Quantitative Structure Activity Relationship (QSAR) Analysis of Substituted 4-Oxothiazolidines and 5-Arylidines as Lipoxygenase Inhibitors

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Abstract: Quantitative structure-activity relationships (QSAR) analyses have been attempted on a new set of 4-oxothiazolidines and 5-arylidines derivatives using linear free energy related (LFER) model of Hansch to explain the structural requirements for lipoxygenase inhibition. The QSAR study showed that successful correlation can be achieved for inhibitory activity of 4-oxothiazolidines and 5-arylidines ($R>0.9$, $Q^2>0.7$). The result of the QSAR study suggests the bulky substituents in the thiazolidine nucleus will decrease the binding affinity of 4-oxothiazolidines derivatives towards lipoxygenase indicated by negative contribution of molar refractivity and connolly accessible area. The positive contribution of topological parameters (BI, MTI, CC and TVC) illustrates that increase in branching and presence of heteroatom are favorable for lipoxygenase inhibitory activity.

Keywords: Quantitative structure-activity relationship, QSAR, lipoxygenase inhibitors, anti-inflammatory, substituted 4-oxathiazolidines and 5-arylidines.

INTRODUCTION

Inflammation is a biological response to a series of chemical reactions whose major function is protection of the body from infection and the resolution of tissue damage caused by tissue injury [1,2]. During these reactions, toxic materials and cellular debris are removed by means of increased capillary permeability and migration of leucocytes to the injured area [3,4]. As a result of cell injury, an intricate system is activated causing the release of numerous inflammatory mediators such as histamine, serotonin, bradykinin, Hageman factor, lysosomal enzymes, prostaglandins and leukotrienes [5,6]. These mediators initiate a three phase process consisting of: vasodilatation, increased vascular permeability, and leukocytic exudation, all of which occur simultaneously in a multiple interaction process resulting in the characteristic clinical sign of heal, redness, swelling, pain and diminished functions [7].

Non steroidal anti-inflammatory agents are of current interest because there are no drugs of choice for the treatment of most of the diseases like rheumatoid arthritis [8-9], allergic rhinitis [10], psoriasis, asthma [11] and ulcerative colitis [12]. The two major approaches for design and synthesis of anti-inflammatory agents are based on the inhibition of two enzymes, cyclooxygenase and lipoxygenase, which are involved in the metabolism of arachidonic acid(AA) [13].Cyclooxygenase has been the common targets for most of the anti-inflammatory drugs but due to the association of some side effects such as ulceration and bleeding in gastrointestinal tract with cyclooxygenase inhibitors [14] and implication of leukotrienes in the above inflammatory and allergic disorders, the attention is focused on the 5-lipoxygenase enzyme inhibitors [15,16], which restrict the synthesis of leukotrienes from AA *via* peroxidation of AA to 5-hydroperoxyeicosatetraenoic acid (5-HPETE) followed by dehydration to 5,6 –epoxy leukotriene A4 (LTA_4). No three dimensional quantitative structure activity relationship (3D QSAR) studies have been attempted so far on series of substituted oxothiazolidines; it appeared of interest to perform 3D QSAR analysis. A Quantitative structure–activity relationship (QSAR) enables the investigators to establish a reliable quantitative structure–activity and structure–property relationships to derive QSAR model to predict the activity of novel molecules prior to their synthesis. The overall process of QSAR model development can be divided into three stages namely, the data preparation, data analysis, and model validation, representing a standard practice of any QSAR modeling.

In this research, an attempt has been made to describe the Quantitative structure–activity relationship (QSAR) analysis of 4-oxothiazolidines and 5-arylidines to study and deduce a correlation between structure and anti-inflammatory activity of these derivatives.

MATERIAL AND METHODS

Twenty-two compounds belonging to 4-oxothiazolidenes and 5- arylidenes derivatives were taken from literature [17] (Table **1** and Fig. **1**). The biological activity data was converted to negative logarithmic dose (pIC_{50}) for QSAR analysis. The conversion was done in order to linearly relate free energy of the interaction of compounds with receptor and to reduce the skewness of the data set.

