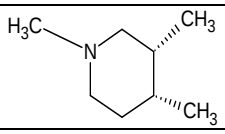
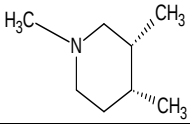
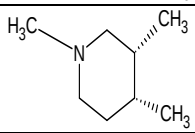
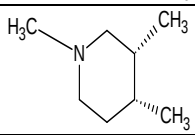
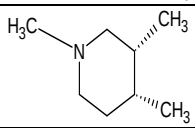
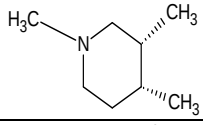
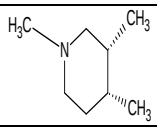
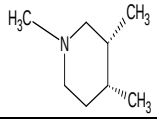
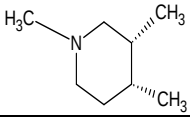
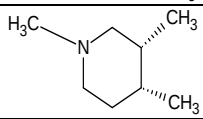
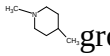
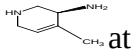
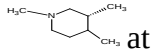
| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 21 | 2-F |  | 0 | 0 | 0 | 0 | 0 | 0 | 8.52 |
| 22 | 3-F |  | 0 | 0 | 0 | 0 | 0 | 0 | 7.85 |
| 23 | 4-F |  | 0 | 0 | 0 | 0 | 1 | 0 | 7.72 |
| 24 | 2-CH3 |  | 0 | 0 | 0 | 0 | 0 | 0 | 8.09 |
| 25 | 4-CH3 |  | 0 | 0 | 0 | 0 | 0 | 0 | 7.60 |
| 26 | 3-$OCH_3$ |  | 0 | 0 | 0 | 0 | 0 | 1 | 8.15 |
| 27 | OCH3 |  | 0 | 0 | 0 | 0 | 0 | 0 | 8.00 |
| 28 | 3,4-OCH2CH2O- |  | 0 | 0 | 0 | 0 | 0 | 0 | 8.70 |
| 29 | 2-F-4-CH3 |  | 0 | 0 | 0 | 0 | 0 | 0 | 8.30 |
| 30 | 2-F-4-OCH3 |  | 0 | 0 | 0 | 0 | 0 | 0 | 8.70 |

