International Journal on Emerging Technologies **10**(4): 465-471(2019)

ISSN No. (Print): 0975-8364
ISSN No. (Online): 2249-3255

QSAR and Molecular Descriptor Analysis of Substituted 5-(-2 – methoxy benzylidene) - Rhodanine Ester Analogs as aldose Reductase Inhibitory Activity

Jyoti Pandey[1], Arun K. Gupta[2] and Ritu M. Gilhotra[3]
[1]Research Scholar, School of Pharmacy., SGVU (Rajasthan), India.
[2]Principal, Chameli Devi Institute of Pharmaceutical Sciences, Indore (Madhya Pradesh), India.
[3]Dean Research, School of Pharmacy, SGVU (Rajasthan), India.

(Corresponding author: Jyoti Pandey)
(Received 04 October 2019, Revised 11 November 2019, Accepted 28 December 2019)
(Published by Research Trend, Website: www.researchtrend.net)

ABSTRACT: Diabetes mellitus have reached worldwide deadly disease proportions with India being selected 'diabetes capital' of the world. Diabetes is a multi-system disorder comprising metabolic and vascular abnormalities resulting from insulin deficiency, with or without insulin resistance. There are a number of groups that make an effort to produce new ant-idiabetic agents. In view of above and as a part of our effort to develop newer anti-diabetic agents, molecular modeling analysis was performed to developed QSAR models that show substantial predictive promise for rhodanine ester analogs. The QSAR model explains 77.8 percent variance in activity with standard error of estimation (0.167). Model showed statistical significant internal predictivity (Q^2= 0.602) and external predictivity (r^2_{pred} = 0.516) values. The mathematically developed and statistically selected QSAR model revealed that Mor09u, Mor20v and RDF130p are contributing positively while BEHv2 contributed negatively to inhibitory activity. The structural insights gleaned from the study are helpful in designing of inhibitors with enhanced potency.

Keywords: QSAR; Rhodanine Ester Analogs; Anti-diabetic Activity; Aldose Reductase; Molecular Descriptors.

Abbreviations: AR, Aldose Reductase; QSAR, Quantitative structure Activity Relationship; DM, Diabetes Mallitus; SEE, Standard Error of estimation; SEQMLR, Sequential Multiple Linear Regression; RMS, Root Mean Square; VIF, Variance Inflation Factor; MLR, Multiple Linear Regression; QF, Quality Factor;

I. INTRODUCTION

Diabetes mellitus is affecting quality of patient's life because it includes micro vascular and macro vascular complications. For prevention of these complications and for management of its progression is very crucial. Current report on survey of diabetes patient shows that it is the 21st century most challenging heath problem for human being with occurrence of 422 million and it may be 642 million by 2040 [1, 2]. India was home to 61.3 million diabetes patients, as it was known as 'Diabetes Capital of The World'. Now India comes in second after china which is home for 92.3 million diabetics. The estimation of international diabetes federation was the numbers of diabetic patients was doubled between 1995 and 2015 and 70 millions diabetics may be by 2025. The current situation of diabetes in India is expected to get worse in the upcoming decade [2].

Diabetes mellitus is defined as it is a metabolic state where hormonal disturbances cause improper metabolism of carbohydrate, proteins, fats and lipids. As the action of polyol path increases it will source elevation of sorbitol stage in cells and obtain accumulated which leads to osmotic stress on cells this mostly influences the retina, kidney and nervous system as a result polyol pathway is generally good enough and important method for accepting pathogenesis of micro vascular diabetic complication [3].

Aldose reductase is the enzyme which catalyses the formation of sorbitol from glucose through polyol pathway it is first and rate limiting enzyme of polyol pathway the second enzyme sorbitol dehydrogenase which catalyse the formation of fructose from sorbitol. ALR2 inhibition is an attractive approach for prevention and protection from chronic diabetic complication. Chronic diabetic complication retinopathy, nephropathy, neuropathy, cataract and also includes some cardiac and cerebral diseases [3, 4]. In retinopathy and cataract eye damage occurs due to osmotic stress. Sorbinil, fidarestat, kinostat and zinarestat has shown potent effect and better efficacy in experimental animal models against diabetic retinopathy and cataract [5].