Molecular Modeling studies and Quantum mechanical calculations were performed using CS Chem Office version 10.0 (Cambridge software) running on a P-IV processor [18]. All molecules were built using Chemdraw Ultra ver 10.0 and subjected to energy minimization using Allinger's MM2 force field. The Minimization is continued until the root

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Table 1. 4-Oxothiazolidines and 5-Arylidenes Derivatives and their Biological Activities

No	R_1	R_2	R_3	IC_{50}	pIC_{50}
1	H	2-ClC_6H_4	-	27.77	-1.4435
2	H	3-ClC_6H_4	-	38.88	-1.59
3	H	4-ClC_6H_4	-	30.55	-1.4854
4	H	2-BrC_6H_4	-	44.44	-1.6478
5	H	3-BrC_6H_4	-	33.33	-1.5228
6	H	4-BrC_6H_4	-	41.66	-1.6197
7	H	2-$NO_2C_6H_4$	-	25.10	-1.3996
8	H	3-$NO_2C_6H_4$	-	27.77	-1.4435
9	H	2-OHC_6H_4	-	11.11	-1.0457
10	H	3-OHC_6H_4	-	8.33	-0.9208
11	H	4-OHC_6H_4	-	13.88	-1.1426
12	H	2-ClC_6H_4	2-ClC_6H_4	30.55	-1.4854
13	H	3-ClC_6H_4	3-ClC_6H_4	33.33	-1.5228
14	H	4-ClC_6H_4	4-ClC_6H_4	27.77	-1.4435
15	H	2-BrC_6H_4	2-BrC_6H_4	38.88	-1.59
16	H	3-BrC_6H_4	3-BrC_6H_4	36.11	-1.5576
17	H	4-BrC_6H_4	4-BrC_6H_4	41.66	-1.6197
18	H	2-NO2C_6H_4	2-NO2C_6H_4	16.67	-1.2219
19	H	3-NO2C_6H_4	3-NO2C_6H_4	19.44	-1.2886
20	H	2-OHC_6H_4	2-OHC_6H_4	11.11	-1.0457
21	H	3-OHC_6H_4	3-OHC_6H_4	13.88	-1.1426
22	H	4-OHC_6H_4	4-OHC_6H_4	8.33	-0.9206

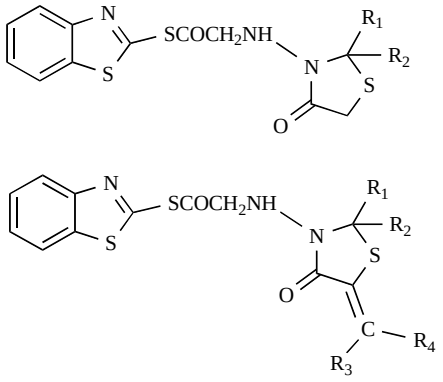

Fig. (1). General structures of substituted 4-oxothiazolidines and 5-arylidene.

mean square (RMS) gradient value reaches a value smaller than 0.1 kcal/molA°. The Hamiltonian approximations [19] Austin model -1(AM-1) method and RHF (restricted Hartee-Fork:closed shell) wave function was adopted for reoptimization until the root mean square (RMS) gradient attains a value smaller than 0.001 kcal/molA° by the use of GAMESS module.