**Table 2: Physicochemical topological and quantum chemical descriptors for series of derivatives.**

| Comp. no. | Activity | $X^0$ | $X^1$ | $X^2$ | $X^3$ | Dipole | JX | MV | PC | Polar | T.E | Lumo |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 7.64 | 18.68990 | 12.17830 | 13.58599 | 3.58599 | .44047 | 1.73 | 279.90 | 747.50 | 42.39 | -1334.40 | -0.08090 |
| 2 | 7.23 | 19.56010 | 12.61580 | 13.15650 | 3.59789 | .59220 | 1.77 | 248.40 | 651.60 | 35.73 | -1372.36 | -0.16314 |
| 3 | 7.24 | 19.56010 | 12.57210 | 13.48470 | 3.87467 | .47111 | 1.70 | 248.40 | 651.60 | 35.73 | -1372.38 | -0.80498 |
| 4 | 6.15 | 20.43040 | 13.00970 | 13.81640 | 3.88656 | .46109 | 1.75 | 269.70 | 697.10 | 37.84 | -1411.30 | -0.07900 |
| 5 | 7.28 | 19.56010 | 13.48470 | 13.48470 | 3.87467 | .47111 | 1.70 | 328.30 | 903.10 | 50.37 | -1372.38 | -.09474 |
| 6 | 8.39 | 24.90500 | 16.67540 | 16.08380 | 3.17104 | .47615 | 1.51 | 349.50 | 948.60 | 52.48 | -1550.54 | -.09809 |
| 7 | 8.39 | 25.77530 | 17.06920 | 16.71760 | 3.45972 | 1.22001 | 1.50 | 352.40 | 948.70 | 52.43 | -1649.20 | -.06898 |
| 8 | 8.39 | 21.04320 | 14.37080 | 13.90580 | 2.70543 | .86166 | 1.61 | 307.40 | 819.90 | 45.91 | -1305.32 | -.07145 |
| 9 | 8.39 | 21.91350 | 14.78150 | 14.78150 | 2.91055 | .93941 | 1.63 | 310.30 | 820.10 | 45.85 | -1403.97 | -.07044 |
| 10 | 8.52 | 21.91350 | 14.78150 | 14.43330 | 2.91055 | 1.53433 | 1.64 | 315.60 | 824.60 | 46.11 | -1387.98 | -.07199 |
| 11 | 7.37 | 20.12060 | 14.02490 | 13.15550 | 2.10797 | 1.35530 | 1.64 | 279.90 | 747.50 | 42.39 | -1310.14 | -.69942 |
| 12 | 7.39 | 20.82770 | 14.52490 | 13.49710 | 2.10797 | 1.69970 | 1.62 | 295.90 | 786.10 | 44.22 | -1349.12 | -.69927 |
| 13 | 7.37 | 21.69790 | 14.93550 | 14.03650 | 2.31309 | 1.66202 | 1.64 | 311.10 | 817.20 | 45.98 | -1388.06 | -.06912 |
| 14 | 7.37 | 21.69790 | 14.93550 | 14.03650 | 2.31309 | 1.66942 | 1.64 | 311.10 | 817.20 | 45.98 | -1388.07 | -.06963 |
| 15 | 8.52 | 21.69790 | 14.93550 | 14.03650 | 2.31309 | 1.45526 | 1.64 | 311.10 | 817.20 | 45.98 | -1388.06 | -.07121 |
| 16 | 8.39 | 20.82770 | 14.52490 | 13.49710 | 2.10797 | 1.74719 | 1.62 | 295.90 | 786.10 | 44.22 | -1360.81 | -.07118 |
| 17 | 7.80 | 22.40500 | 15.47360 | 14.20560 | 2.22853 | 1.73172 | 1.61 | 327.10 | 855.80 | 47.80 | -1439.43 | -.07337 |
| 18 | 8.52 | 21.69790 | 14.91870 | 14.14280 | 3.58599 | 1.19819 | 1.63 | 311.10 | 817.20 | 45.98 | -1388.07 | -.07216 |
| 19 | 8.30 | 21.69790 | 14.91870 | 14.13090 | 2.39644 | .50177 | 1.62 | 311.10 | 817.20 | 45.98 | -11388.1 | -.07387 |
| 20 | 8.52 | 21.69790 | 14.91870 | 14.14280 | 2.39664 | .74854 | 1.63 | 311.10 | 817.20 | 45.98 | -1388.07 | -.66824 |
| 21 | 7.85 | 21.69790 | 14.91870 | 14.14280 | 2.39664 | 1.33326 | 1.63 | 323.40 | 848.10 | 47.78 | -1328.35 | -.06757 |
| 22 | 7.72 | 21.69790 | 14.91870 | 14.14280 | 2.39664 | 1.31418 | 1.63 | 323.40 | 848.10 | 47.78 | -1329.35 | -.06676 |
| 23 | 8.09 | 22.40500 | 15.45670 | 14.30000 | 2.31209 | 1.29149 | 1.60 | 329.90 | 867.30 | 48.33 | -1403.04 | -.68287 |
| 24 | 7.60 | 22.40500 | 15.45670 | 14.31100 | 2.31209 | 1.69521 | 1.63 | 329.90 | 867.30 | 48.33 | -1403.04 | -.68287 |
| 25 | 8.15 | 22.40500 | 15.47360 | 14.22760 | 2.24405 | 2.10056 | 1.64 | 329.90 | 867.30 | 48.33 | -1403.02 | -.06447 |
| 26 | 8.00 | 22.56820 | 15.32940 | 14.67030 | 2.60176 | 1.03481 | 1.64 | 314.00 | 817.40 | 45.92 | -1486.71 | -.07467 |
| 27 | 8.70 | 23.98240 | 16.42220 | 14.94610 | 2.38013 | 2.11305 | 1.66 | 351.50 | 917.50 | 50.64 | -1516.66 | -.07450 |
| 28 | 8.30 | 26.81080 | 18.42220 | 16.41410 | 2.38013 | 2.20480 | 1.63 | 379.80 | 1021.10 | 55.11 | -1743.89 | -.06146 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 29 | 8.70 | 22.56820 | 15.32840 | 14.67030 | 2.60176 | .72386 | 1.64 | 326.30 | 848.30 | 47.73 | -1427.02 | -.06873 |
| 30 | 8.70 | 23.27530 | 15.86740 | 14.86130 | 2.53272 | .74377 | 1.65 | 324.40 | 861.50 | 48.14 | -1501.69 | -.06907 |

