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Exploration and Rationalization of Physicochemical Character towards Aldose Reductase Inhibitory Activity of Quinoxalinones Analogs

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Abstract

Aldose reductase, play an important role in the pathogenesis of diabetic complications such as neuropathy, nephropathy and retinopathy. Numerous synthetic organic compounds with diverse structures have been reported as potent aldose reductase inhibitors (ARIs). However, most of them have been retreated since undertaking clinical assays, because of unfavorable side effects, low efficacy, or toxicity. Recently quinoxalinone analogs are reported as potent ARIs. Diverse scaffold of quinoxalinone analogs might be having different interactions with macromolecule; therefore in present research work we explored the structure feature of quinoxalone analogs for further optimization. Series was divided into a training set of 27 compounds and a test set of 10 compounds on the basis of structural diversity and variations in inhibitory activity. The present study helps in identification of tri-parametric QSAR model which elucidate that the atomic electro-negativity and connectivity of atom affects activities of quinoxalinone analogs toward aldose reductase inhibition. Statistically validated model can be used to predict the activity of new analogues and saving synthetic efforts.

Key word: Aldose reductase, Physicochemical, Quinoxalinones

Introduction

Diabetes mellitus (DM) is a multisystem disorder comprising metabolic and vascular abnormalities resulting from insulin deficiency, with or without insulin resistance. More than 220 million people worldwide suffer from DM, and this figure is expected to increase to 400 million cases by 2030.[1,2] Aldose reductase (ALR2) enzyme plays a critical role in the development and progression of chronic diabetic complications including neuropathy, nephropathy, cataracts, retinopathy, accelerated atherosclerosis, and increased cardiovascular risk.[3-5] Therefore Aldose Reductase received attention from researchers all over the world in preventing the onset or checking the progression of diabetic complication.

A variety of ALR2 inhibitors (ARIs) have been reported; however, in clinical studies many of them have exhibited low efficacy or a narrow spectrum of tissue activity, generally because of unfavorable pharmacokinetics, or have proved to produce toxic side-effects[6-10].

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Recently quinoxalin-2(1*H*)-one containing aldose reductase inhibitors were reported[11], the diverse scaffold of quinoxalinone analogs might be having different interactions with macromolecule. In the past years, quantitative structure activity relationship (QSAR) has been increasingly used in medicinal chemistry and drug design. The emphasis was focused on the quantification of structure activity relationship with a view to delineate the influence of key physicochemical properties on aldose reductase inhibitory activity, which will aid in the designing of potent and safer inhibitors. The quantification of physicochemical properties was done with the help of regression technique. This methodology is very helpful in screening a large library of possible drug candidates for selectivity and potency. In this methodology mathematical models are formed that correlate molecular structure to an activity, toxicity, or property of interest.

Hence, QSAR study on quinoxalin-2(1H)-one analogues is carried out to endow with the rationale for drug design and explore the possible structural and molecular requirements influencing the ALR2 inhibitory activity. The objective of the study is to develop a robust and predictive mathematical model

which correlates the inhibitory activity with their physicochemical descriptors.

Material and Methods

Molecules

A series of 37 molecules belonging to the quinoxalin-2(1H)-one nucleus as aldose reductase agent was taken from the literature and used for the present study **(Table-1)**. Selection of training and test set molecules was made on structure diversity and biological activity. The QSAR models were generated using a training set of 27 molecules. Predictive power of the resulting models was evaluated by a test set of 10 molecules with uniformly distributed biological activity.

Biological Activity

The biological activity data of quinoxalin-2(1H)-one analogues, reported by Qin et. al. was used for the present study **(Table -1)**. The fifty percent inhibitory concentration (IC_{50}) data was converted into negative logarithmic mole dose.[12]

Molecular Modeling

The molecular modeling studies were carried out on CS ChemOffice.[13] Structures were constructed from the builder module of the program. All the molecules were minimized until the root mean square (RMS) gradient value becomes smaller than0.1 kcal/mol Å using molecular mechanics (MM2), subsequently subjected to re-optimization via AM1 Method using close shell restricted wave function of MOPAC module until the root mean square (RMS) gradient value becomes smaller than 0.0001 kcal/mol Å. The geometry optimization of the lowest energy structure was carried out using EF routine. The minimized molecule was saved as MOL file format.

Calculation of Descriptors

Different types of descriptors were calculated for each molecule in the study through DRAGON[14] software. These descriptors include constitutional, topological, geometrical, charge, GETAWAY (Geometry, Topology and Atoms-Weighted AssemblY), WHIM (Weighted Holistic Invariant Molecular descriptors), 3D-MoRSE (3D-Molecular Representation of Structure based on Electron diffraction), molecular walk counts, BCUT descriptors, 2D-Autocorrelations, aromaticity indices, Randic molecular profiles, radial distribution functions, functional groups and atom-centered fragments.

