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# Prediction of Acidity Constants of Thiazolidine-4-Carboxylic Acid Derivatives by Qsar Method

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**ABSTRACT**: Modelling of the acidity constant of thiazolidine-4-carboxylic acid derivatives as a function of molecular structures was established by means of the partial least squares algorithm. The subset of descriptors, which resulted in a low prediction error, was selected by genetic algorithm. This model was applied for the prediction of the acidity constant of some thiazolidine-4-carboxylic acid derivatives, which were not in the modelling procedure. Results of statistical analysis found with value of Variance as 0.8033, Cross validated regression coefficient and Fisher- value as 0.7552 and 13.885 respectively which may be useful for (medicinal) chemists in selecting the most suitable substituent for the development of more potent, effective and selective Thiazolidine-,4- carboxylic acid based acidity constant in future.

**Key words:** QSAR, Thiazolidine-4-carboxylic acid, PLS.

## I. INTRODUCTION

Acidity constants can be a crucial parameter for understanding and quantifying chemical marvels, similar as response rates, natural exertion, natural uptake, natural transport, and environmental fate.[1] It has been shown that acid-base parcels affect the toxicity[2-3], chromatographic retention gets, and pharmaceutical properties[4] of organic acids and bases. Important of the theoretical foundation of ultramodern organic chemistry is grounded on the observation of the goods on acid- base equilibrium of changing molecular structure.[5] Ali NIAZI, Turk J Chem. 30 (2006), 619 – 628.

A successful strategy for the vatic nation of the acidity constant is the construction of quantitative structure- exertion connections (QSARs).[6] QSARs are fine equations relating chemical structure to a wide variety of physical, chemical, natural and technological parcels. QSAR models can be used to prognosticate parcels of composites as yet unmeasured or indeed unknown. Therefore, the QSAR approach saves coffers and expedites the process of development of new motes.[7]

A major step in constructing QSAR models is chancing one or further molecular descriptors that represent variation in the structural property of the motes by a number. A wide variety of descriptors have been reported to be used in QSAR analysis.[8–10] Recent progress in computational tackle and the development of effective algorithms have supported the routine development of molecular amount chemical computations. Quantum chemical computations are therefore an seductive source of new molecular descriptors, which can, in principle, express all of the electronic and geometric parcels of motes and their relations.[11] Infinitesimal charges, loftiest engaged molecular orbital (HOMO) and smallest unoccupied molecular orbital (LUMO) powers, molecular polarizability, dipole moments, and powers of patch are exemplifications of quantum chemical descriptors used in QSAR studies.

Multiple direct retrogression (MLR) is generally used in QSAR modelling.[12] The co-linearity problem of the MLR system has been overcome through the development of the partial least places (PLS) system, which plays an important part in QSAR analysis PLS is a factor analysis- grounded system that was firstly suggested and chemically applied by Wold et al. [14] We've lately reported the operation of PLS modelling in spectrophotometric multivariate estimation.[15–22] PLS is used in confluence with optimization ways for point selection.[23] It has formerly been shown that inheritable algorithms ( GAs) [24–30] can be successfully used as a point selection fashion.[31–35]

## II. PRESENTATION OF DATA

In present study table-1 represents the structure of thiazolidine-4-carboxylic acid derivatives, while table-2 shows the calculated Constitutional, topological & connectivity descriptors with acidity constants of thiazolidine-4-carboxylic acid derivatives; table-3 represents the

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correlation matrix between different constitutional, topological and connectivity descriptors.
Descriptor and acidity constants are given in table-2, table-3 and table-4 represents the residual report from best model of, topological and connectivity descriptors. Table-5 represent the Cross validation of best models. Ridge regression (fig-3) is representing the multicollinearity is not present in this study.

## III. RESULT AND DISCUSSION

Multiple linear regression analysis and other statistical analysis were carried out on all the 23 molecules. The outlier molecules were then removed to improve the equation's predictive power. Descriptors were selected for the final equation based on their correlation coefficients and those descriptors having intercorrelation coefficient below 0.7 were considered, to select the best equation. Cross validation by leave one out method was carried out on these final set of 23 molecules to further enhance and validate the predictive power of the equation. Acceptability of the regression equation was judged by examining the statistical parameters.