## RESULTS AND DISCUSSION

QSAR studies were performed on set of 30 compounds of optimized protein kinase inhibitors. The biological activity data of these compounds were correlated with different physio chemical parameter given in Table 2 such as molar volume (Mv), parachor (Pc), polarizibility (polar), and quantum chemical descriptors such as total energy (TE), highest occupied molecular orbital energy (HOMO) and lowest unoccupied molecular orbital energy (LUMO). The monoparametric models cannot be used for modeling the $pIC_{50}$ because the quality of statistical data is not very good. Biparametric models were also discarded because of poor quality of statistical data. Hence, an attempt has been made to obtain multi-parametric models. In order to study the role of different substituents at different positions, indicator parameters $I_6$ which represent  group at $R_1$ position, $I_8$ which represent  at $R_1$ position and $I_7$ which represent  at $R_1$ position were introduced. Multiple regression analysis[6] resulted in several significant tri parametric QSAR models. Descriptors were selected for the final equation having inter-correlation coefficient below 0.5 were considered. The stepwise development of equation along with changes in statistical qualities on gradual addition of descriptors was done.

### Modeling of $pIC_{50}$ using empirical parameters

$PIC_{50}$=3.14(±0.69)Mv -2.40(±0.046)Pc +2.94(±0.589)pz - 0.684(±1.369)$I_6$ +0.631(±1.262)$I_8$ – 3.420 n =30 R= 0.876 , $R^2$ = 0.601 , $R^2A$ = 0.493 , S.E = 0.47 F = 4.62 Q = 1.864 …… (1)

Equation 1 explains only 96.7% variance in the drug activity. It shows that group presented by $I_8$ contributes positively while indicated by $I_6$ and parameter parachor (Pc) contributes negatively. It is the best equation, obtained using physiochemical parameter.

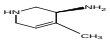
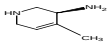
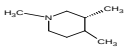
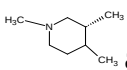
Lowest unoccupied molecular orbital energy (LUMO ) has also been found to be an effective parameter in modeling of $pIC_{50}$. For this muti-parametric equation, $R^2$ comes out to be 0.719. The equation is given below:

$PIC_{50}$ = 1.532(±1.492) LUMO+0.435(±0.714) dipole - 474 (±0.043) Te - 0.981(±1.962) $I_6$ - 0.396(±0.792) $I_7$ – 7.665 n = 30, R = 0.896, $R^2$ = 0.719 , $R^2A$ =0.515 , S.E = 0.458 , F = 3.96, Q = 1.957…… (2)

Equation 2 explains only 86.7% variance in the drug activity. It shows that lowest unoccupied molecular orbital energy (LUMO) contribute positively. Introducing lowest unoccupied molecular orbital energy (LUMO) parameter in place of molar volume has also been found effective in modeling of $pIC_{50}$. For this equation, $R^2$ comes out to be 0.719. The equation is given below:

**$PIC_{50}$** =1.046 (±1.304) $X^1$-0.918 (±1.495) $X^0$+0.768 (±1.486) $X^2$-0.370(±0.0.8) $I_{11}$+ 0.721(± 1.442) $I_{14}$ + 0.730 n =30, R = 0. 875, $R^2$ = 0.701 , $R^2A$ =0.615 , S.E = 0.398, F = 5.93 , Q = 2.198…….(3)

Equation 3 explains only 73.5% variance in the drug activity. It shows that Information unoccupied molecular orbital energy (LUMO) contribute positively.

Equations obtained using parameter in the present analysis (eq.1to3), show that the coefficient of parachor is negative (equations 1) i.e. decrease in the value of this parameter enhances the activity of the drug. The above equations show that the coefficient of LUMO and Mv are positive (equation 1 & 2) and this indicates that bulkier substituent with more branching should be preferred for future modeling. In equation 1 to 3 indicator parameter, $I_8$, which represent  at $R_1$ position, has a positive coefficient suggesting that the presence of  at $R_1$ position is favorable for the activity while coefficient of indicator parameter, $I_6$ &, $I_7$ which represent  &  at $R_1$ position, is negative suggesting that the presence of  &  at $R_1$ position is not favorable for the activity.