Recently novel substituted (E)-2-(5-(4-(benzoyloxy)-2-methoxy benzylidene)-4-oxo-2-thioxothiazolidin-3-yl) acetic acid and (E)-3-methoxy-4-((4-oxo-2-thioxothiazolidin-5-ylidene)methyl)phenyl benzoate analogs were reported as aldose reductase inhibitory activity. A number of *in silico* techniques are utilized in the progression of drug design and development, one such technique is quantitative structure activity relationship (QSAR), has been traditionally perceived as means of establishing correlation between trends in chemical structure modification and respective changes of biological activity. This quantitative technology can be utilized to improve the structure of the agonist/inhibitor molecule and to interpret the improved structure in terms of favorable biological interactions.

Thus, the use of predictive computational (*in silico*) QSAR models allows the biological properties of virtual structures to be predicted, and a more informed choice of target to be selected for synthesis. The use of computational approaches for the estimation of the activity of various molecules as drug candidates prior to their synthesis can save the resources and accelerate the drug discovery procedure. We carried out QSAR analysis and established QSAR models to guide further structural optimization and predict the potency and physiochemical properties of rhoanine ester analogs [6].

II. MATERIAL AND METHODS

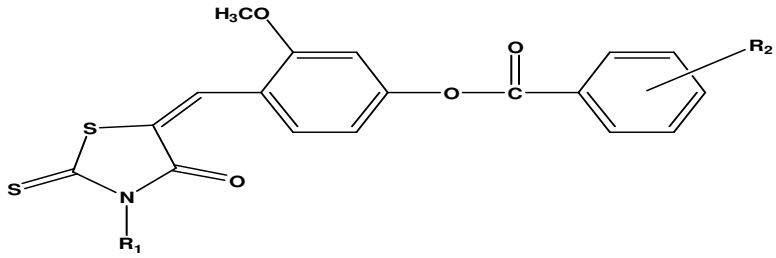
Aldose Reductase inhibitory activity of rhoanine ester analogs was taken from Pandey *et al.,* [6] (Table 1). In attempting QSAR, these inhibitory data (IC_{50}) were converted to negative logarithmic dose in moles (pIC50). As a QSAR is a linear free energy relationship, and commencing the Van't Hoff isotherm, change in free energy during a process is proportional to the logarithm of the rate or equilibrium constant of the process.

G = -2.303 RT log K:

The molecular modeling study was performed using Chemoffice [8] and *DRAGON* [9] program whereas the regression analysis was carried out on VALSTAT [9]. Structure of all the compounds was sketched using builder module of the program. The sketched structures were subjected to energy minimization using molecular mechanics (MM2) until the root mean square (RMS) gradient value became smaller than 0.1 kcal/mol Å [7, 8]. The energy minimized molecules were subjected to reoptimization via Austin model-1 (AM1) method until the RMS gradient attained a value smaller than 0.0001 kcal/mol Å using MOPAC. The geometry optimization of the lowest energy structure was carried out using EF routine. The minimized molecule was saved as "MOL file". These files were used for calculation of various molecular descriptors with the help of *DRAGON* [9].

All the data was transferred to the statistical program with the intention of establish a correlation between physicochemical parameters as independent variables and pIC50 as dependent variable employing sequential multiple linear regression (SEQ-MLR) analysis method. In sequential multiple linear regression, the program searches for all the variation and combination consecutively for the given data set. The statistical quality of the SEQ-MLR equations were assessed by parameters like correlation coefficient (r), standard error of estimate (SEE), sequential Fischer test (F) at specified degree of freedom (df) and explained variance (r^2adj).

Table 1: Structure and aldose reductase inhibitory activity (IC_{50} in μM) of substituted 5-(-2-methoxybenzylidene)- Rhodanine ester analogs.