The activity data pKa representing the concentration of compounds that inhibited the visible growth in various bacterial species is used as dependent variable to get a linear relationship in the QSAR models. These were correlated with different molecular descriptors like the constitutional descriptor; MW, topological descriptors; χt, Ram, Pol, MSD, $ZM^1$, $ZM^1V$ and connectivity descriptor; $\chi^0$, $\chi^1$, $\chi^2$. The values of the selected descriptors used in the regression analysis are presented in Table-2 were calculated for the lowest energy conformers of the compounds in the series of software E-Dragon developed by VCC lab.
The essential feature of multiple regression analysis is cross-validation which asses the productivity of the computed model. Cross-validation provides the values of PRESS, SSY, $S_{PRESS}$ and $R^2cv$ from which we can investigate the predictive power of the proposed model.

In order to determine the correlation between the observed biological activity, in terms pKa of the reported compounds and their structural parameters, QSAR investigation has been carried out model proposed by Hansch et. al. By using the data of table-3, correlation matrixes as well as the collinearity among the descriptors were calculated. A high inter relationship is observed between **Ram, MSD, $\chi^2$, $ZM^1V$ and MW** ($R^2$ = 0.8033), while low inter relationship is observed **$ZM^1V$** ($R^2$ = 0.6152). The results table-3 shows that some of the descriptors are mutually correlated. Thus, if a combination of them is present in the regression expression, them the model may suffer from a defect due to collinearity.

**pKa = 7.3619, -0.0057(±0.0010) $ZM^1V$** ……1
N=23, MSE= 7.1396, $R^2$= 0.6152, $AR^2$= 0.5969, Q-VALUE= 0.1098

**pKa = 6.4486, -0.2616(±0.1724) χ0, -0.0513(±0.0208) $ZM^1$** ….....2
N=23, MSE= 7.0384, $R^2$= 0.6387, $AR^2$= 0.6026, Q-VALUE= 0.1135

**pKa = 6.8545, 0.4603(±0.2273)Ram, 0.7615(±0.3022)MSD, -1.0500(±0.3433) $\chi^2$** .....3
N=23, MSE= 6.2339, $R^2$= 0.696, $AR^2$= 0.648, Q-VALUE= 0.1338

**pKa = 7.1027, -0.0074(±0.0033)Ram, 0.6279(±0.2186)MSD, 0.9532(±0.2864)$\chi^2$, -0.9639(±0.3132) $ZM^1V$**
.....……4
N=23, MSE = 5.1131, $R^2$ = 0.7638, $AR^2$ = 0.7113, Q-VALUE = 0.1709

The developed QSAR model eq. 4, demonstrated the importance of topological and connectivity descriptors which are used in the modeling especially topological. **Ram** coefficient is negative indicates that as their values increases the biological activity decreases, positive coefficient of **$\chi^2$** is directly proportional to activity. The correlation coefficient between the descriptors and activity is $R^2$ = 0.7638, which is quite good with the variance of 76.38% with the smallest standard error of estimation.

**pKa = 7.1477, -0.0122(±0.0040) Ram, 0.0075(±0.0041) MSD, 0.7074(±0.2098) $\chi^2$, 1.0463(±0.2736) $ZM^1V$, -1.1028(±0.3036) MW**…….....….5
N=23, MSE = 4.5082, $R^2$ = 0.8033, $AR^2$ = 0.7454, Q-VALUE = 0.1988

The QSAR model described by eq. 5, demonstrated the importance of constitutional, connectivity and topological indices in describing the biological activity. The positive correlation is shown by **MSD**, **$\chi^2$**, **$ZM^1V$** biological activity reveals that increase in value of topological descriptors decrease in biological activity. While negative coefficient is shown by **Ram** and **MW** with biological activity reveals that increase in value of constitutional descriptor **MW** will lead in activity.

The correlation coefficient between the descriptors and activity is $R^2$ = 0.8033, which is quite good with the variance of 80.33% with the

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smallest standard error of estimation. The PRESS/SSY value is 0.2448 indicates that the developed model is reasonable model to explain the biological activity.