Out of several QSAR model, model (1) show best result. In order to confirm that the model with excellent statistics has also excellent prediction power too, we have evaluated quality factor Q. The predictive power as determined by the Pogliani $Q^7$ parameter for the model expressed by eq. (1) [Q = 1.864] confirms that this model has excellent statistics as well as

excellent predictive power. Predicted and residual activity values for model (1) are given in Table 4. Predicted values are the calculated activities obtained from model (1) and the residual values are the difference between the observed biological activities and calculated activities. The cross validation analysis was performed using leave one out (LOO) method[8] 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[9] provides the values of PRESS, SSY, PSE, $R^2_{CV}$ and $R^2_A$ from which we can test the predictive power of the proposed model. These statistical parameters can be calculated form following equations:

$$PRESS = \sum(X_{obs} - X_{cal})^2 \quad \text{.....(i)}$$

$$SSY = \sum(X_{obs} - X_{mean})^2 \quad \text{.....(ii)}$$

$$PSE = \sqrt{PRESS/n} \quad \text{.....(iii)}$$

$$R^2_{cv} = 1 - \frac{PRESS}{SSY} \quad \text{.....(iv)}$$

$$R^2_A = 1 - (r^2)\left(\frac{n-1}{n-p-1}\right) \quad \text{.....(v)}$$

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 of PRESS/SSY can be used to calculate approximate confidence intervals of prediction of a 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)[10], 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 these models 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 does not 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) [11 - 17] 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. The plot of observed and predicted activity for the model no. has been shown in the figure 1.

**Table 3: Comparison between observed and predicted activities and their residual values for the model 1.**

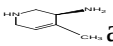
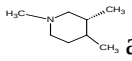
| Sr. No. | Observed Activity | Predicted Activity | Residual Activity |
|---|---|---|---|
| 1 | 7.64 | 7.5952 | 4.47 |
| 2 | 7.23 | 6.8526 | .3774 |
| 3 | 7.24 | 6.8526 | .3874 |
| 4 | 6.15 | 7.1158 | -.9658 |
| 5 | 7.28 | 7.8750 | -.5950 |
| 6 | 8.39 | 8.1347 | .2553 |
| 7 | 8.39 | 8.2178 | .1722 |
| 8 | 8.39 | 7.8408 | .5492 |
| 9 | 8.39 | 7.9186 | .4714 |
| 10 | 8.52 | 8.0701 | .4499 |
| 11 | 7.37 | 7.5952 | -.2252 |
| 12 | 7.39 | 7.7587 | -.3687 |
| 13 | 7.37 | 8.0542 | -.6842 |
| 14 | 7.37 | 7.5952 | 6.21 |
| 15 | 8.52 | 7.5952 | .4658 |
| 16 | 8.39 | 8.3900 | -3.5 |
| 17 | 7.80 | 8.2147 | -.4147 |
| 18 | 8.52 | 8.0542 | .4658 |
| 19 | 7.64 | 8.0542 | .2458 |
| 20 | 8.30 | 8.0542 | .4658 |
| 21 | 8.52 | 8.2661 | -.4161 |
| 22 | 7.85 | 8.2661 | -.5461 |
| 23 | 7.72 | 8.1909 | -.1009 |
| 24 | 8.09 | 8.1909 | -.5909 |
| 25 | 7.60 | 8.1909 | -4.09 |
| 26 | 8.15 | 8.1320 | -.1320 |
| 27 | 8.00 | 8.4103 | .2897 |
| 28 | 8.70 | 8.2128 | 8.72 |
| 29 | 8.30 | 8.3468 | .3532 |
| 30 | 8.70 | 8.346 | .2458 |

**Table 4: Cross validated parameters and predictive error of coefficient of correlation (PE) for the model 1.**

| N | R | 1-$R^2$ | P.E | 6PE | PRESS | SSY | PRESS/SSY | $R^2_{CV}$ | PSE |
|---|---|---|---|---|---|---|---|---|---|
| 30 | 0.876 | 0.399 | 0.0886 | 0.5316 | .965 | 5.8 | 0.166 | 0.834 | 0.179 |

It is argued that if the values R < PE, then such correlation is not significant; however if values are R > PE in several times (at least three times), then values are correlated. However, if values are R > 6PE, then mathematically the correlation is unquestionably good. For all the models developed the condition R > 6PE is satisfied and hence they can be said to have a good predictive power.