The physicochemical properties calculated include thermodynamic, steric and electronic descriptors. Torsion energy (TOE), stretch bend energy (SBE), log p and bend energy (BE) are descriptors of thermodynamic property. The steric descriptors calculated were molar refractivity (MR), connolly accessible area (CAA), connolly molecular area (CMA), connolly solvent excluded volume (CSEV), molecular weight, principal moments of inertia-x component (PMI-X), principal moment of inertia-Y (PMI-Y), principal moment of inertia-Z (PMI-Z) and ovality. Electronic descriptors such as dipole moment (DM), electronic energy (EE), highest occupied molecular orbital energy (HOMO), lowest unoccupied molecular orbital energy (LUMO), vander wall forces (VDW), repulsion energy, and total energy were also calculated. The topological parameters calculated were Balaban index (BI), cluster count (CC), diameter(D), Molecular topological index (MTI), radius (R),shape attributes (SA), shape coefficient (SC), sum of degree (SOVD), sum of total

connectivity (TC), total valence connectivity (TVC), and the Wiener index (WI) [20, 21].

Different combinations of descriptors were subjected to sequential regression analysis employing VALSTAT software [22]. In stepwise multiple linear regression analysis [23] the independent variables are individually added or deleted from the model at each step of the regression depending on the Fischer ratio values selected to enter and to remove until the 'best' model is obtained. The descriptors found in the best models for antinflammatory activity of 4-oxothiazolidines and their 5-arylidenes are summarized in Table **2**. Statistical qualities of the models were gauged by parameters [24] like; correlation coefficient (r) standard error of estimate (SEE), variance ratio F (ratio between the described and non-described part of variance), explained variance (%EV) and adjusted squared correlation coefficient (R^2a). To ascertain the predictivity of models, cross validation was done by mean of leave-one-out (LOO) procedure/jack-knife validation test [20] using in-house program VALSTAT. Each compound is eliminated once and a model is derived from the remaining compounds and the eliminated compound is predicted from this model. The same procedure is repeated after elimination of another compound, until all the compounds have been eliminated once. The predictivity of the QSAR models was given by parameters cross-validated correlation coefficient (R^2cv or q^2), standard error of predictions (S_{DEP}), and standard deviation of prediction (S_{PRESS}), chance statistics evaluated as the ratio of the equivalent regression equations to the total number of randomized sets; a chance value of 0.01 corresponds to 1% chance of fortuitous correlation and boot-strapping square correlation coefficient (r^2bs) which confirm the robustness and applicability of QSAR equation on the structure analogs.

RESULTS AND DISCUSSION

The correlation between different physicochemical and topological descriptors as independent variable and antinflammatory activity as dependent variable was found out. Statistical processing by stepwise regression method gave many QSAR models. Only those parameters having intercorrelation below 0.6 and confidence interval limit >95% were considered to select the best model. The triparametric (1 and

Table 2. Descriptors Contributing to the Lipoxygenase Inhibitory Activity

No	MR	BI	MTI	CAA	CC	TVC
1	11.5402	656210	14235	562.646	27	9.666
2	11.5402	662495	14322	605.182	27	9.666
3	11.5402	668634	14409	593.413	27	9.666
4	11.8258	656210	14235	565.107	27	8.5251
5	11.8258	662495	14322	590.089	27	8.5251
6	11.8258	668634	14409	597.466	27	8.5251
7	11.6603	902473	16822	588.191	29	6.3542
8	11.6603	924162	17163	612.705	29	6.3542
9	11.2019	656210	14413	579.14	27	3.8125
10	11.2019	662495	14520	577.011	27	3.8125
11	11.2019	668634	14627	539.853	27	3.8125
12	15.2852	1792319	27981	716.819	35	1.2429
13	15.2852	1817100	28229	763.149	35	1.2429
14	15.2852	1841340	28477	755.264	35	1.2429
15	15.8564	1792319	27981	700.905	35	9.6676
16	15.8564	1817100	28229	782.434	35	9.6676
17	15.8564	1841340	28477	721.577	35	9.6667
18	15.5254	2876366	35691	703.455	39	5.3709
19	15.5254	2974327	36723	795.487	39	5.3709
20	14.6086	1792319	28499	598.299	35	1.9355
21	14.6086	1817100	28005	730.639	35	1.9335
22	14.6086	1841340	29111	722.422	35	1.9335

Table 3. Observed, Calculated, Residual, Predicted and Predicted Residual Activities of Compounds for Lipoxygenase Inhibitory Activities in Model-1