The ratio PRESS/SSY can be used to calculate approximate confidence intervals of prediction of new compounds. To be a reasonable QSAR model PRESS/SSY should be smaller 0.4 and the value of this ratio smaller than 0.1 indicates an excellent model. Also if PRESS VALUE is transformed in a dimension less term by relating it to the initial sum of squares, be obtain $R^2_{CV}$ ($Q^2$) i.e. the complement to the trace on of unexplained variance over the total variance. Thus, 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 PSE (predictive square error), is directly related to the uncertainty of the prediction. This parameter, namely PSE is much more useful when $S_{PRESS}$ (uncertainty of prediction) comes out to be the same as MSE (mean square error). All cross-validated parameters given in Table-5 are in accordance with the aforementioned findings.

The validity of the models has been tested using cross-validation method and the tetra parametric model discussed above has been found to be the best. The $R^2_{CV}$ comes out to be 0.7552 also the lowest value of $S_{press.}$ A comparison between observed and estimated activity has also been demonstrated in figure-1.

According the result of biological screening summary of biological activity analogues a graph is plotted between observed and predicted pKa (Fig-1). Further a bar graph is also obtained to show the reliability of selected model between observed biological activities (Fig-2).

**Table-1: The structures of compounds studied and their pKa activity**

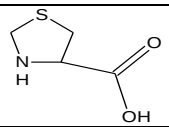
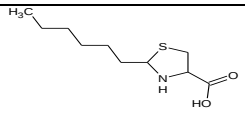
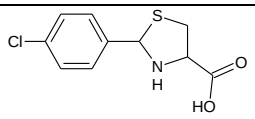
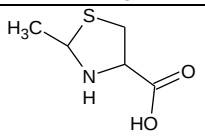
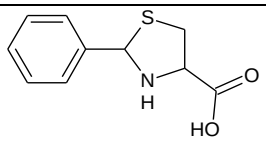
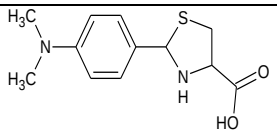
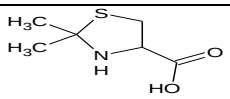
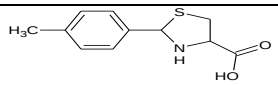
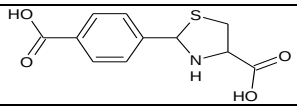
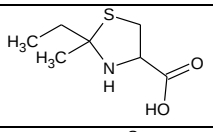
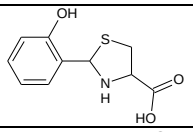
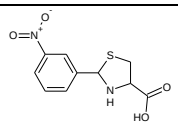
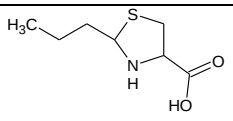
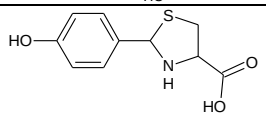
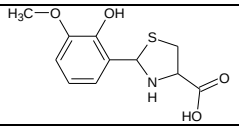
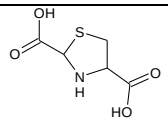
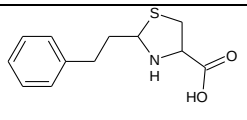
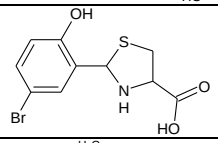
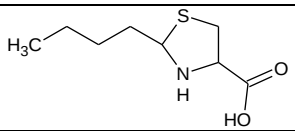
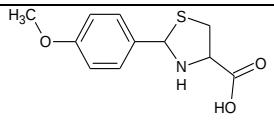
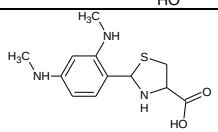
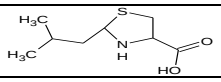
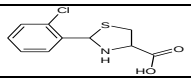
| S. No. | Structure of compounds | S. No. | Structure of compounds | S. No. | Structure of compounds |
|---|---|---|---|---|---|
| 1 |  | 9 |  | 17 |  |
| 2 |  | 10 |  | 18 |  |
| 3 |  | 11 |  | 19 |  |
| 4 |  | 12 |  | 20 |  |
| 5 |  | 13 |  | 21 |  |
| 6 |  | 14 |  | 22 |  |
| 7 |  | 15 |  | 23 |  |
| 8 |  | 16 |  | | |