Generation of QSAR models

In the present study, QSAR model generation was performed by using the statistical program VALSTAT.[15] The sequential multiple regression analysis method was used in construction of high-quality predictive models. The set of equations generated were evaluated on the basis of following statistical parameters: correlation coefficient (r), standard error of estimate (SEE), sequential Fischer test (F) at specified degree of freedom (df) and explained variance (r^2_{adj}). The internal predictive powers of the equations were validated by (leave-n-out) method using predicted residual sum of squares (PRESS), cross validation squared correlation coefficient (Q^2), standard error of prediction (S_{PRESS}) and standard deviation of prediction (S_{DEP}). Chances of fortuitous correlation were tested with the help of Y-scrambled test. Uniformity of compound contribution to the expression was tested with the help of bootstrapping technique. Finally, selected equations have been validated using test set considering predictive squared correlation coefficient (r^2_{pred}).

Results and Discussion

In the present study, QSAR analysis has been performed to explore structural requirement for inhibitory activity of quinoxalin-2(1*H*)-one against aldose reductase enzyme. Series was subjected to QSAR analysis employing sequential multiple regression (SEQ-MLR) technique to establish a correlation between physicochemical parameters and inhibitory activity. The maximum number of parameter in equations was selected on the basis of adjustable correlation coefficient (r^2_{adj}) and Akaike's Information Criterion (AIC). Adjustable correlation coefficient takes into account of regulation of coefficient of determination (r^2). This parameter explains statistical significance of incorporated physicochemical descriptors in regression. If r^2_{adj} value decline by the addition of a physicochemical descriptor to the equation it is indicated that descriptor was not contributed reasonably. 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. Study has furnished uni and bi-variant expression with moderate correlation coefficient (Eqs. 1 & 2), but the r_2^{adj} value is increasing significantly from uni to bi-variant expression (Fig. 1). Similarly Akaike's Information Criterion (AIC) is a general criterion for choosing the best number of parameters to include in a regression expression. The expression that has the smallest value of AIC is considered the best. The tri-variant expression has low AIC value as shown in Fig. 2.

pIC_{50} = 18.967(±4.493) ATS5e -16.088
n=27, r=0.645, r^2_{adj}=0.393, SEE=0.419, F=17.820, AIC=0.204 (Eqs. 1)

pIC_{50} = 15.633(±2.857)ATS6e +1.449(±0.258)MATS8e -12.012
n=27, r=0.853, r^2_{adj}=0.705, SEE=0.292, F=32.036, AIC=0.107 (Eqs. 2)

Several significant equations with coefficient of correlation (r) ≅ 0.900 were obtained (Eqs. 3–7), these equations were subjected for primary statistical screening **(Table -2)**.

pIC_{50} = 0.070(±0.008)DELS - 0.632(±0.0696)GATS8e - 0.206(±0.0246)RDF065u+5.512
n=27, r=0.913, r^2_{adj}=0.811,SEE=0.234, F=38.217, AIC=0.074 (Eqs. 3)

pIC_{50} = 10.084(±1.132) ATS7e -0.004 (±0.8e-03) VRA1 -0.924(±0.092) GATS8e-2.196
n=27, r=0.912, r^2_{adj}=0.811, SEE=0.234, F=38.108, AIC=0.074 (Eqs. 4)

pIC_{50} = 0.084(±0.009)DELS -7.473e-05(±8.946e-06)GMTIV -0.648(±0.070)GATS8e +6.441
n=27, r=0.912, r^2_{adj}=0.810, SEE=0.234, F=37.965, AIC=0.074 (Eqs. 5)

pIC_{50} = 29.418(±2.923) ATS5e +1.392(±0.207) GATS6e +0.220(±0.044) RDF060u -32.365
n=27, r=0.909, r^2_{adj}=0.804, SEE=0.238, F=36.542, AIC=0.076 (Eqs. 6)

pIC_{50} = 0.516(±0.064) RTe -7.474(±1.052) H6u - 15.686(±2.064) R4e+ + 0.797
n=27, r=0.893, r^2_{adj}=0.771, SEE=0.257, F=30.238, AIC=0.089 (Eqs. 7)

A high correlation coefficient merely is not enough to select the equation as a model. These equations account for more than 75.0% of the explained variance in the activity data calculated as adjusted squared correlation coefficient. Equations were screened through various internal and external statistical validation techniques. Internal statistical significance level of the equations was confirmed using sequential Fischer test, all the equations have significance level more than 99.9% as it exceeded the tabulated F(3,23α0.001) = 8.657. Sequential Fischer test recommended that equations are applicable for more than 999 times out of 1000. We have also made efforts to investigate predictive power of the proposed models using quality factor (QF) considering Pogliani's method.[16,17] QF is defined as the ratio of correlation coefficient to standard error of estimation (SEE). The larger value of QF (≥3.4) signifies better predictive power of the expression **(Table 2)**. For reliability of the regression, we have calculated regression associated statistical parameter called probable error of correlation (PE). The value of correlation coefficient is significantly higher than 6PE supporting reliability and goodness of the regression expression **(Table 2)**. Preliminary screening of tri-variant expressions (Eqs. 3–7) put forward for rigorous statistical screening of these expressions.