No	Observed activity	Calculated Activity	Residual	Predicted	Predicted Residual activity
1	-1.4435	-1.4600	0.0165	-1.4618	0.0183
2	-1.59	-1.4600	-0.129	-1.4455	-0.1445
3	-1.4854	-1.46	-0.025	-1.4571	-0.0283
4	-1.6478	1.5325	-3.1803	1.5173	-3.1651
5	-1.5228	-1.5325	0.0097	-1.5337	0.0109
6	-1.6197	-1.5325	-0.087	-1.5210	-0.0986
7	-1.3996	-1.3352	-0.064	-1.3228	-0.0767
8	-1.4435	-1.3660	-0.077	-1.3496	-0.0939
9	-1.0457	1.1801	-2.2258	1.2026	-2.2483
10	-0.9208	-1.1993	0.278	-1.2427	0.3219
11	-1.1426	-1.1993	0.0567	-1.2082	0.0656
12	-1.4854	-1.4911	0.0057	-1.4921	0.0067
13	-1.5228	-1.4911	-0.031	-1.4855	-0.0373
14	-1.4435	1.4911	-2.9346	1.4995	-2.943
15	-1.59	1.6354	-3.2254	-1.6448	-3.2348
16	-1.5576	-1.6354	0.077	-1.6515	0.0939
17	-1.6197	-1.6354	0.015	-1.6386	0.0189
18	-1.2219	-1.2717	0.049	-1.3054	0.0835
19	-1.2886	-1.3025	0.0139	-1.3127	0.0241
20	-1.0457	-0.9499	-0.0957	-.0.9119	-0.1337
21	-1.1426	-0.9691	-0.1735	-0.9073	-0.2352
22	-0.9208	-0.9691	0.048	-0.9863	0.0655

2) and quarter parametric models (3 and 4) were significant for lipoxygenase inhibitory activity.

The best triparametric models along with its statistical measures are given below.

BA = [-0.3850 (± 0.1090)] M.R + [0.3795 (± 0.1364)] B.I.+ [0.0639(± 0.0263)] M.T.I. -4.41973 (**Model 1**)

n =22, r = 0.908, r^2 = 0.825, variance = 0.011, std = 0.106, F = 28.451

r^2_{bs} = 0.817, chance< 0.01, Q^2 = 0.745, S_{PRESS} = 0.128, S_{DEP} = 0.116

Where n is the number of data points, r is correlation coefficient, %EV is explained variance, SEE is standard error of estimate, and values given in the parentheses are standard error of the coefficients.

The model has a correlation coefficient of 0.908 with 82.5% explained variance in the lipoxygenase inhibitory activity. F statistics indicate statistical significance at 99% level as the calculated F value exceeds the tabulated F value, which is $F_{(3,18)}$ = 5.09. The model also exhibits good predictivity as established by the cross validation of the model. Predicted activity values were calculated using the correlation developed and a comparison was made with the observed values (Table **3**, Figs. **2** and **3**). The absence of any serious multicollinearity between the descriptors present in the model was confirmed by the calculation of correlation matrix (Table **4**).