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**Table-2: Calculated Constitutional, topological & connectivity descriptors and pKa activity of Compound**

| Com.no. | pKa | χt | Ram | Pol | MSD | $\chi^0$ | $\chi^1$ | $\chi^2$ | $ZM^1$ | $ZM^1V$ | MW |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 6.19 | 0.449 | 2 | 6 | 2.435 | 5.983 | 3.805 | 3.289 | 36 | 197 | 126.12 |
| 2 | 6.17 | 0.431 | 3 | 8 | 2.682 | 6.853 | 4.198 | 3.922 | 42 | 213 | 138.13 |
| 3 | 5.86 | 0.42 | 4 | 10 | 2.813 | 7.776 | 4.512 | 4.911 | 50 | 229 | 150.14 |
| 4 | 5.73 | 0.397 | 4 | 13 | 3.066 | 8.483 | 5.072 | 4.911 | 54 | 245 | 162.15 |
| 5 | 6.12 | 0.385 | 3 | 11 | 3.414 | 8.268 | 5.236 | 4.472 | 50 | 245 | 162.15 |
| 6 | 5.86 | 0.393 | 4 | 12 | 3.211 | 8.431 | 5.109 | 4.821 | 52 | 285 | 170.13 |
| 7 | 6.08 | 0.366 | 3 | 12 | 3.834 | 8.975 | 5.736 | 4.825 | 54 | 261 | 174.16 |
| 8 | 6.1 | 0.374 | 4 | 12 | 3.641 | 9.138 | 5.592 | 5.313 | 56 | 261 | 174.16 |
| 9 | 5.94 | 0.336 | 3 | 14 | 4.71 | 10.389 | 6.736 | 5.533 | 62 | 293 | 198.18 |
| 10 | 5.31 | 0.317 | 4 | 17 | 3.898 | 9.966 | 6.771 | 5.975 | 70 | 293 | 198.18 |
| 11 | 5.5 | 0.311 | 5 | 19 | 4.194 | 10.836 | 7.165 | 6.597 | 76 | 309 | 210.19 |
| 12 | 5.67 | 0.311 | 5 | 20 | 3.965 | 10.836 | 7.182 | 6.503 | 76 | 329 | 214.18 |
| 13 | 5.51 | 0.311 | 5 | 19 | 4.194 | 10.836 | 7.165 | 6.597 | 76 | 329 | 214.18 |
| 14 | 5.35 | 0.297 | 4 | 18 | 4.856 | 11.38 | 7.754 | 6.765 | 78 | 325 | 222.2 |
| 15 | 5.8 | 0.301 | 5 | 21 | 4.537 | 11.544 | 7.703 | 6.766 | 80 | 345 | 226.19 |
| 16 | 4.95 | 0.311 | 5 | 20 | 3.965 | 10.836 | 7.182 | 6.503 | 76 | 342 | 233.63 |
| 17 | 5.24 | 0.311 | 5 | 19 | 4.194 | 10.836 | 7.165 | 6.597 | 76 | 342 | 233.63 |
| 18 | 5.83 | 0.296 | 6 | 23 | 4.772 | 12.414 | 8.075 | 7.496 | 86 | 350 | 236.21 |
| 19 | 5.01 | 0.296 | 6 | 23 | 4.772 | 12.414 | 8.075 | 7.496 | 86 | 381 | 242.19 |
| 20 | 4.7 | 0.296 | 6 | 23 | 4.494 | 12.414 | 8.075 | 7.508 | 86 | 390 | 244.19 |
| 21 | 5.39 | 0.296 | 6 | 25 | 4.317 | 12.414 | 8.13 | 7.199 | 86 | 381 | 242.19 |
| 22 | 5.53 | 0.305 | 6 | 22 | 4.117 | 11.707 | 7.575 | 7.137 | 82 | 378 | 294.08 |
| 23 | 5.17 | 0.287 | 6 | 26 | 4.598 | 13.121 | 8.651 | 7.497 | 90 | 375 | 250.22 |