The persuasive QSAR model should not have any outlier. The outlier test helps in the identification of unexplainable structurally diverse analogs. The Z_{value} for individual compounds for eqn. 4, 6 and 7 lies within the specific range (<|2.5|), which indicated the absence of outliers in these regression expressions **(Table 3)**. At this level we drop equation 3 and 5 for further screening. The equations (4, 6 & 7) confirming for the contribution of physicochemical properties of the molecules to the activity whether equi-intense or of the different rank through bootstrapping technique. The value of the bootstrapping squared correlation coefficient and the bootstrapping standard deviation implies that the equations were proper representatives of the group of analogs (**Table 3).**

Chance value (less than 0.001) of expressions 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 **(Table 3).** The internal consistencies of the training set were confirmed through leave-one-out (LOO) cross-validation method. Equations showed good internal consistency with Q^2 value in the ranges 0.784–0.734 with low S_{DEP} value ranging from 0.245 to 0.271.

They may not be applicable for the analogs, which were never used in the generation of the correlation. Therefore, the predictive power of equations (Eqs. 3–7) was further confirmed by a test set of ten compounds. Equations showed r^2_{pred} value more than 0.3, which revealed robustness and wide applicability of these equations (**Table 3**).

In statistical assessment equation 7 showed ICAP ≅ or < 0.75 and VIF[18,19] for descriptor touches the value up to 2.7 as compared to equations 4 and 6 therefore equation was dropped **(Table 4)**. On comparison of

equations 4 and 6, the ICAP value for equation 6 is less while predictive ability of training set and test set are best for equation 4. Equation 4 fulfill all the corroboration criteria up-to significant echelon hence its considered as QSAR model for the quinoxalinones analogs as aldose reductase inhibitory activity.

The QSAR model has a correlation coefficient (r=0.912), which accounts for more than 81.0 % of the explained variance in the activity[20] **(Table 5)**. The t-value of the descriptors in the model revealed that the dependent variable can be predicted from a linear combination of the independent variables. The p-value is less than 0.001 for each physiochemical parameters involved in model generation **(Table 6)**. The percentage contribution of descriptors to the QSAR model is shown in **Fig 3.**

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 $F_{(3,14\alpha0.001)} = 9.729$. Fischer value suggested that the equations are applicable for more than 999 out of 1000 times. The orthogonality of the descriptors in the model was established through variance inflation factor (VIF) values and pair-wise correlation among the descriptors. VIF value larger than 10 indicates that the information of the descriptors may be hidden by the correlation of the other descriptors. VIF is less than 2.53 for all the contributing descriptors revealed that the descriptors are fairly independent to each other **(Table 6)**. The low value of pair-wise correlation (PWC) among the descriptors also supported comparatively independent contribution.

We have also made efforts to investigate predictive power of the proposed model by Pogliani's method using quality factor (QF). QF is defined as the ratio of correlation coefficient (r) to standard error of estimation (SEE). The larger value of QF (3.897) signifies better predictive power of the model. For reliability of the model, probable error of correlation (PE) was calculated. The value of correlation coefficient (r) is significantly more than six times of PE revealed that the expression is good and reliable. The QSAR model has absence of outlier, the calculated z-value for each compound falls within ± 2.5 range **(Table 7)**. This indicates that the model is able to explain the structurally diverse analogs and is helpful in the designing of more potent compounds using model descriptors.

Y-scrambling data test was considered to verify the chance of fortuitous correlation of descriptors in the model. Chance value (less than 0.001) of model revealed that the result was not based on prospective 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. This model was built by n-1 compounds and the n^{th} compound was predicted. The value of $Q^2>0.5$ is the basic requirement for declaring a model to be a valid one. The internal consistency of the model supported by Q^2 (0.784), S_{PRESS} (0.266) and S_{DEP} (0.245) values **(Table 5 & 7** and **Fig 4 & 5)**. Although equation shows good internal consistency, 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 ten compounds. The value of predictive squared correlation coefficient $r^2_{pred} = 0.592$ of test set supported robustness, predictiveness and applicability of the model **(Table 5 & 7** and **Fig 6 & 7)**. In general the model fulfills the statistical validation criteria to a significant extent. The aforementioned discussion indicated that the regression and statistical parameters are good enough to establish expression as predictive model.

The QSAR Model positively contributed by Broto-Moreau autocorrelation descriptor (ATS7e) while negatively contributed by Randic type eigenvector base index (VRA1) & Geary autocorrelation descriptor (GATS8e).

