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QSAR study of 2,4-dioxothiazolidine antidiabetic compounds

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ABSTRACT

A series of 2,4-thiazolidinedione derivatives were synthesized and studied for antihyperglycemic activity with QSAR study. 3-(2,4-Dimethoxyphenyl)-2-{4-[4-(2,4-dioxothiazolidin-5-ylmethyl)phenoxy]-phenyl}- acrylic acid methyl ester (Thz7) was found the most active compound in this series. Antihyperglycemic activity of these synthesized derivatives was described by 5 models in which the bi-parametric model-3 containing χ^3 and log P was found to be the best model. Some parameters proves the effectiveness of QSAR model-3, like correlation coefficient (0.947), observed square correlation coefficient (0.896), predicted square correlation coefficient (0.872) and standard error (0.079) was lowest for this model.

INTRODUCTION

Development of novel antidiabetic agent is an important and challenging task for the medicinal chemists and many research programs are directed towards the design and synthesis of new antidiabetic drugs. Quantitative structure activity relationships (QSAR) attempt to find relationships between the molecular properties of molecules and the biological responses they elicit when applied to a biological system. QSAR models allow 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 [1].

Thiazolidinediones was found a good antidiabetic activity [2,3], so there is an urgent need for identification of novel lead structure for the designing of new, potent, and less toxic antidiabetic agents which ideally shorten the duration of therapy.

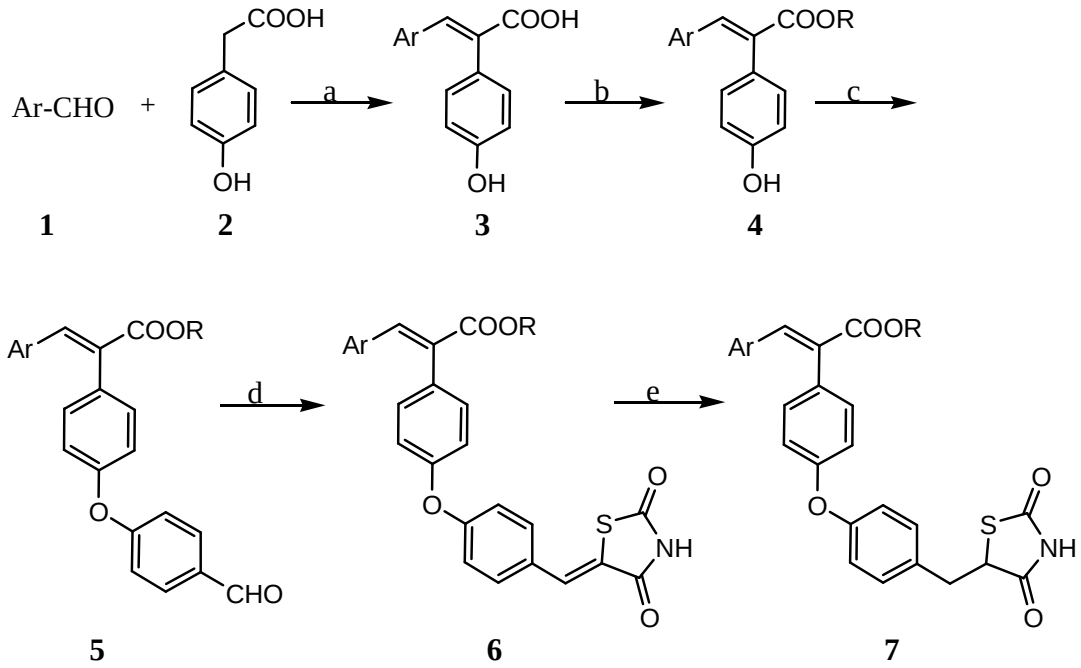
Thiazolidinediones have been demonstrated to possess antidiabetic [4,5], antihyperlipidemic [6-8], anti-inflammatory [9,10], antioxidant [11,12], antithyroid [13], antibacterial[14,15], antimalarial [16] and anticancer [17,18] activities. These reports prompted us to synthesize the novel derivatives of 2,4-Dioxothiazolidine which would be effective against diabetes.