S.No.	CODE	R1	R2	IC_{50} (μM)
1	5a	-CH_2COOH	-H	0.40
2	5b	-CH_2COOH	-2-Cl	6.36
3	5c	-CH_2COOH	-4-Cl	6.94
4	5d	-CH_2COOH	-2,4-Cl	5.42
5	5e	-CH_2COOH	-4-OCH_3	10.48
6	5f	-CH_2COOH	-2-OCH_3	8.87
7	5g	-CH_2COOH	-2-CH_3	19.73
8	5h	-CH_2COOH	-3,4-OCH_3	0.712
9	5i	-CH_2COOH	-4-CH_3	5.98
10	5j	-CH_2COOH	-4-Br	8.32
11	5k	-CH_2COOH	-4-F	6.14
12	5l	-CH_2COOH	-2-Br	10.65
13	6a	-H	-H	7.08
14	6b	-H	-2-Cl	4.72
15	6c	-H	-4-Cl	5.73
16	6d	-H	-2,4-Cl	13.51
17	6e	-H	-4-OCH_3	4.79
18	6f	-H	-2-OCH_3	6.99
19	6g	-H	-2-CH_3	7.77
20	6h	-H	-3,4-OCH_3	8.13
21	6i	-H	-4-CH_3	12.63
22	6j	-H	-4-Br	20.51
23	6k	-H	-4-F	3.23
24	6l	-H	-2-Br	16.23

The internal predictive powers of the equations were validated by (leave one out or loo) method using predicted residual sum of squares (PRESS), cross validation squared correlation coefficient (Q^2), standard deviation based on PRESS (S_{PRESS}), total sum of squares (SSY) and standard deviation of error of prediction (S_{DEP}). Chances of fortuitous correlation were tested with the help of Y scrambled test. Finally, selected equations have been validated using test set considering predictive squared correlation coefficient r^2_{pred}. The data within the parenthesis is the t-value at 95% associated with the coefficient of descriptor in regression equation.

III. RESULTS AND DISCUSSION

QSAR analysis in computational research is responsible method for the generation of models to show a relationship between biological activity and physicochemical properties of a series of compounds. The excellence of a QSAR model, though, depends mainly on the type and class of the data, and is applicable only for the compound structure analogs to those used to build the model. QSAR models can stand on your own, augment other computational approaches, or be examined in tandem with equations of a related mechanistic generate to establish their accuracy and reliability. In the present study, QSAR analysis has been performed to find out structural requirement for aldose reductase inhibitory activity of rhodanine ester analogs. In order to obtain an insight to the essential structural and physiochemical requirements for the aldose reductase inhibitory activity of this class of molecules, analogs were divided into training set of 20 compounds and test set of 04 compounds. The data was transferred to the statistical program *VALSTAT* in order to start a correlation between molecular descriptors as independent variables and pIC_{50} as dependent variable employing sequential multiple linear regression (SEQMLR) analysis method. The multi-variant expressions were developed on the basis of adjustable correlation coefficient (r^2_{adj}). This parameter explains statistical significance of incorporated physicochemical descriptors in regression. r^2_{adj} takes into account of adjustment of coefficient of determination (r^2). If r^2_{adj} value decline by the addition of a physicochemical descriptor to the equation it is indicated that descriptor was not contributed fairly. Adjustable correlation coefficient is a measure of % explained variation of regression expression. Whereas r^2 value is always increase when an independent variable added to the regression expression [11].

pIC50 = -24.413(± 9.338) BEHv2 + 98.930
n=20, r=0.525, r^2adj=0.235, SEE=0.312, F=6.835 (1)

pIC50 = 0.692(±0.247) Mor09u -24.899(±7.951) BEHv2 + 101.362
n=20, r=0.710, r^2_{adj}=0.446, SEE=0.265, F=8.635 (2)

IC50 = 0.856(±0.165) Mor09u -29.553(±5.290) BEHv2 +0.180(±0.037) RDF130p + 118.967
n=20, r=0.894, r^2_{adj}=0.763, SEE=0.174, F=21.347 (3)

SEQ-MLR revealed that the r^2_{adj} value is increasing considerably from the uni to the trivariant expressions i.e. 0.235, 0.446 and 0.763 respectively. Boosting of r^2_{adj} value from uni to trivariant discovered that inclusion of physicochemical descriptors develop the quality of mathematical expression in understandable manner. Significant improvement in r^2_{adj} value emphasizes to investigate the higher variant expressions. Therefore a number of tetravariant expressions were developed through SEQ-MLR method.

pIC50 = 0.830(±0.338) Mor09u -28.905(±10.795) BEHv2 + 0.153(±0.083) RDF130p -0.152(± 0.195) Mor11e + 116.508
n=20, r=0.912, r^2adj=0.786, SEE=0.165, F=18.489 (4)

pIC50 = 0.892(±0.346) Mor09u -28.643(±11.044) BEHv2 +0.190(±0.078) RDF130p + 0.458 (± 0.671) Mor20v +115.038
n=20, r=0.908, r^2adj=0.778, SEE=0.168, F=17.686 (5)

pIC50 = 0.850(±0.366) Mor09u -31.186(±16.208)BEHv2 + 0.186(±0.093)RDF130p + 0.073 (±0.505) Mor14u + 125.205
n=20, r=0.895, r^2adj=0.748, SEE=0.179, F=15.132 (6)