**Detailed Name of Descriptors:-**

| S. No. | Name of Descriptors | Detailed Name of Descriptors |
|---|---|---|
| 1 | Xt | Total structure connectivity index |
| 2 | Ram | Ramification index |
| 3 | Pol | Polarity number |
| 4 | MSD | Mean square distance index |
| 5 | $\chi^0$ | Connectivity index of order 0 |
| 6 | $\chi^1$ | Connectivity index of order 1 |
| 7 | $\chi^2$ | Connectivity index of order 2 |
| 8 | $ZM^1$ | First Zagreb index |
| 9 | $ZM^1V$ | First Zagreb index by valence vertex degrees |
| 10 | MW | Molecular weight |

**Table-3: Correlation Matrix of different descriptors**

| | pKa | Xt | Ram | Pol | MSD | $\chi^0$ | $\chi^1$ | $\chi^2$ | $ZM^1$ | $ZM^1V$ | MW |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **pKa** | 1 | 0.7303 | -0.7256 | -0.7608 | -0.5843 | -0.7271 | -0.7328 | -0.7703 | -0.7727 | -0.7843 | -0.7227 |
| **Xt** | | 1 | - | - | - | - | - | - | - | - | - |

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| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 0.8045 | 0.94266 | 0.9333 | 0.9673 | 0.9858 | 0.9565 | 0.9706 | 0.9331 | 0.9187 |
| **Ram** | | | 1 | 0.93111 | 0.6597 | 0.8806 | 0.8411 | 0.9266 | 0.9106 | 0.9095 | 0.8732 |
| **Pol** | | | | 1 | 0.8321 | 0.9757 | 0.969 | 0.9755 | 0.9884 | 0.9692 | 0.9334 |
| **MSD** | | | | | 1 | 0.9248 | 0.9366 | 0.8779 | 0.8803 | 0.8456 | 0.8218 |
| $\chi^0$ | | | | | | 1 | 0.9918 | 0.9825 | 0.9856 | 0.9646 | 0.9327 |
| $\chi^1$ | | | | | | | 1 | 0.973 | 0.9857 | 0.9556 | 0.9283 |
| $\chi^2$ | | | | | | | | 1 | 0.9937 | 0.9626 | 0.9371 |
| **$ZM^1$** | | | | | | | | | 1 | 0.967 | 0.9404 |
| **$ZM^1V$** | | | | | | | | | | 1 | 0.9616 |
| **MW** | | | | | | | | | | | 1 |

| C. No. | Obs. pKa | Est. pKa | Residual |
|---|---|---|---|
| 1 | 6.033 | 6.19 | 0.157 |
| 2 | 6.196 | 6.17 | -0.026 |
| 3 | 5.846 | 5.86 | 0.014 |
| 4 | 6.006 | 5.73 | -0.276 |
| 5 | 6.147 | 6.12 | -0.027 |
| 6 | 5.829 | 5.86 | 0.031 |
| 7 | 6.092 | 6.08 | -0.012 |
| 8 | 6.06 | 6.1 | 0.04 |
| 9 | 6.019 | 5.94 | -0.079 |
| 10 | 5.39 | 5.31 | -0.08 |
| 11 | 5.616 | 5.5 | -0.116 |
| 12 | 5.267 | 5.67 | 0.403 |
| 13 | 5.403 | 5.51 | 0.107 |
| 14 | 5.312 | 5.35 | 0.038 |
| 15 | 5.471 | 5.8 | 0.329 |
| 16 | 5.255 | 4.95 | -0.305 |
| 17 | 5.391 | 5.24 | -0.151 |
| 18 | 5.634 | 5.83 | 0.196 |
| 19 | 5.301 | 5.01 | -0.291 |
| 20 | 4.902 | 4.7 | -0.202 |
| 21 | 5.152 | 5.39 | 0.238 |
| 22 | 5.439 | 5.53 | 0.091 |
| 23 | 5.251 | 5.17 | -0.081 |