Table 4. Correlation Matrix for Model-1

	MR	BI	MTI
MR	1.0000		
BI	0.5472	1.0000	
MTI	0.5289	0.0955	1.0000

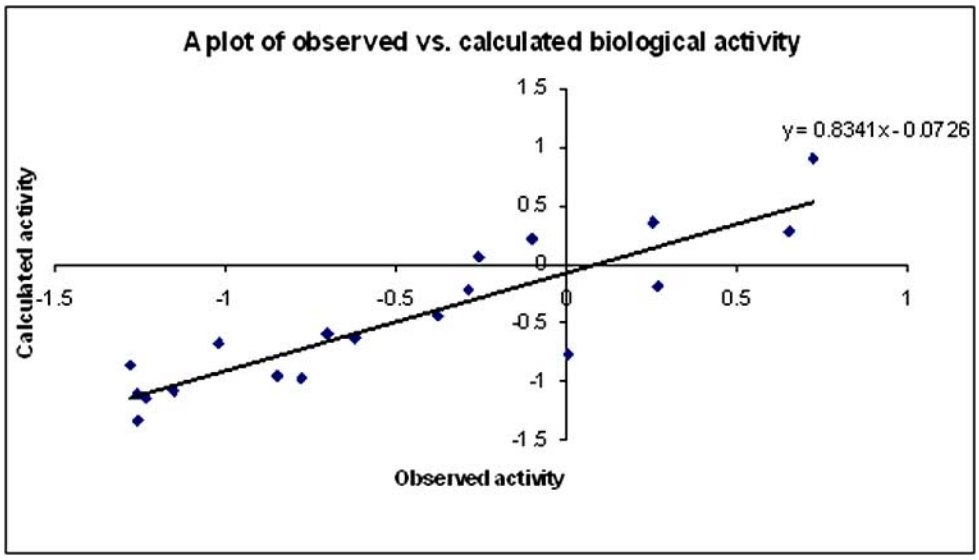

Fig. (2). A plot of observed activity *vs.* calculated activity for model 1.

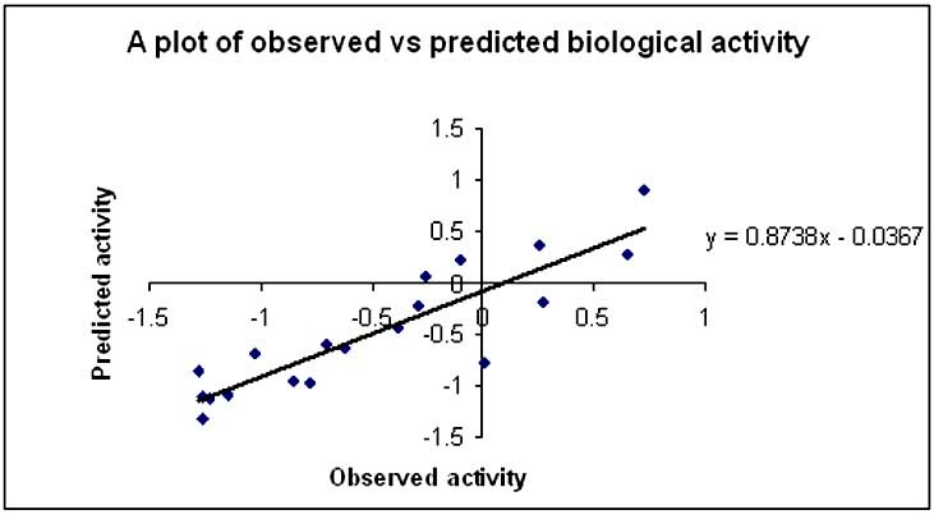

Fig. (3). A plot of observed activity *vs.* predicted activity for model 1.

MR is measure of the volume occupied by an atom or group of atoms, the negative contribution of descriptors suggests bulky substituents are not tolerable for lipoxygenase inhibitory activity of 4-oxothiazolidenes and 5-arylidines derivatives.

Balaben index J (or average distance sum connectivity index).Each distance sum Di is the sum of the elements of the ith row of the distance matrix. The coefficient bears positive sign in the model, which suggests that increased activity can be achieved by increasing the structure size and degrees of branching and unsaturation.

MTI is molecular topological index weighed by valence vertex degrees and it is calculated by subjecting the valence, adjacent and distance matrices to matrix algebraic operations. However, the MTI used in the present study is valence weighed i.e., valence information and information regarding presence and absence of unshared electron pair is incorporated into adjacent matrix. The coefficient bears positive sign in the model, which suggests that increased activity can be achieved by increasing the heteroatom content and flexibility of the substituent side chain.