## CONCLUSIONS

The current study was performed to examine the applicability of the empirical and DFT-based descriptors in QSAR analysis for studying the biological activity of a series of optimized protein kinase derivatives which are known as potent non-steroidal anti-inflammatory and analgesic agents. The obtained QSAR results based on empirical parameter such as molar volume, parachor, polarizibility with highest statistical quality $R^2$ (0.601) demonstrate that molecule with more branching, bulkier substituent and having low value of parachor(Pc) should be preferred for future modeling. With reference of indicator parameter the presence of  at $R_1$ position is favorable for the activity and the presence of  &  at $R_1$ position is not favorable for the activity of optimized protein kinase derivatives towards drug activity.

## REFERENCES


1. Turesson C., O' Fallon W. M., Crowson C. S., Gabriel S. E., Matteson E. L. "Extra-articular disease manifestations in rheumatoid arthritis: incidence trends and risk factors over 46 years". *Ann. Rheum. Dis*., 2003; 62(8): 722–7.
2. Cohen S., Fleischmann R., Kinase inhibitors: a new approach to rheumatoid arthritis treatment. Curr Opin Rheumatol., 2010; 22(3): 330-5.
3. Genta, Marcia S., Genta, Robert M., Gabay, Cem, "Systemic rheumatoid vasculitis: a review". *Seminars in Arthritis and Rheumatism*, 2006; 36(2): 88–98.
4. George D. M., Breinlinger E. C., Argiriadi M. A., Zhang Y., Wang J., Bansal-Pakala P., Duignan D. B., Honore P., Lang Q. Y., Mittelstadt S., Rundell L., Schwartz A., Sun J., Edmunds J. J., Optimized protein kinase CΘ (PKCΘ) inhibitors reveal only modest anti-

inflammatory efficacy in a rodent model of Arthritis, Journal of Medicinal Chemistry, 2015; 58: 333-346.

5. Ishikawa T, Hirano H, Saito H, Sano K, Ikegami Y, Yamaotsu N, Hirono S., Quantitative structure-activity relationship (QSAR) analysis to predict drug-drug interactions of ABC transporter ABCG2. Mini Rev Med Chem., 2012; 12(6): 505-14.
6. Srivastava A. K., Shukla N. and Pathak V. K., Quantitative Structure Activity Relationship (QSAR) Studies on a series of off-target ion channel selective diltiazem sodium derivatives., *J. Indian Chem. Soc*., 2010; 87: 1-7.
7. Srivastava A.K., Shukla N., Pandey A. and Srivastava A. QSAR Based Modeling on a series of alpha-Hydroxy amides as a novel class of Braykinin B1 selective antagonists. J. Saudi Chem. Soc., 2011; 15: 215-220.
8. QSAR based modeling of hepatitis C virus NS5B inhibitors . Srivastava A.K., Pandey A., Srivastava A.and Shukla N., *J. Saudi Chem. Soc*., 2011; 15: 25-28.
9. Srivastava A. K., Shukla N., Quantitative structure activity relationship (QSAR) studies on a series of imidazole derivatives as novel ORL1 receptor antagonists, Journal of Saudi Chemical Society, 2013; 17(3): 321-328.
10. Srivastava A. K., Shukla N., QSAR based modeling on a series of lactam fused chroman derivatives as selective 5-HT transporters, , Journal of Saudi Chemical Society, 2012; 16(4): 405-412
11. Shukla N., Srivastava A. K.QSAR based modeling on a novel series of 2-chlorobenzamide derivatives as potent P2X (7) receptor antagonist, Oxidation Communications, 2014; 37(1): 290-300.
12. Srivastava A. K., Shukla N., Pathak V. K. Quantitative Structure Activity Relationship (QSAR) Studies on a series of carbamate appended N-alkylsulfonamides as inhibitors of peptide amyloid- β (Aβ), Oxidation Communications, 2013; 36(4): 1090-1101.
13. Shukla N., Srivastava A. K., QSAR studies on a novel cyclohexanamine class of human serotonin transporter (hSERT) inhibitory activities , Oxidation Communications, 2013; 36(1): 133-142.
14. Srivastava A. K., Shukla N., QSAR-based Modelling on a Novel Series of Pyrimidine-4-carboxamides as Antagonists of the Human A1 Receptor, , Oxidation Communications, 35(2): 423-437.
15. Shukla N., "QSAR-methods and applications", Gyandhara International Academic Publications, 2016.

16. Shukla N., QSAR studies on a series of 9-THC analogues as cannabinoid receptor modulators, International Journal of Student Research in Technology & Management, 2014, 2, 29-36,,
17. Diudea, M.V., QSPR/QSAR Studies for Molecular Descriptors. Nova Science, Huntington, New York, 2000.