ATSke and GATSke are autocorrelation descriptors, have their origin in autocorrelation of topological structure of Broto-Moreau and of Geary respectively. The computation of these descriptors involves the summation of different autocorrelation functions corresponding to the different fragment lengths and lead to different autocorrelation vectors corresponding to the lengths of the structural fragments. Also a weighting component in terms of a physicochemical property has been embedded in these descriptors. As a result, these descriptors address the topology of the structure or parts thereof in association with a selected physicochemical property

GATS8e: Related to the "autocorrelation Geary" at a distance of 8 bonds, weighted by electronegativity. Thus, greater electronegativity difference between two atoms at a distance of 8 bonds, leads to greater the value of the descriptor.[21-23] The higher values of

this descriptor, decreases the activity. Electronegative atoms in *para* position of phenyl ring leads to a greater value of the descriptor, decreasing the activity (compounds TR-2, TR-3 and TT-1 are the less active, with presence of fluoro on this position).

ATS7e: Related to Broto-Moreau autocorrelation of a topological structure it's also known as Autocorrelation of a Topological Structure (ATS) - lag 7 / weighted by atomic Sanderson electronegativity.[21,22,24] The more electronegative atoms in the molecules at R_1 and R_2 position, the higher the value of this descriptor and vice versa. The presence of un-substituted moiety or poor electronegative group at R_1 and R_2 position lowers the activity (compounds TR-1,TR-14, TR-16,TR-17,TR-25, TR-26 and TT-7)

VRA1: It is eigenvalue-based descriptor, in which The VRA indices are defined by applying the Randic operator to the coefficients l_{iA} of the eigenvector associated with the largest negative eigenvalue.[21,22]

$$VRAl = \sum_b (l_{iA}. L_{jA})_b^{-1/2}$$

where the sum runs over all of the bonds in the molecular graph; liA.and LjA are the LOVIs of the two vertices incident to the considered bond.

QSAR results elucidate that the atomic electro-negativity and connectivity of atom affects activities of quinoxalinone analogs toward aldose reductase inhibition.

Conclusion

In relation to the explored data set, three descriptors were very important to explain the biological activity of the compounds and obtained QSAR model can be used to make predictions of other quinoxalinone analogs ideally designed based on these characteristics. Substitution on R_1 position decreases the activity (7^{th} position of 2-oxoquinoxalin with p-fluoroaryl moiety) in comparison to non aryl electronegative moiety (7^{th} position of 2-oxoquinoxalin). Molecules with a moderate electronegative substituent's (other than fluoro) on R_2 position, should lead to more active analogues against aldose reductase inhibitory activity. In addition, the generated equation can be used to predict the activity of new analogues compounds, saving synthetic efforts.

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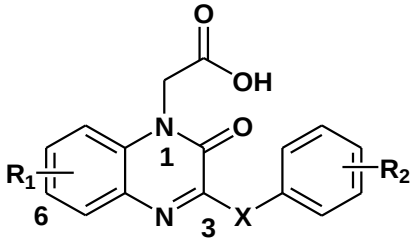
Table 1: Structure and aldose reductase inhibitory data of quinoxalin-2(1*H*)-one analogs



Compound Code	Substitutions			IC50(µM)[a]
	R_1	R_2	X	
TR-1	H	H	-	5.981
TR-2	H	5-F	-	3.380
TR-3	7-F	5-F	-	0.874
TR-4	H	4-OH	-	2.592
TR-5	H	2,4-$(OH)_2$	-	0.397
TR-6	6-F	2,4-$(OH)_2$	-	0.063
TR-7	6-Br	2,4-$(OH)_2$	-	0.139
TR-8	7-Cl	2,4-$(OH)_2$	-	0.069

TR-9	7-Br	2,4-$(OH)_2$	-	0.091
TR-10	4- fluorophenyl	2,4-$(OH)_2$	-	3.340
TR-11	7-Br	3-indole[b]	-	0.368
TR-12	H	4-OH	CH =CH	0.182
TR-13	7-F	4-OH	CH =CH	0.153
TR-14	H	3-OCH_3, 4-OH	CH =CH	0.419
TR-15	H	4-OH	CH_2-CH_2	0.798
TR-16	H	H	O	0.468
TR-17	H	H	S	0.421
TR-18	H	4-Br	S	0.296
TR-19	7-Cl	4-Br	S	0.326
TR-20	7-Br	4-Br	S	0.467
TR-21	6-Br	4-Br	S	0.319
TR-22	7-F	4-Cl	S	0.056
TR-23	7-Cl	4-Cl	S	0.158
TR-24	7-Br	4-Cl	S	0.395
TR-25	H	H	CH_2	1.112
TR-26	H	H	CH =CH	0.820
TR-27	H	H	CH_2-CH_2	0.143
TT-1	7-Cl	5-F	-	1.516
TT-2	5- fluorophenyl	5-F	-	2.131
TT-3	6-Cl	2,4-$(OH)_2$	-	0.095
TT-4	7-F	2,4-$(OH)_2$	-	0.032
TT-5	H	3-indole[b]	-	0.639
TT-6	7-Cl	2-benzethiophene[b]	-	0.238
TT-7	H	4-OCH_3	CH =CH	4.181
TT-8	7-H	4-OH	CH_2-CH_2	0.652
TT-9	F	4-Br	S	0.191
TT-10	H	4-Cl	S	0.273

[a]IC_{50} values represent the concentration required to decrease enzymatic activity by 50%.
[b]R_2 was directly connected with the C3 position of quinoxalin-2(1*H*)-one.