Quantitative structure–activity relationship (QSAR) studies are indubitably of great importance in modern chemistry and biochemistry. To obtain a significant correlation, it is essential that appropriate descriptors are employed, whether they are theoretical, empirical or derived from readily available experimental characteristics of structures. Many descriptors reflect simple molecular properties and can thus provide insight into the physicochemical nature of the activity under consideration [19].

MATERIALS AND METHODS

2.1. Synthesis of 2,4-Dioxothiazolidine Derivatives

Perkin condensation of aryl aldehyde with 4-hydroxyphenyl acetic acid yielded the 3-Aryl-2-(4-hydroxyphenyl)–acrylic acid. Esterification of this substituted acid followed by condensation with 4-fluorobenzaldehyde yielded 3-Aryl-2-[4-(4-formylphenoxy)-phenyl]-acrylic acid alkyl ester. Knovenagel condensation of this ester with 2,4-thiazolidinedione in the presence of piperidinium benzoate followed by hydrogenation gave a good yield of final compound 3-Aryl-2-{4-[4-(2,4-dioxothiazolidin-5-ylmethyl)-phenoxy]-phenyl} -acrylic acid alkyl ester. The synthesized compounds were characterized physicochemically by determination of melting point, Rf values and % yield. Their structures were confirmed by IR and NMR spectral studies.



Scheme- Reagents and conditions: (a) acetic anhydride, Et_3N, 6 hrs, 130°C; (b) ROH, H_2SO4, 15 hrs, reflux; (c) 4-fluorobenzaldehyde, NaH, DMF, 18 hrs, 80°C; (d) 2,4-thiazolidinedione, piperidine, benzoic acid, toluene, 5 hrs, reflux; (e) Pd/C (10%), AcOH–$HCOONH_4$, 15 hrs, 125°C

2.2. QSAR Analysis

The independent variables such as log of octanol-water partition coefficient (Clog P), molar refractivity (CMR), total structure connectivity index (X_t), balaban topological index (J), eccentric connectivity index (CSI), kier's molecular connectivity index (χ^0, χ^1, χ^2, χ^3), total energy (Te), energy of highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) were calculated for synthesized compounds by using the computer software CS ChemOffice 8.0 version and DRAGON 5.5 evaluation version. The regression analysis were performed by the SPSS^{TM} software.

2.3. Determination of physiochemical parameters and regression analysis

Structures of all the compounds were sketched using CS Chemoffice 8.0 version and HYPERCHEM 8.0 evaluation version. 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 A°. The geometry optimizations were done by using HYPERCHEM 8.0 version. The various descriptors for all the energy minimized compounds were calculated using DRAGAN 5.5 and ChemOfiice 8.0. The data was transferred to the statistical program and a correlation matrix was constructed showing correlation between various descriptors as well as between descriptors and biological activity. Then various regression equations were derived using multiple linear regression method. The statistically significant equations were taken in consideration on the basis of correlation coefficient (R), observed squared correlation coefficient (R^2_{obs}), standard error of estimate (Se) and Fischer's statistic. The internal predictive

powers of the equations were validated by Leave Group Out (LGO) cross-validation method considering predicted residual sum of square (PRESS) and predicted square correlation coefficient (R^2_{pred}).