**Table-4: Residual Report**

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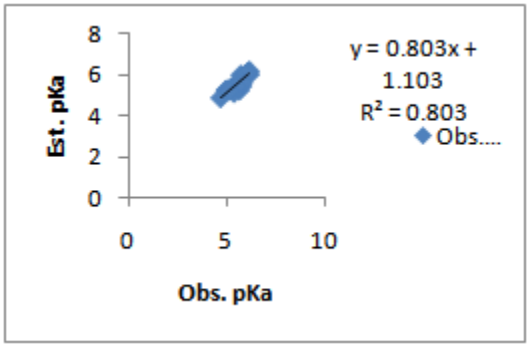


**Figure-1: The graph plotted between observed pKa and experimentally pKa**

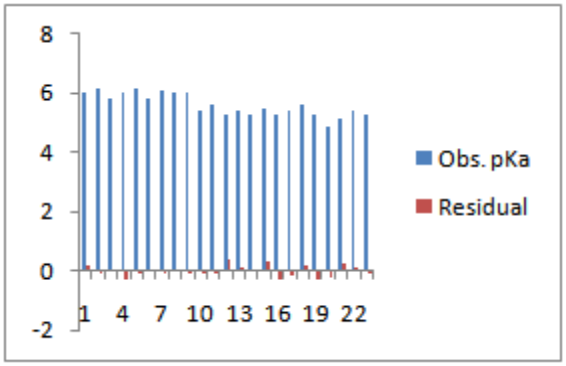


**Figure-2: Graph plotted between the residual and observed activity**

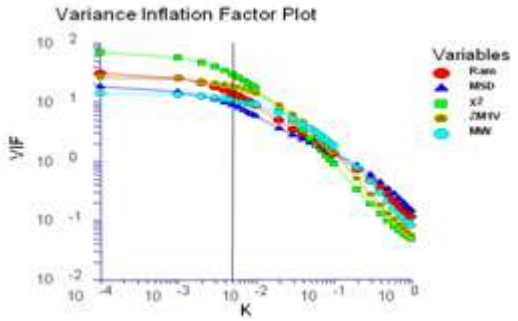


**Figure -3: Plot between VIF and K**

**TABLE – 5 – Result of Cross Validation**

| Model No | N | PRESS | SSY | PRESS/SSY | $R^2$ | $R^2_{CV}$ | PSE | $S_{press}$ |
|---|---|---|---|---|---|---|---|---|
| 1 | 23 | 1.4993 | 2.3968 | 0.6255 | 0.6152 | 0.3745 | 0.0532 | 0.2670 |
| 2 | 23 | 1.4076 | 2.4884 | 0.5656 | 0.6387 | 0.4344 | 0.0515 | 0.2651 |
| 3 | 23 | 1.1844 | 2.7117 | 0.4367 | 0.6960 | 0.5633 | 0.0473 | 0.2495 |
| 4 | 23 | 0.9203 | 2.9758 | 0.3092 | 0.7638 | 0.6908 | 0.0417 | 0.2260 |
| 5 | 23 | 0.7663 | 3.1297 | 0.2448 | 0.8033 | 0.7552 | 0.0380 | 0.2121 |

$PRESS = \sum(Y_{obs} - Y_{calc})^2$

$SSY = \sum(Y_{obs} - Y_{mean})^2$

$S_{press} = [\ press / (n-k-1)\ ]^{1/2}$

$PSE = \sqrt{press}/n$

$R^2_{cv} = 1 - \frac{PRESS}{SSY}$

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Where, $Y_{obs}$,$Y_{calc}$ and $Y_{mean}$ are observed, calculated and mean values; n is number of the compounds, k is number of parameters.

## IV. CONCLUSION

The following conclusions are obtained from this analysis:

(1) Topological, Constitutional indices & Connectivity parameters may be used for modeling of these compounds.

(2) Connectivity indices parameters are more effective in this QSAR study.

(3) **χt**, **Ram**, **Pol**, **MSD**, $\chi^0$, $\chi^1$, $\chi^2$, **ZM$^1$**, **ZM$^1$V** and **MW** parameters is useful for this study.

(4) The highest value $R^2$ = 0.8033 are obtained in QSAR models.

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