Table 2: Primary statistical parameters of tri-variant expressions

Eqs.	n	r^2	r^2_{adj}	SEE	F	QF	PE	AIC
3	27	0.833	0.811	0.234	38.217	3.903	0.021	0.074
4	27	0.833	0.811	0.234	38.108	3.897	0.021	0.074
5	27	0.832	0.810	0.234	37.965	3.890	0.022	0.074
6	27	0.827	0.804	0.238	36.542	3.817	0.022	0.076
7	27	0.797	0.771	0.257	30.238	3.471	0.025	0.089

Table 3: Internal and external statistics of tri-variant expressions

Eqs.	Bootstrapping			Randomized			Leave-one-out			VIF	Outlier	Test set (n = 10)	
	r^2_{bs}	SE_{bs}	Chance	R^2_{max}	R^2_{mean}	SE_{rand}	$_1Q^2$	S_{PRESS}	S_{DEP}			r^2_{pred}	SEP
3	0.895	0.065	<0.001	0.477	0.116	0.084	0.747	0.288	0.266	≅<1.951	Yes	0.398	0.257
4	0.858	0.094	<0.001	0.591	0.114	0.085	0.784	0.266	0.245	≅<2.532	Nil	0.592	0.482
5	0.889	0.079	<0.001	0.508	0.115	0.083	0.743	0.290	0.268	≅<2.655	Yes	0.687	0.657
6	0.842	0.112	<0.001	0.496	0.112	0.083	0.761	0.280	0.258	≅<1.311	Nil	0.308	0.535
7	0.830	0.094	<0.001	0.522	0.114	0.085	0.734	0.294	0.271	≅<2.700	Nil	0.546	0.406

Table 4: Inter-correlation matrix of the descriptors used in tri-variant expressions

Descriptors	ATS7e	VRA1	GATS8e	GATS6e	ATS5e	RDF060u	RTe	R4e+	H6u	DELS	RDF065u	GMTIV
ATS7e	1.000											
VRA1	0.290	1.000										
GATS8e	0.627	0.622	1.000									
GATS6e	0.540	0.111	0.589	1.000								
ATS5e	0.677	0.509	0.254	0.348	1.000							
RDF060u	0.158	0.812	0.301	0.188	0.270	1.000						
RTe	0.761	0.548	0.657	0.573	0.653	0.085	1.000					
R4e+	0.270	0.671	0.806	0.358	0.093	0.522	0.349	1.000				
H6u	0.409	0.069	0.466	0.614	0.110	0.290	0.742	0.093	1.000			
DELS	0.801	0.133	0.359	0.625	0.482	0.491	0.695	0.036	0.636	1.000		
RDF065u	0.034	0.821	0.175	0.312	0.393	0.844	0.090	0.363	0.397	0.527	1.000	
GMTIV	0.181	0.740	0.094	0.401	0.233	0.826	0.088	0.350	0.522	0.666	0.963	1.000

Table 5. QSAR statistics of significant equation against aldose reductase inhibitory activity

Statistical parameters	QSAR Model
r	0.912
r^2_{adj}	0.811
SEE	0.234
F	38.107
PE	0.021
QF	3.897
PWC	0.630
AIC	0.074
Chance	<0.001
$r^2_{randmean}$	0.114
S_{rand}	0.085
Q^2	0.784
S_{PRESS}	0.263
S_{DEP}	0.245
r^2_{pred}	0.593

Table 6. Pair wise correlation, t-value and VIF values of the descriptors used in QSAR model

Descriptors	*Pair wise correlation*			t-value	VIF
	VRA1	ATS7e	GATS8e		
VRA1	1.000			5.389	1.677
ATS7e	0.290	1.000		8.906	1.695
GATS8e	0.622	0.627	1.000	10.050	2.532

Table 7. Calculated, calculated (loo), residual and Z-score of training set data and Predicted and residual value of test set of quinoxalin-2(1*H*)-one analogs obtained from QSAR model