The strong QSAR models should have to satisfy both statistical value and predictive power. Therefore, all the expressions were tested for internal and external validation. Both the validations place onward decision-making input for selection of QSAR models. Internal corroboration was carried out using leave-one out cross-validation (LOO) method and Y-scrambling test while external corroboration confirmed with the help of test set data (Table 2). Tetra-variant eqn. 4-6 shows correlation coefficient value in the range of 0.912-0.895, which accounts for more than 74.8% of the explained variance in the activity, calculated as r^2 adj = $r^2(1 - 1/F)$ that accounts in percentage when multiplied by 100 [12,13] . Model revealed that the dependent variable can be predicted from a linear combination of the independent variables. The data show an overall internal statistical significance level better than 99.9% as calculated variance ratio i.e. Fischer value (F) exceeded the tabulated $F_{(4,15\alpha0.001)}$ = 8.253. Fischer value suggested that the equations are applicable for more than 999 out of 1000 times.

Table 2: Statistical data of tetra-variant expressions.

Statistical Parameter	Eqn. 4	Eqn. 5	Eqn. 6
r	0.912	0.908	0.895
r^2	0.831	0.825	0.801
SEE	0.165	0.168	0.179
r^2_{adj}	0.786	0.778	0.748
F	18.489	17.686	15.132
PE	0.025	0.026	0.030
QF	5.534	5.413	5.007
FIT	2.054	1.965	1.681
LOF	1.346	1.396	1.585
AIC	0.045	0.047	0.053
Q^2	0.632	0.602	0.496
S_{PRESS}	0.243	0.253	0.285
S_{DEP}	0.211	0.219	0.247
chance	< 0.001	< 0.001	< 0.001
r^2_{BS}	0.798	0.798	0.788
S_{BS}	0.237	0.235	0.230
$r^2_{RANDMEAN}$	0.208	0.208	0.221
S_{RAND}	0.125	0.123	0.132
$r^2_{RANDMAX}$	0.708	0.688	0.736
r^2_{pred}	0.269	0.516	0.307

The equations were analyzed for the outlier by the Z score method (Z value), the outlier test useful in the detection of unexplainable structurally varied analogs [11]. The winning QSAR model should not have any outlier. The Z value for individual compounds lies within

the specific range (<2.5), which indicated the absence of outliers. Test revealed that the Eqns. 4, 5 and 6 are able to explain the structurally varied analogs and is helpful in the designing of more effective compounds using physiochemical descriptors (Table 3).

Calculated data of the compounds using model; [b]Residual value of calculated data; [c]Outlier Z-score value obtained from model; [d]Calculated (loo) data of training set compounds using leave-one-out method or predicted data of test set; [e]Residual value of calculated (loo) data / predicted data [13].

The orthogonality of the descriptors in the equations was established through variance inflation factor (VIF) and pair-wise correlations among the descriptors, values are shown in Table 4 and 5 respectively. In case of Eqns. 4, 5 and 6, the value of VIF is less than <2.000 for all the contributing descriptors revealed that the descriptors are fairly independent to each other. The low value of pair-wise correlation (PWC) among the descriptors (<0.605) also supported comparatively independent contribution [14, 15].

Table 3: Value of calculated, calculated (leave one out), residual and Z-score of rhodanine ester analogs as aldose reductase inhibitory activity towards activity obtained from model.