Table 2- Antihyperglycemic activity of thiazolidinedione derivatives

Compound	%Plasma Glucose Reduction(B.A.)	Compound	%Plasma Glucose Reduction(B.A.)
Thz1	10.74 ± 2.23[a]	Thz14	36.53 ± 2.95[b]
Thz2	9.80 ± 2.58[a]	Thz15	37.24 ± 4.39[b]
Thz3	8.60 ± 3.64	Thz16	18.81 ± 3.02[b]
Thz4	16.30 ± 3.44[a]	Thz17	18.16 ± 2.07[b]
Thz5	14.61 ± 2.58[a]	Thz18	17.48 ± 2.92[b]
Thz6	13.00 ± 2.64[a]	Thz19	13.26 ± 1.93[a]
Thz7	46.13 ± 4.96[b]	Thz20	12.40 ± 2.75[a]
Thz8	46.03 ± 3.08[b]	Thz21	12.45 ± 2.39[a]
Thz9	45.91 ± 4.51[b]	Thz22	15.58 ± 2.5[b]
Thz10	38.11 ± 3.67[b]	Thz23	13.63 ± 2.74[a]
Thz11	37.15 ± 4.06[b]	Thz24	13.42 ± 3.01[a]
Thz12	35.85 ± 3.29[b]	Rosiglitazone	56.73 ± 3.09[b]
Thz13	37.05 ± 3.6[b]	Control	0.433 ± 1.17

Values are presented as mean ±S.E.M..
One way ANOVA followed by Dunnett's test (a = p < 0.05 and b = p < 0.01)

RESULTS AND DISCUSSION

In an attempt to determine the relationship between structure of the molecule and the antidiabetic activity, quantitative structure activity relationship (QSAR) studies were under taken using Hansch analysis. Antihyperglycemic activity (biological activity) data was first transformed into log BA, which was used as dependent variable in QSAR study and is listed in Table 2. The values of selected molecular descriptors were used in QSAR studies are depicted in Table 4.

In the present work a set of 2,4-thiazolidinedione derivatives consisting of 24 molecules was used for multiple linear regression model generation. Preliminary analysis was carried out in terms of correlation analysis. A correlation of different parameters with antihyperglycemic activity of 2,4-thiazolidinedione derivatives is presented in Table 5. The highest correlation (0.79) was found between third order connectivity descriptor (χ^3) and biological activity. Therefore correlation involving χ^3 as a correlating parameter will give statistically significant models for modeling the activity. Based on these assumptions, a mono-parametric linear regression equation was derived using χ^3 descriptor.

QSAR model for Antihyperglycemic activity with χ^3 parameter :

$$\log BA = 0.295\ (\pm\ 0.099)\ \chi^3 - 2.485\ (\pm\ 1.281) \qquad \text{(Eq.1)}$$

Eq. 1 shows that χ^3 is positive indicating thereby that antihyperglycemic activity of synthesized compounds is directly proportional to the magnitude of χ^3. The antihyperglycemic activity increases with an increase in magnitude ofχ^3. This is evidenced by the values of χ^3 in Table 4. The values of χ^3 for compounds Thz7-15 lies in range of 13-14 which are higher than the χ^3 values of other compounds, making them to be the most effective.

Further the sample size and 'Rule of Thumb' allowed us to go for development of multi-parametric model using multiple linear regression analysis. The first step in analyzing multivariate correlation is to investigate auto-correlation which is achieved by obtaining correlation matrix [20]. Table 5 shows that χ^3 is poorly correlated with log P, HOMO, LUMO and Te. Therefore the models involving χ^3 with either of above four mentioned parameters will not suffer from the defect due to colinearity. Hence the multi-parametric models were developed using χ^3 as the common parameter for all models. Different statistically significant equations were obtained by multiple linear regression analysis are given below:

QSAR model for Antihyperglycemic activity with χ^3 and LUMO :

$$\log BA = 0.280\ (\pm 0.054)\ \chi^3 + 0.071\ (\pm 0.235)\ E_{LUMO} - 2.216\ (\pm 1.577) \qquad \text{(Eq.2)}$$

QSAR model for Antihyperglycemic activity with χ^3 and log P :

$$\log BA = 0.342\ (\pm 0.056)\ \chi^3 - 0.196\ (\pm 0.556)\ \log P - 1.879\ (\pm 0.716) \quad \text{(Eq.3)}$$