Compound Code	Experimental pIC50	Calculated pIC50	Calculated Residual	Z-Score	Predicted pIC50	Predicted Residual
TR-1	5.223	5.406	-0.183	-0.829	5.470	-0.247
TR-2	5.471	5.397	0.074	0.336	5.364	0.107
TR-3	6.058	6.256	-0.198	-0.898	6.330	-0.271
TR-4	5.586	5.651	-0.065	-0.295	5.666	-0.080
TR-5	6.401	6.454	-0.053	-0.241	6.459	-0.058
TR-6	7.201	7.194	0.006	0.028	7.193	0.008
TR-7	6.857	6.811	0.046	0.209	6.806	0.051
TR-8	7.161	6.812	0.350	1.588	6.758	0.403
TR-9	7.041	6.765	0.276	1.255	6.731	0.310
TR-10	5.476	5.419	0.057	0.260	5.340	0.136
TR-11	6.434	6.604	-0.169	-0.769	6.617	-0.183
TR-12	6.740	6.335	0.405	1.839	6.289	0.451
TR-13	6.815	6.924	-0.109	-0.493	6.955	-0.140
TR-14	6.378	6.460	-0.082	-0.371	6.472	-0.094
TR-15	6.098	6.335	-0.237	-1.077	6.362	-0.264
TR-16	6.330	6.406	-0.076	-0.345	6.419	-0.090
TR-17	6.376	6.053	0.323	1.468	6.000	0.376
TR-18	6.529	6.256	0.272	1.237	6.228	0.301
TR-19	6.487	6.720	-0.233	-1.060	6.734	-0.247
TR-20	6.331	6.569	-0.238	-1.081	6.581	-0.250
TR-21	6.496	6.389	0.108	0.489	6.382	0.114
TR-22	7.252	7.200	0.052	0.237	7.191	0.061
TR-23	6.801	6.837	-0.036	-0.161	6.839	-0.038
TR-24	6.403	6.693	-0.290	-1.315	6.710	-0.306
TR-25	5.954	6.075	-0.121	-0.549	6.094	-0.140
TR-26	6.086	6.406	-0.320	-1.452	6.439	-0.353
TR-27	6.845	6.406	0.439	1.993	6.361	0.484
TT-1	5.819	-	-	-	5.990	-0.171
TT-2	5.671	-	-	-	5.651	0.021

TT-3	7.022	-	-	-	7.045	-0.022
TT-4	7.495	-	-	-	6.965	0.530
TT-5	6.194	-	-	-	6.330	-0.136
TT-6	6.623	-	-	-	7.035	-0.411
TT-7	5.379	-	-	-	5.936	-0.558
TT-8	6.186	-	-	-	6.924	-0.738
TT-9	6.719	-	-	-	7.100	-0.381
TT-10	6.564	-	-	-	6.393	0.171

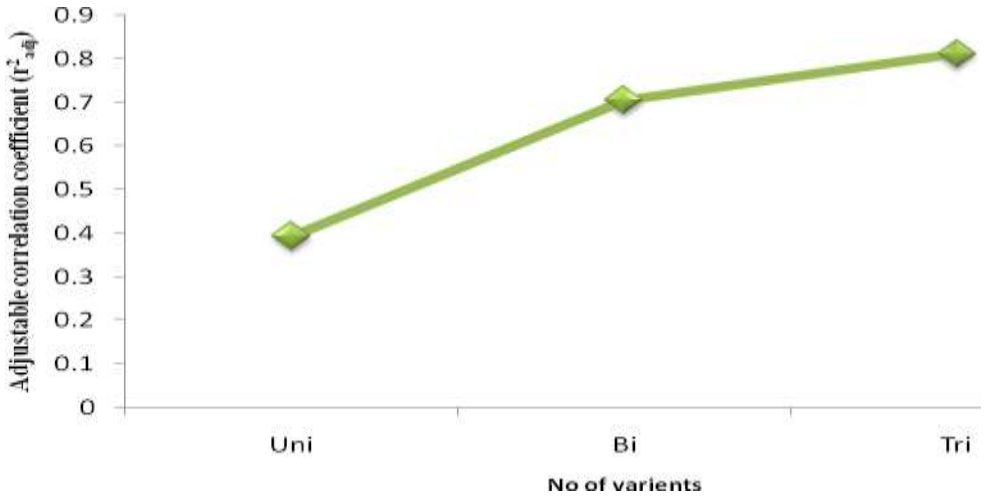


Fig 1. Graphical representation of adjustable correlation coefficient contributing to uni to tri-variant expression