Comp. No.	Cal[a]	Calres[b]	Zvalue[c]	Cal(loo)/ Pred[d]	Cal(loo)res / Predres[e]
1	6.160	0.238	1.594	5.829	0.569
2	5.190	0.006	0.043	5.187	0.009
3	5.056	0.103	0.690	5.023	0.136
4	5.318	-0.052	-0.352	5.351	-0.085
5	5.141	-0.161	-1.082	5.185	-0.205
6	5.132	-0.080	-0.534	5.142	-0.090
7	4.560	0.145	0.975	4.500	0.205
9	5.305	-0.082	-0.547	5.345	-0.122
10	4.890	0.190	1.275	4.796	0.284
11	5.151	0.060	0.405	5.131	0.081
12	5.154	-0.181	-1.215	5.184	-0.211
13	5.040	0.110	0.736	4.981	0.169
14	5.273	0.053	0.356	5.267	0.059
18	5.174	-0.019	-0.127	5.178	-0.023
19	4.813	0.296	1.986	4.705	0.405
20	5.158	-0.068	-0.455	5.178	-0.088
21	5.067	-0.169	-1.132	5.096	-0.198
22	4.960	-0.272	-1.822	5.026	-0.337
23	5.588	-0.098	-0.654	5.612	-0.121
24	4.811	-0.021	-0.140	4.815	-0.025
8	-	-	-	5.632	0.515
15	-	-	-	4.940	0.302
16	-	-	-	4.760	0.110
17	-	-	-	5.089	0.231

Table 4: t-value and VIF value of the descriptors used in tetra-variant equations.

Equations	Intercept/descriptors	t -value	VIF
Eqn. 4	Mor09u	5.277	1.053
	BEHv2	5.743	1.040
	RDF130p	3.977	1.299
	Mor11e	1.668	1.208
Eqn. 5	Mor09u	5.525	1.069
	BEHv2	5.563	1.049
	RDF130p	5.224	1.115
	Mor20v	1.463	1.077
Eqn. 6	Mor09u	4.977	1.054
	BEHv2	4.127	1.991
	RDF130p	4.295	1.400
	Mor14u	0.312	2.127

Table 5: Pair wise correlation matrix of physicochemical properties used in QSAR analysis of rhodanine ester analogs towards aldose reductase inhibitory activity.

Parameters	Mor09u	BEHv2	RDF130p	Mor20v	Mor11e	Mor14u
Mor09u	1.000					
BEHv2	0.022	1.000				
RDF130p	0.197	0.173	1.000			
Mor20v	0.119	0.156	0.182	1.000		
Mor11e	0.003	0.005	0.400	0.408	1.000	
Mor14u	0.162	0.605	0.289	0.358	0.063	1.000

We have also made hard work to investigate predictive power of the planned model by using quality factor (QF) considering Pogliani's method. The larger value of QF (5.53 - 5.00) signifies better predictive power of tetra-variant equations. For reliability of the QSAR equation, we have calculated regression related statistical parameter called probable error of correlation (PE), if the value of correlation coefficient (r) is more than six times of PE than the expression is superior and reliable. In model the value of correlation coefficient is significantly higher than 6PE supporting reliability and goodness.

The chance of unexpected correlation is checked with the help of Y-scrambling data test considering *Chance* parameter, which is evaluated as ratio of the equivalent regression equations to the total number of randomized sets. *Chance* value of 0.001 corresponds to 0.1% chance of fortuitous correlation. *Chance* value (less than 0.001) of equations revealed that the result was not based on prospective correlation. Similarly mean randomized r^2 ($r^2_{RANDMEAN}$) values and randomized standard deviation (S_{RAND}) are also supporting that the results are not based on chance correlation. Internal predictivity of the model was assured with the help of cross-validated constraints like Q^2, S_{PRESS} and S_{DEP} obtained by 'leave one out (LOO)' cross validation method. The value of Q2 > 0.5 is the basic requirement for declaring a model to be a valid one. The internal consistency of the equations (4 and 5) fall within acceptable level i.e. Q^2 value between 0.60-0.63, S_{PRESS} between 0.253 to 0.243 and S_{DEP} lies within 0.219 to 0.211 range (Table 2). Although equations show good internal uniformity, the high Q^2 does not imply automatically a high predictive ability of the model. Studies indicated that while high Q^2 is the necessary condition for a model to have a high predictive power, it is not a sufficient condition. Such models may not be applicable for the analogs which were never used in the generation of the correlation. Therefore, the external extrapolation power of the equation was further authenticated by a test set of four compounds. The value of predictive squared correlation coefficient (r^2 pred) for equations 4 and 5 are found to be 0.269 and 0.516 respectively (Table 2). On the basis of statistical data and predictive power of test set tetra-variant expressions (Eqn. 5) which carry out all the corroboration criteria up to important echelon was considered as QSAR model. The above mentioned discussion indicated that the regression and statistical parameters are fine enough to set up model as predictive model. The mathematically developed and statistically selected QSAR model revealed that *Mor20v, Mor09u* and *RDF130p* are contributing positively while *BEHv2* contributed negatively to aldose reductase inhibitory activity. The best QSAR model having coefficient of correlation (r=0.908) which explain 77.8% variance in the activity (Table 3). The linear contribution of each physicochemical parameter to the model was significant by more than 99.0% (p<0.01) except Mor20v. The model showed overall internal statistical significance level more than 99.9% as it exceeded the tabulated F(4,16 α 0.001) =8.253. The value of the bootstrapping squared correlation coefficient (r^2 *BS* = 0.798) and the bootstrapping standard deviation (*SBS* = 0.235) implies that the equations were proper representatives of the group of analogs. *Chance* value of 0.001 corresponds to 0.1 % chance of casual correlation. *Chance* value (less than 0.001) of model revealed that the result was not based on prospective correlation. Similarly mean randomized squared correlation coefficient ($R^2_{RANDMEAN}$ = 0.208) and randomized standard deviation (S_{RAND} = 0.123) are also supporting that the results are not based on chance correlation. The model showed good internal consistency in leave out test, the cross validated squared correlation coefficient (Q^2) was found to be 0.602 with S_{PRESS} and S_{DEP} 0.253 and 0.219 respectively (Table 3 and Fig. 1). The selected mathematical expression (model) is able to predict the activity of test set compound, which supported by r^2 *pred* (0.516). The predicted activity of test set compounds are very close to their actual activity, which indicate the robustness of model (Table 3 and Fig. 1). The contributions of descriptors to the model are shown in Fig. 2.