Compound 10 found successively to be outliers as their residual value exceeded twice the standard error of estimate of the model. The reason for the outlying behavior of this compound may probably due to resonance unstablization (OH) at the meta position of the phenyl ring. Exclusion of compound 10 from data set as outliers resulted in model 2.

BA = [-0.3590 (± 0.0856)]M.R + [0.3574 (± 0.1063)]B.I.+ [0.0595(± 0.0205)]M.T.I. - 4.34937 (**Model 2**)

n = 21, r = 0.938, r^2 = 0.881, variance = 0.006, std = 0.081, F = 42.041

r^2_{bs} = 0.876, chance< 0.01, Q^2 = 0.786, S_{PRESS} = 0.101, S_{DEP} = 0.091

The model is statistically significant, as it has a correlation coefficient of 0.938 with 88.1% of the variance in activity. The model showed overall internal statistical signifi-

Table 5. Observed, Calculated, Residual, Predicted and Predicted Residual Activities of Compounds for Lipoxygenase Inhibitory Activities in Model-2

No	Observed Activity	Calculated Activity	Residual	Predicted	Predicted Residual activity
1	-1.4435	-1.4863	0.0428	-1.4952	0.0517
2	-1.59	-1.4863	-0.1036	-1.4737	-0.1163
3	-1.4854	-1.4863	0.0009	-1.4864	0.001
4	-1.6478	1.5538	-3.2016	1.5409	-3.1887
5	-1.5228	-1.5538	0.031	-1.5581	0.0353
6	-1.6197	-1.5538	-0.0659	-1.5447	-0.075
7	-1.3996	-1.3612	-0.0383	-1.3534	-0.0462
8	-1.4435	-1.3899	-0.0536	-1.3781	-0.0654
9	-1.0457	1.2248	-2.2705	1.2604	-2.3061
10	-0.9208	*	*	*	*
11	-1.1426	-1.2427	0.1001	-1.2612	0.1186
12	-1.4854	-1.4847	-0.0007	-1.4840	-0.0014
13	-1.5228	-1.4847	-0.038	-1.4780	-0.0448
14	-1.4435	1.4847	-2.9282	1.4920	-2.9355
15	-1.59	1.6193	-3.2093	1.6254	-3.2154
16	-1.5576	-1.6193	0.0617	-1.6323	0.0747
17	-1.6197	-1.6193	-0.0004	-1.6192	-0.0005
18	-1.2219	-1.2627	0.0408	-1.2904	0.0685
19	-1.2886	-1.2914	0.0436	-1.2935	0.0049
20	-1.0457	-0.9791	-0.023	-0.9514	-0.0943
21	-1.1426	-0.9971	-0.1455	-0.9429	-0.1997
22	-0.9208	-0.9971	0.0763	-1.0255	0.1047

*Compound removed as outlier.

cance level better than 99.9% as it exceeded the tabulated F value, which is $F_{(3,17)} = 5.19$. To ascertain the predictivity of model, internal validation using leave one out method of cross validation process, bootstrapping techniques and randomized test was performed. The model was further subjected to cross validation method to confirm the internal consistency; the cross validated squared correlation coefficient (Q^2=0.786), standard deviation of error (S_{press} =0.101), standard deviation of error of prediction (SDEP =0.091) suggested good predictive ability of the activity. The robustness and wide pragmatism of the equation was further supported by r^2bs=0.876, chance< 0.01. At per value of bootstrap squared correlation coefficient (r^2bs) with conventional squared correlation coefficient (r^2), suggested that the model is a proper representative of analogs.

Predicted activity values were calculated using the correlation developed and a comparison was made with the observed values (Table **5**). The absence of any serious multicollinearity between the descriptors present in the model was confirmed by the calculation of correlation matrix (Table **6**).

The best quarter parametric models along with its statistical measures are given below.