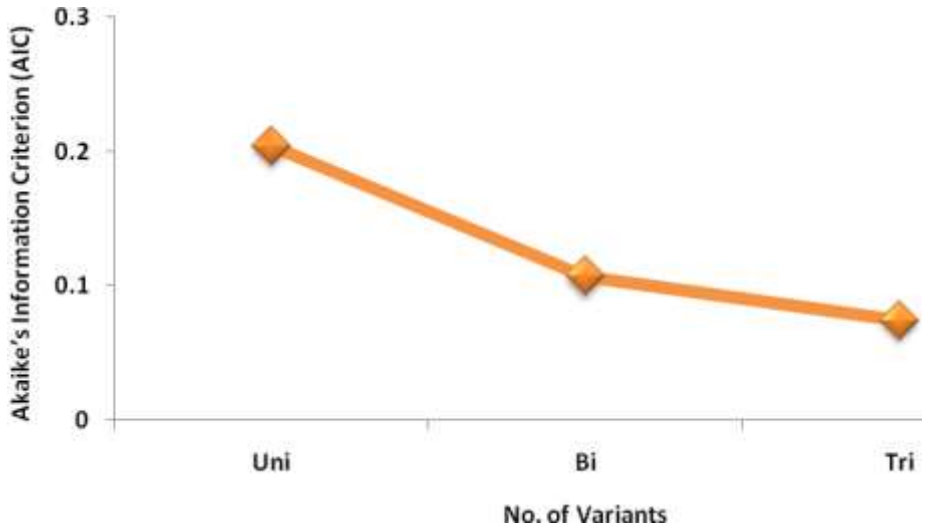


Fig 2. Graphical representation of Akaike's Information Criterion (AIC) contributing to uni to tri-variant expression

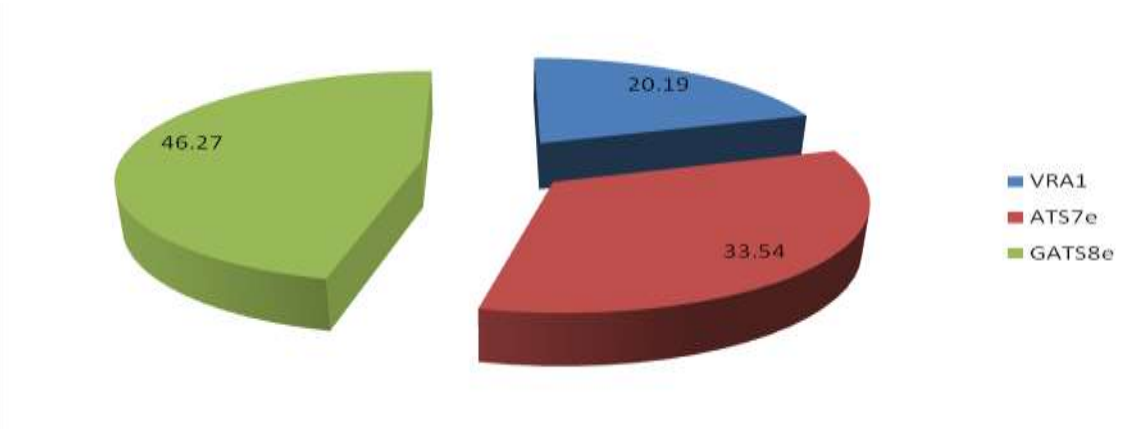


Fig 3. Graphical representation of percentage contribution of descriptors to QSAR model

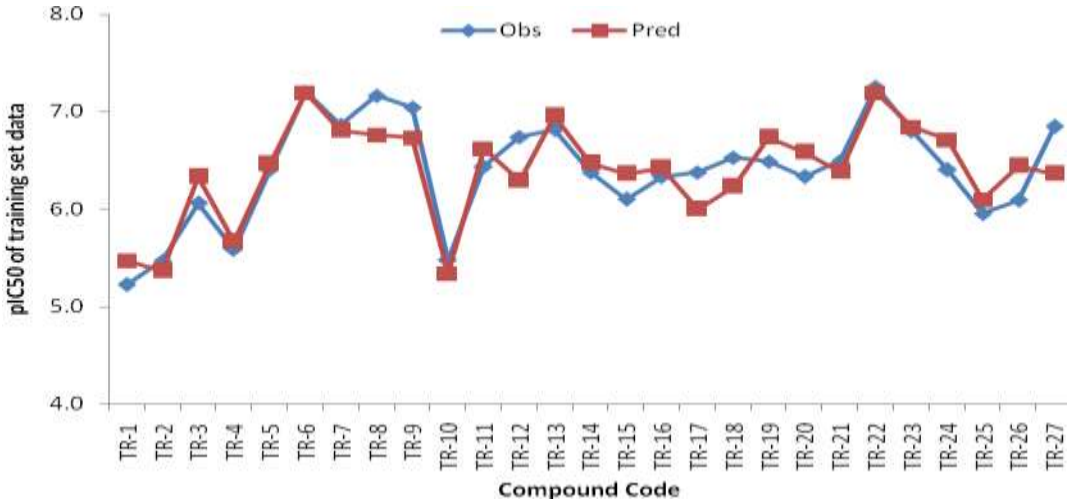


Fig 4. Predicted pIC50 derived from QSAR model are aligned with actual pIC50 value for various compounds in training set