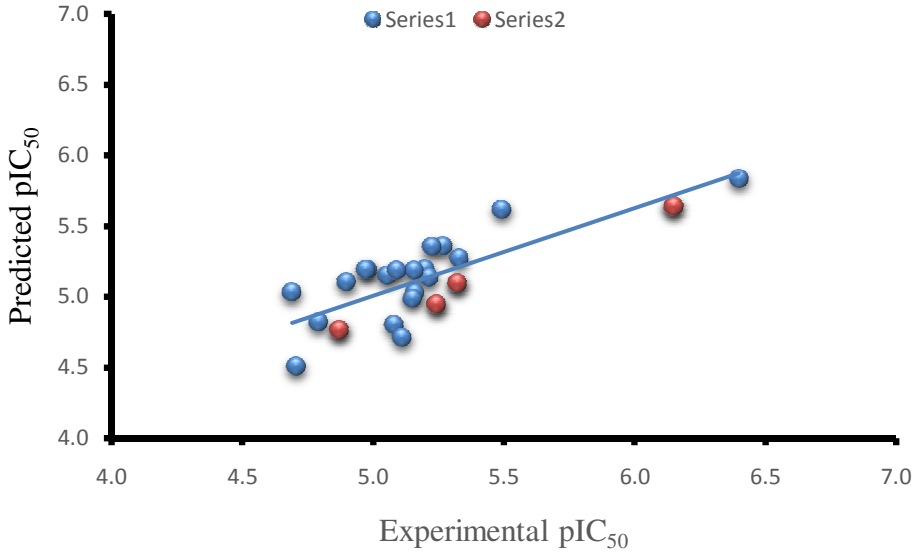


Fig. 1. Graphical representation of experimental versus calculated loo pEC50 of training set and predicted pEC50 of test set.

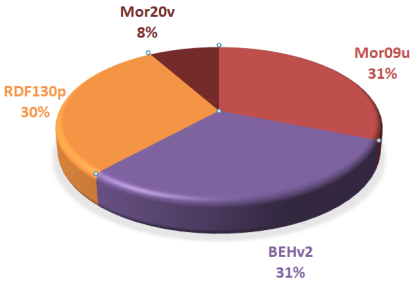


Fig. 2. Percentage contribution of descriptors to the model.