QSAR model for Antihyperglycemic activity with χ^3 and Te :

$$\log BA = 0.309\ (\pm 0.095)\ \chi^3 - 0.0002\ (\pm 2.207)\ Te - 2.093\ (\pm 1.271) \quad \text{(Eq.4)}$$

QSAR model for Antihyperglycemic activity with χ^3, HOMO and LUMO :

$$\log BA = 0.292\ (\pm 0.116)\ \chi^3 + 0.107\ (\pm 0.251)\ E_{LUMO} - 0.090\ (\pm 0.213)\ E_{HOMO} - 3.059\ (\pm 2.555) \quad \text{(Eq.5)}$$

The quality of the regression model is indicated by the following parameters depicted in the following Table 3.

Table 3- Parameters of different QSAR model equation

Eq. no.	N	R	R^2_{obs}	F	Se	R^2_{pred}
1	24	0.894	0.799	37.516	0.145	0.729
2	24	0.870	0.757	16.700	0.150	0.691
3	24	0.947	0.896	91.00	0.079	0.872
4	24	0.890	0.792	23.345	0.136	0.711
5	24	0.877	0.769	12.418	0.148	0.708

n- no. of compounds, R- correlation coefficient, R^2_{obs}- observed square correlation coefficient, F- Fischer's statistic, Se- standard error.

As opposed to traditional regression models, cross validation method evaluate the validity of a model by how well it predicts data rather than how well it fits data. Therefore cross validation parameters were calculated using Leave Group Out (LGO) technique [21]. The predicted square correlation coefficient ($R^2_{pred} > 0.5$) values obtained for the best QSAR models indicated their reliability in predicting the antihyperglycemic activity of different synthesized compounds. Obtaining most appropriate model does not mean that it will also have the highest predictive ability. Therefore the aptness of the regression model have to be decided. It was achieved by predicted square correlation coefficient- R^2_{pred}. The closer this correlation is to unity, the better the predictive ability.

Some parameters proves the effectiveness of QSAR model-3, like correlation coefficient (0.947), observed square correlation coefficient (0.896) and predicted square correlation coefficient (0.872) are highest among all the models. Standard error (0.079) was lowest for this model which further confirmed the good quality of this model. The coefficient of log P is negative in equation-3, which shows that log P is inversly proportional to the biological activity. This fact is confirmed by the observed activities (BA) of all compounds as shown in Table 4. In all synthesized compounds methyl ester have higher activity than ethyl and propyl esters which is due to the reason that antihyperglycemic activity decreases with increase in the value of log P. Based on all above mentioned statistical calculations model 3 was found to be the best model.

QSAR studies were carried out to find out correlation between antihyperglycemic activity and physicochemical parameters of synthesized compounds indicated that antihyperglycemic activity of these synthesized derivatives are governed by connectivity parameter χ^3. The bi-parametric model containing χ^3 and log P was found to be the best mode.