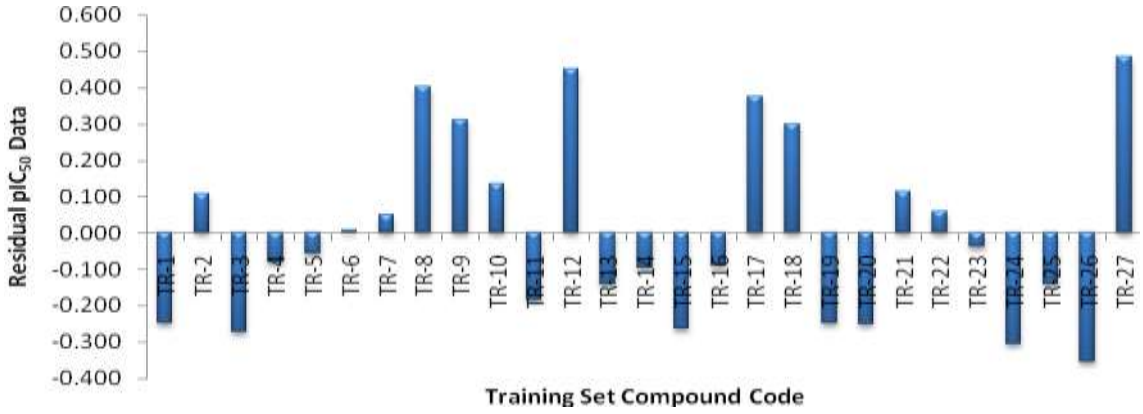


Fig. 5. Residual value of predicted pIC50 derived from QSAR model against actual pIC50 value for various compounds in training set

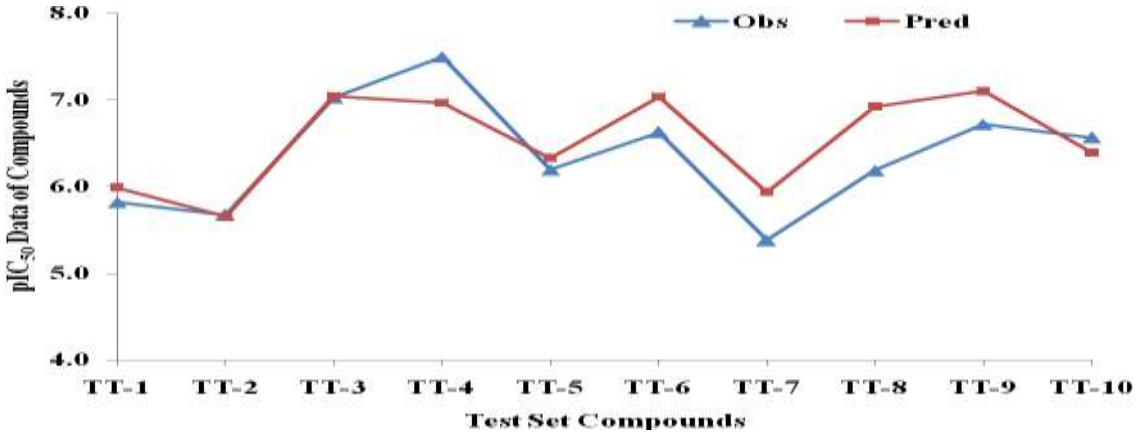


Fig 6. Predicted pIC50 derived from QSAR model are aligned with actual pIC50 value for various compounds in test set

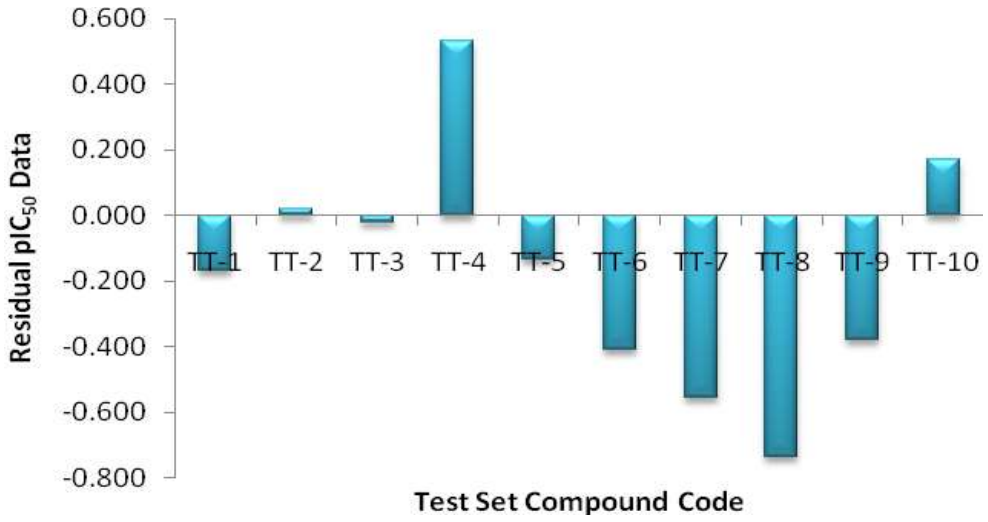


Fig. 7. Residual value of predicted pIC50 derived from QSAR model against actual pIC50 value for various compounds in test set

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