Mor20v is 3D MoRSE code descriptor; Morse code is a 3D molecular representation of structure based on electron diffraction. MoRSE code [24-27] was calculated by summing atom weights viewed by a different angular scattering function. The values of these code functions were calculated at 32 evenly distributed values of scattering angle(s) in the range of 0-31 Å-1 from the three dimensional atomic co-ordinates of a molecule. The 3D-MoRSE code was calculated using following expression

$$I(s) = AiAj \sum_{i=2}^{N} \sum_{j=1}^{i-1} (\sin(srij)/(srij)$$

Where, s is scattering angle, r^{ij} is interatomic distance of i^{th} and j^{th} atom, A_i and A_j are atomic properties of i^{th} and j^{-} atom respectively including van der Waals volume, atomic mass, Sanderson atomic electronegativity and atomic polarizability. The positively contribution of Mor20v revealed that at 20.0 Å interatomic distance non-bonded interaction favour for the activity. Similarly Mor09u contribution at 9 Å interatomic distance

RDF130p appears in the multiple linear regression (MLR) equation, belongs to the radial distribution function (RDF), which is based on the distance distribution in the geometrical representation of the molecule. In addition to interatomic distances in the entire molecule, the RDF also provides valuable information about bond distances, ring types, planar and non-planar systems, atom types, and other important structural motifs. The RDF code has been proven to be a good representation for the 3D structure which has several merits like independence from the number of atoms; disambiguity regarding the three-dimensional (3D) arrangement of the atoms and invariance against translation and rotation of the entire molecule. Each molecule was represented by a vector of length 32. The parameter B was set to 25 $A^{\circ -2}$ corresponding to a total resolution of 0.2 A° in the defined distance r. The RDF for the structure derivations was calculated with the atomic properties which are weighted by atomic mass, van der Waals volume, Sanderson electronegativity, polarizability. The RDF of an ensemble of N atoms can be interpreted as the probability distribution to find an atom in a spherical volume of radius r. The RDF used in this study is as follows:

$$g(r) = f \sum_{1}^{N-1} \sum_{j>1}^{N} A_i A_j e^{-B(r-r_{ij})^2}$$

$$f = 1/\sqrt{\sum_{r} [g(r)]^2}$$

where *f* is a scaling factor, *N* is the number of atoms, A is the atomic properties of atoms i and j, B is smoothing parameter that defines the probability distribution of the individual distances, rij is distance between the atoms i and j, g(r) was calculated at a number of discrete points with defined intervals. RDF130p is the radial distribution function at 13 Å interatomic distance weighted by polarizability and contributed positively to the activity.

BEHv2 belongs to BCUT descriptors, BCUT descriptors (Burden - CAS - University of Texas eigenvalues) are based on a significant extension of the Burden approach, considering three classes of matrices whose diagonal elements correspond to 1) atomic charge-related values, 2) atomic polarizability-related values, and 3) atomic H-bond abilities. Additionally, a variety of definitions were considered for the off diagonal terms, including functions of interatomic distance, overlaps, computed bond orders, etc. Moreover, for the off-diagonal terms not only was a 2D approach used, but also a 3D approach, to account for geometric interatomic distances.[14] Negative contribution of BEHp5 revealed that 2nd highest eigenvalue of Burden matrix correspond to Vander wall volume is unfavorable for the inhibitory activity.

IV. CONCLUSIONS

In this study, molecular feature based quantification of aldose reductase inhibitory activity has been explored. QSAR results elucidate that the topological distance and eigen value-based descriptors affect activities of rhodanine ester analogs towards aldose reductase inhibitory activity. The values of coefficient of determination and cross validated coefficient of prediction obtained from model are 0.825 and 0.602, respectively. Moreover, test set data showed coefficient of prediction 0.516. The results show that the QSAR model is robust and has good predictive ability. These models are not only able to predict the activity of test compounds but also explained the important structural features of the molecules in a quantitative manner. The study provided useful clues about the structural requirement for effective aldose reductase inhibitory activity and hence for the improvement of the biological activity. In conclusion, the results derived in present study can provide a preliminary valuable guidance for continuing search for potential aldose reductase inhibiton prior to synthesis.

V. FUTURE SCOPE

Current study offers substituted ester of (E)-2-(5-(2-methoxybenzylidene)-4-oxo-2-thioxothiazolidin-3-yl) acetic acid will be used as promising scaffolds for a future drug discovery program. The field is open for exhaustive study of new compounds with respect to pharmacokinetic studies, toxicity studies and clinical phases studies, so as to found these analogs as improved and safer drug molecules. It provide a preliminary valuable guidance for continuing search for potential aldose reductase inhibiton. Further 3D QSAR techniques like CoMSIA, CoMFA, Pharmacophoric Mapping, Receptor and enzyme Surface Model Generation and Molecular Shape Analysis could be used to explore the physicochemical properties vital to design more effective drug molecules devoid of side effects shown by usual antidiabetic agents for the treatment and management of Diabetes Mellitus.