Table 4- Molecular descriptors of synthesized compounds

Comp.	Zm1	CSI	J	Xt	X^0	X^1	X^2	X^3	LUMO (eV)	HOMO (eV)	Total Energy (E-Kcal/mol)	CLog P	CMR	logBA
Thz1	170	1054	1.165	0.203	23.209	16.012	14.242	11.755	-1.07904	-8.4899	2375.5	5.755	13.110	1.068
Thz2	174	1089	1.176	0.201	23.916	16.512	14.622	11.855	-1.047	-7.9489	2944.14	6.284	13.574	1.015
Thz3	178	1126	1.183	0.198	24.623	17.012	14.976	11.124	-1.0388	-7.931	2935.45	6.813	14.038	0.946
Thz4	180	1203	1.165	0.199	27.786	16.944	15.033	12.974	-1.1299	-8.4516	2387.82	5.674	15.727	1.221
Thz5	184	1238	1.179	0.196	25.493	17.444	15.413	12.674	-1.0982	-7.9609	2956.79	6.203	14.191	1.162
Thz6	188	1275	1.188	0.194	26.2	17.944	15.767	12.043	-1.089	-7.942	2943.10	6.732	14.635	1.099
Thz7	190	1235	1.21	0.195	26.363	17.893	15.754	13.35	-1.0279	-8.2678	2406.37	5.783	14.344	1.647
Thz8	194	1270	1.226	0.192	27.07	18.393	16.134	13.33	-0.9912	-7.8162	2975.48	6.292	14.808	1.639
Thz9	198	1307	1.237	0.19	27.777	18.893	16.488	13.32	-0.986	-7.7968	2667.01	6.821	15.272	1.622
Thz10	190	1279	1.188	0.195	26.363	17.893	15.754	13.328	-1.1765	-8.8479	2439.46	5.413	14.344	1.564
Thz-11	194	1314	1.204	0.192	27.07	18.393	16.134	13.32	-1.149	-7.9585	3008.4	5.942	14.808	1.542
Thz12	198	1351	1.215	0.19	27.777	18.893	16.488	13.09	-1.1409	-7.9391	2999.68	6.471	15.272	1.515
Thz13	190	1307	1.238	0.195	26.363	17.91	15.669	13.05	-1.0251	-8.2159	2436.64	5.413	14.344	1.552
Thz-14	194	1270	1.227	0.192	27.07	18.41	16.05	13.056	-0.9909	-7.7719	3005.74	5.942	14.808	1.534
Thz15	198	1307	1.238	0.19	27.777	18.91	16.403	13.025	-0.9861	-7.757	2997.23	6.971	15.272	1.53
Thz16	176	1091	1.173	0.202	24.079	16.406	14.876	12.17	-1.1492	-8.4811	2381.85	5.088	13.264	1.296
Thz17	180	1126	1.186	0.199	24.786	16.906	15.256	12.07	-1.887	-7.9804	2950.83	5.617	13.727	1.268
Thz18	184	1163	1.193	0.196	25.493	17.406	15.61	12.04	-1.1101	-7.9691	2942.14	6.646	14.191	1.239
Thz19	176	1126	1.167	0.202	24.079	16.406	14.864	12.166	-1.8121	-8.9901	2422.55	5.498	13.722	1.119
Thz20	180	1161	1.179	0.199	24.786	16.906	15.244	12.266	-1.8163	-8.3779	2991.66	6.027	14.186	1.111
Thz21	184	1198	1.187	0.196	25.493	17.406	15.598	12.035	-1.8903	-8.3796	2983.81	6.556	14.650	1.068
Thz22	186	1202	1.184	0.197	25.656	17.317	15.775	11.797	-1.3102	-8.691	2375.83	6.618	13.887	1.16
Thz23	190	1237	0.199	0.195	26.363	17.817	16.155	11.097	-1.2866	-8.0792	2944.36	7.147	14.351	1.091
Thz24	194	1274	1.209	0.192	27.07	18.317	16.509	11.066	-1.2779	-8.06	2935.66	7.826	14.815	1.074

Table 5- Correlation matrix of different molecular descriptors with Antihyperglycemic activity of thiazolidinedione derivatives

	ZM1	CSI	J	Xt	X^0	X^1	X^2	X^3	LUMO energy	HOMO energy	Total energy	Clog P	CMR	log BA
Zm1	1.00													
CSI	0.947	1.00												
J	0.002	0.037	1.00											
Xt	-0.978	-0.927	-0.053	1.00										
X^0	0.897	0.904	0.017	-0.881	1.00									
X^1	0.990	0.942	0.045	-0.994	0.893	1.00								
X^2	0.975	0.897	-0.089	-0.954	0.857	0.956	1.00							
X^3	0.974	0.958	0.076	-0.934	0.902	0.960	0.907	1.00						
LUMO energy	0.346	0.345	0.089	-0.381	0.379	0.394	0.227	0.419	1.00					
HOMO energy	0.484	0.384	0.012	-0.603	0.422	0.567	0.469	0.384	0.443	1.00				
Total energy	0.333	0.260	-0.107	-0.460	0.217	0.401	0.398	0.268	-0.083	0.746	1.00			
Clog P	0.395	0.304	-0.292	-0.482	0.325	0.427	0.520	0.241	0.087	0.451	0.530	1.00		
CMR	0.757	0.797	0.077	-0.781	0.938	0.779	0.721	0.756	0.251	0.409	0.300	0.350	1.00	
LogBA	0.698	0.658	0.270	-0.621	0.635	0.675	0.566	0.793	0.407	0.230	-0.107	-0.309	0.46	1.00