BA = [-0.0052 (±0.0035)] C.A.A – [0.1932 (± 0.0535)] M.R. + [0.0004 (± 0.0001)] C.C + [0.0030 (± 0.0011)] T.V.C - 2.05312 (**Model 3**)

n = 22, r = 0.923, r^2 = 0.852, variance = 0.010, std = 0.1007, F = 24.547

Table 6. Correlation Matrix for Model-2

	MR	BI	MTI
MR	1.0000		
BI	0.0738	1.0000	
MTI	0.5062	0.3245	1.0000

Table 7. Observed, Calculated, Residual, Predicted and Predicted Residual Activities of Compounds for Lipoxygenase Inhibitory Activities in Model-3

No	Observed Activity	Calculated Activity	Residual	Predicted	Predicted Residual activity
1	-1.4435	-1.5174	0.0739	-1.5306	0.0871
2	-1.59	-1.4767	-0.1133	-1.4637	-0.1263
3	-1.4854	-1.5081	0.0227	-1.5109	0.0255
4	-1.6478	1.5377	-3.1855	0.5183	-2.1661
5	-1.5228	-1.5030	-0.0198	-1.5007	-0.0221
6	-1.6197	-1.5251	-0.0946	-1.5132	-0.1065
7	-1.3996	-1.3291	-0.0705	-1.3186	-0.081
8	-1.4435	-1.3255	-0.118	-1.3043	-0.1392
9	-1.0457	1.1367	-2.1824	1.1573	-2.203
10	-0.9208	-1.1606	0.2398	-1.2069	0.2861
11	-1.1426	-1.2257	0.0831	-1.2392	0.0966
12	-1.4854	-1.5110	0.0256	-1.5158	0.0304
13	-1.5228	-1.5069	-0.0159	-1.5037	-0.0191
14	-1.4435	1.5779	-3.0214	1.6003	-3.0438
15	-1.59	1.5718	-3.1618	1.5674	-3.1574
16	-1.5576	-1.5232	-0.0328	-1.5111	-0.0465
17	-1.6197	-1.6677	0.048	-1.6756	0.0559
18	-1.2219	-1.2862	0.0643	-1.3382	0.1163
19	-1.2886	-1.2650	-0.0236	-1.2430	-0.0456
20	-1.0457	-0.9799	-0.0658	-0.8030	-0.2427
21	-1.1426	-1.1425	-0.0001	-1.1424	-0.0002
22	-0.9208	-0.8244	-0.0964	-0.7141	-0.2067

$r^2_{bs} = 0.863$, chance< 0.01, $Q^2 = 0.716$, $S_{PRESS} = 0.139$, $S_{DEP} = 0.122$

In this model MR and CAA are steric parameters; the negative contribution of descriptors suggests that bulky substituents will decrease the binding affinity of 4-oxothiazolidines derivatives towards lipoxygenase whereas CC and TVC are topological parameters; the overall connectivity's increase both with molecule size and complexity, as expressed in branching and cyclicity of molecular skeleton. The positive contribution of these descriptors illustrates that increase in branching is favorable for inhibitory activity.

The model (3) is statistically significant, as it has a correlation coefficient of 0.923 with 85.2% explained variance in the activity. F statistics indicate statistical significance at 99% level as the calculated F value exceeds the tabulated F value, which is $F_{(4,17)} = 4.67$. The model also exhibits good predictivity as established by the cross validation of the model. Predicted activity values were calculated using the correlation developed and a comparison was made with the observed values (Table **7**, Figs. **4** and **5**). The absence of any serious multicollinearity between the descriptors present in the model was confirmed by the calculation of correlation matrix (Table **8**).

Compound 10 found successively to be outliers as their residual value exceeded twice the standard error of estimate of the model. Exclusion of compound 10 from data set as outliers resulted in model 4.