REFERENCES

[1]. Tiwari A. K. & Rao J. Madhusudana, (2002). Diabetes Mellitus and Multiple Therapeutic Approaches of Phytochemicals: Present Status and Future Prospects *Current Science,* 83, 30-38.

[2]. Agrawal, Y. P., Agrawal M. Y. & Gupta, A. K., (2015). Design, Synthesis and Evaluation of Rhodanine Derivatives as Aldose Reductase Inhibitors. *Chem Biol Drug Des. 85*, 172-180.

[3]. Salim, B. (2005). Diabetes mellitus and its treatment, *Int J Diabetes & Metabolism, 13,* 111-134.

[4]. O'Moore-Sullivan T. M., & Prins, J. B., (2002). *Med. J. Aust.,*176, 381-386.

[5]. Imoto, H., Imamiya, E., Momose, Y., Sugiyama, Y., Kimura, H., & Sohda T. (2002)., Chem. Pharm. Bull., *50*, 1349-1357.

[6]. Pandey J., Gilhotra R. & Gupta, A. K. (2019). Design, Synthesis and Evaluation of Substituted 5-(2-methoxybenzylidene)-rhodanine Ester Analogs as Aldose Reductase Inhibitors; *Biological Forum – An International Journal, 11*(1), 217-221.

[7]. Imoto H., Sugiyama Y., Kimura, H., & Momose, Y. (2003). Studies on Non- Thiazolidinedione Antidiabetic Agents. 2.1) Novel Oxyiminoalkanoic Acid Derivatives as Potent Glucose and Lipid Lowering Agents *Chem. Pharm. Bull., 51*(2), 138-151.

[8]. Chem, C.S. Office, Version 11.0, Cambridge Soft Corporation, Software Publishers Association, 1730 M. Street, Suite 700, Washington D.C.20036, USA.Tel., (202), 452- 1600.

[9]. Todeschini, R., & Consonni, V. (2001). DRAGON Software for the Calculation of Molecular Descriptors, rel.1.12 for Windows.

[10]. Gupta, A. K., Arockia, B. M. & Kaskhedikar, S. G. (2004). VALSTAT: Validation Program for Quantitative Structure Activity Relationship Studies. *Indian J. Pharm. Sci.*, *66,* 396-402.

[11]. Gupta, A. K., Sabarwal, N., Agrawal, Y. P., Prachand, S., & Jain, S. (2010). Insights through AM1 calculations into the structural requirement of 3, 4, 6-substituted-2-quinolone analogs towards FMS kinase inhibitory activity. *European journal of medicinal chemistry*, *45*(8), 3472-3479.

[12]. Gupta, A. K., Singh, P., & Sabarwal, N. (2014). Rationalization of Molecular Descriptors of Aurone Analogs toward Anti-malarial Activity, *Asian J. Pharm. Clin. Res.,* 7, 186-192.

[13]. Pandey J., & Gupta A. K. (2016). Molecular Descriptors Analysis of Oxyiminoalkanoic Acid Analogs towards PPARγ Agonist Activity, *Int. J. of Pharm. Life Sci. 7*(3), 4942-4951.

[14]. Gupta, R. A., & Kaskhedikar S. G., (2010). Investigation of the Structural Requirement for 3, 5-disubstituted 4, 5 dihydroisoxazole analogs against *M. tuberculosis*: QSAR Study. *International Journal of Drug Design and Discovery*, *1*, 81-92.

[15]. Gupta, R. A., Gupta, A. K., Soni, L. K., & Kaskhedikar, S. G. (2010). 2-(pyrazin-2-yloxy) acetohydrazide Analogs QSAR Study: An Insight into the Structural Basis of Antimycobacterial Activity. *Chemical biology & drug design*, *76*(5), 441-450.

How to cite this article: Pandey, Jyoti, Gupta, Arun K. and Gilhotra, Ritu M. (2019). Soil Quarrying for Brick Kiln and Its Impact on Environment: A Study in Tufanganj Block-I, Koch Bihar, West Bengal. *International Journal on Emerging Technologies*, *10*(4): 465–471.