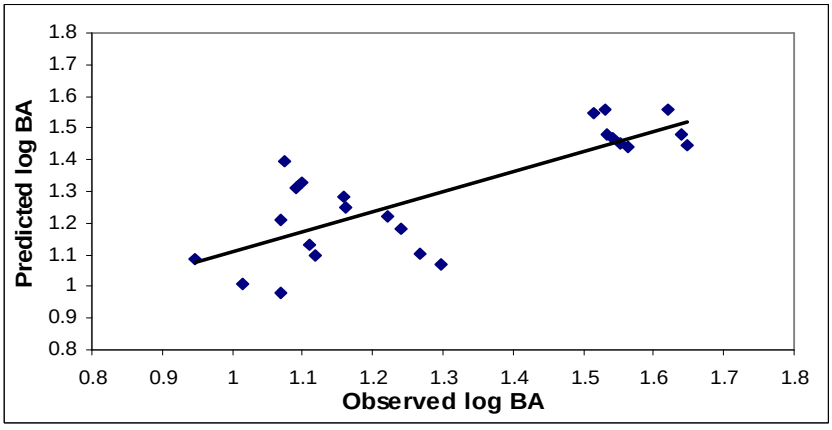


Fig. 1- Plot of observed logBA values against predicted logBA values for the QSAR model by Eq.- 1

3.1. Plots between observed and predicted activities for qsar models:

In order to confirm our results we have predicted the activities of different compounds using all models expressed by Eq. 1 to 5. Here Fig. 1 to 5 shows that predicted activities calculated by best model- 3 (Fig. 3) were very close to each other as evidenced by low values of residual activity (Table 6).

Table 6- Comparison of observed and predicted antihyperglycemic activities of synthesized derivatives using corresponding QSAR models

Comp.	log BA by using Eq.1			log BA by using Eq.2			log BA by using Eq.3			log BA by using Eq.4			log BA by using Eq.5		
	Obs.	Pred.	Res.	Obs.	Pred.	Res.	Obs.	Pred.	Res.	Obs.	Pred.	Res.	Obs.	Pred.	Res.
Thz1	1.068	0.978	0.090	1.068	1.068	0.000	1.068	1.024	0.044	1.068	1.012	0.056	1.068	1.044	0.024
Thz2	1.015	1.007	0.008	1.015	1.013	0.002	1.015	1.009	0.006	1.015	0.942	0.073	1.015	0.954	0.061
Thz3	0.946	1.087	-0.141	0.946	1.093	-0.147	0.946	1.086	-0.141	0.946	0.930	0.016	0.946	1.039	-0.093
Thz4	1.221	1.219	0.002	1.221	1.221	0.000	1.221	1.255	-0.034	1.221	1.308	-0.087	1.221	1.296	-0.075
Thz5	1.162	1.249	-0.087	1.162	1.252	-0.090	1.162	1.244	-0.082	1.162	1.238	-0.076	1.162	1.205	-0.043
Thz6	1.099	1.328	-0.229	1.099	1.331	-0.232	1.099	1.322	-0.223	1.099	1.227	-0.128	1.099	1.292	-0.193
Thz7	1.647	1.448	0.199	1.647	1.454	0.193	1.647	1.476	0.171	1.647	1.552	0.095	1.647	1.532	0.115
Thz8	1.639	1.477	0.162	1.639	1.486	0.153	1.639	1.469	0.170	1.639	1.486	0.153	1.639	1.442	0.197
Thz9	1.622	1.557	0.065	1.622	1.565	0.057	1.622	1.546	0.076	1.622	1.474	0.148	1.622	1.591	0.031
Thz10	1.564	1.441	0.123	1.564	1.440	0.124	1.564	1.506	0.058	1.564	1.617	-0.053	1.564	1.518	0.046
Thz11	1.542	1.471	0.071	1.542	1.471	0.071	1.542	1.458	0.084	1.542	1.547	-0.005	1.542	1.428	0.114
Thz12	1.515	1.550	-0.035	1.515	1.550	-0.035	1.515	1.536	-0.021	1.515	1.535	-0.020	1.515	1.513	0.002
Thz13	1.552	1.450	0.102	1.552	1.456	0.096	1.552	1.474	0.078	1.552	1.627	-0.075	1.552	1.527	0.025
Thz14	1.534	1.479	0.055	1.534	1.487	0.047	1.534	1.467	0.067	1.534	1.557	-0.023	1.534	1.437	0.097
Thz15	1.530	1.558	-0.028	1.530	1.567	-0.037	1.530	1.545	-0.014	1.530	1.545	-0.015	1.530	1.523	0.007
Thz16	1.296	1.072	0.224	1.296	1.073	0.223	1.296	1.110	0.186	1.296	1.252	0.044	1.296	1.142	0.154
Thz17	1.268	1.102	0.166	1.268	1.063	0.205	1.268	1.015	0.253	1.268	1.182	0.086	1.268	1.052	0.216
Thz18	1.239	1.181	0.058	1.239	1.183	0.056	1.239	1.176	0.063	1.239	1.171	0.068	1.239	1.137	0.102
Thz19	1.119	1.099	0.020	1.119	1.065	0.054	1.119	1.111	0.008	1.119	1.203	-0.084	1.119	1.162	-0.043
Thz20	1.111	1.129	-0.018	1.111	1.094	0.017	1.111	1.085	0.026	1.111	1.133	-0.022	1.111	1.071	0.040
Thz21	1.068	1.208	-0.140	1.068	1.169	-0.101	1.068	1.156	-0.088	1.068	1.121	-0.053	1.068	1.157	-0.089
Thz22	1.160	1.285	-0.125	1.160	1.277	-0.117	1.160	1.323	-0.163	1.160	1.198	-0.038	1.160	1.367	-0.207
Thz23	1.091	1.314	-0.223	1.091	1.307	-0.216	1.091	1.299	-0.208	1.091	1.129	-0.038	1.091	1.277	-0.186
Thz24	1.074	1.394	-0.320	1.074	1.387	-0.313	1.074	1.377	-0.303	1.074	1.087	-0.013	1.074	1.362	-0.288

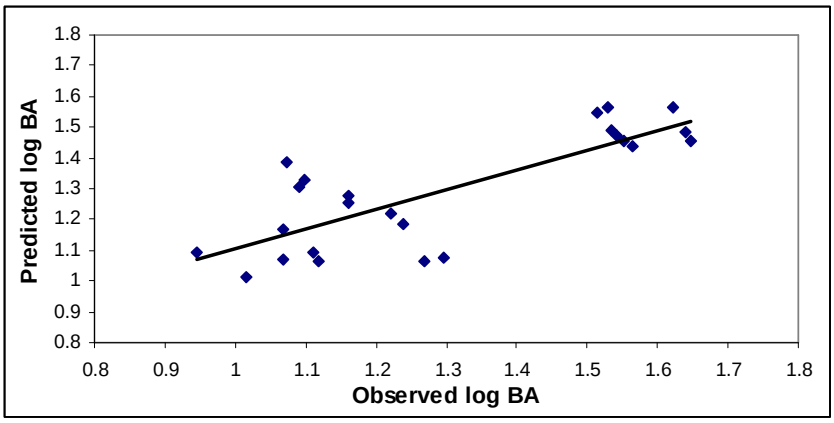


Fig. 2- Plot of observed logBA values against calculated logBA values for the QSAR model using Eq.- 2

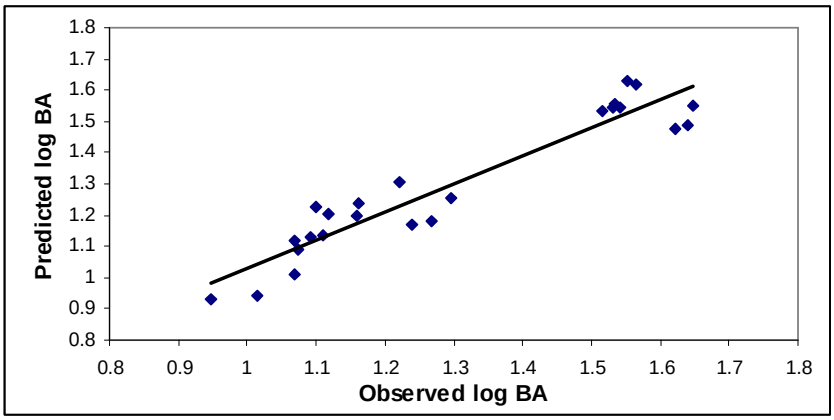


Fig. 3- Plot of observed logBA values against calculated logBA values for the QSAR model using Eq.- 3

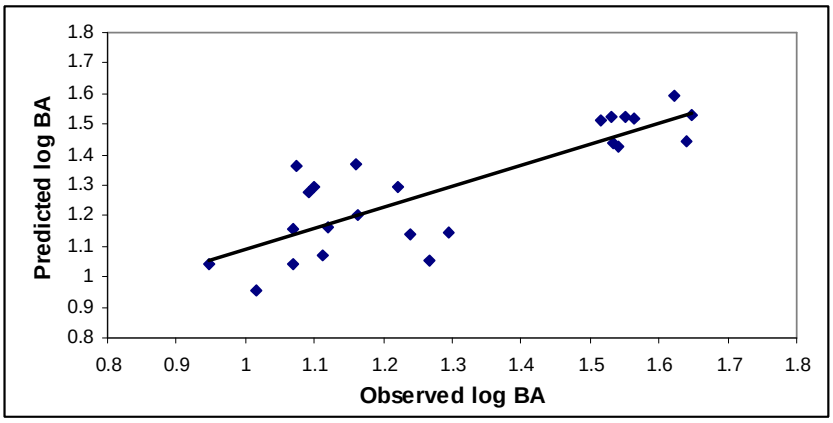


Fig. 4- Plot of observed logBA values against calculated logBA values for the QSAR model using Eq.- 4

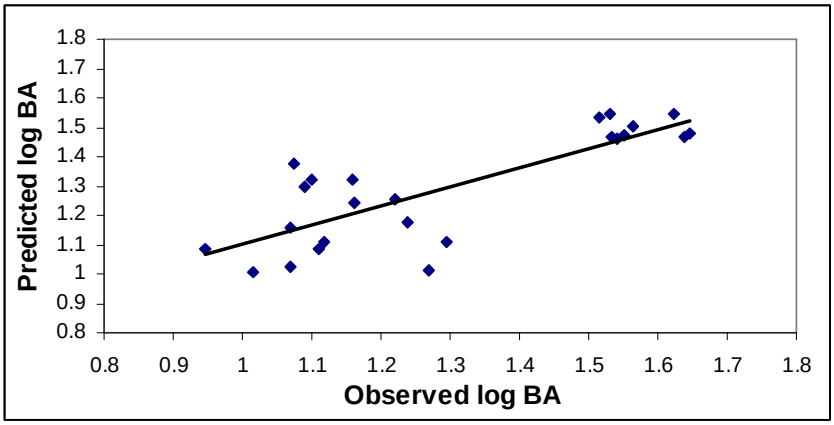


Fig. 5- Plot of observed logBA values against calculated logBA values for the QSAR model using Eq.- 5

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