BA= [-0.3536 (± 0.0836)] CAA - [0.2485 (± 0.1885)] MR + [5.9822 (± 8.664] C.C + [0.0595 (± 0.0199)] TVC -2.2806

Table 8. Correlation Matrix for Model-3

	CAA	MR	CC	TVC
CAA	1.0000			
MR	0.2385	1.0000		
CC	0.3562	0.5342	1.0000	
TVC	0.5473	0.0286	0.0973	1.0000

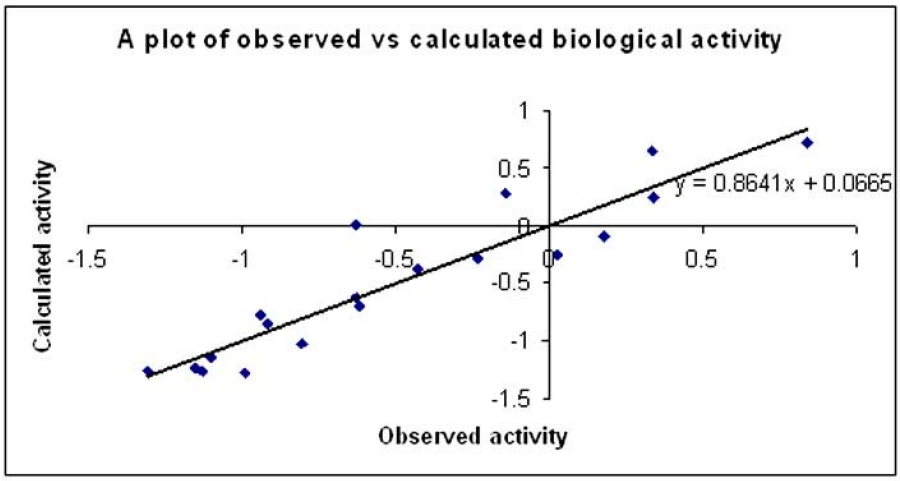

Fig. (4). A plot of observed activity *vs.* calculated activity for model 3.

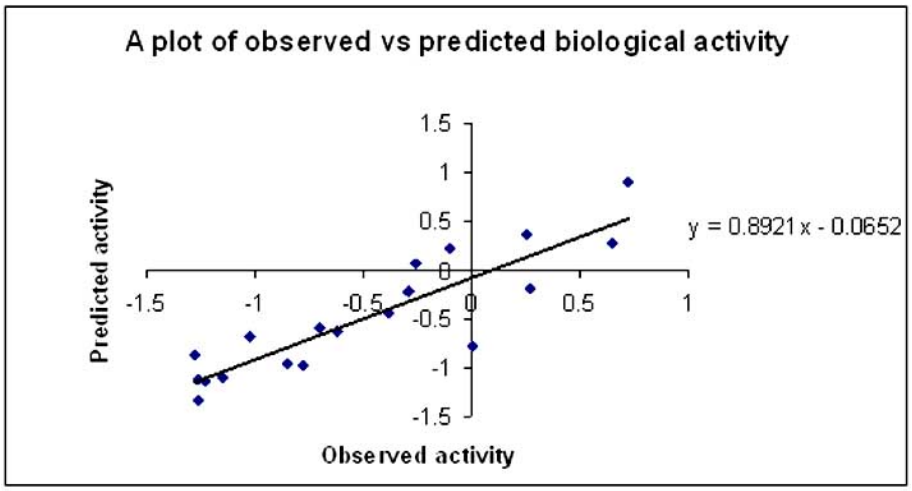

Fig. (5). A plot of observed activity *vs.* predicted activity for model 3.

(**Model 4**)

n = 21, r =0.946, r^2 = 0.895, variance = 0.006, std = 0.0792, F = 34.231

The model is statistically significant, as it has a correlation coefficient of 0.946 with 89.5% of the variance in activity. The model showed overall internal statistical significance level better than 99.9% as it exceeded the tabulated F value, which is $F_{(4,16)}$ = 4.77. To ascertain the predictivity of model, internal validation using leave one out method of cross validation process, bootstrapping techniques and randomized test was performed. The model was further subjected to cross validation method to confirm the internal consistency; the cross validated squared correlation coefficient (Q^2=0.816), standard deviation of error (S_{press} =0.113), standard deviation of error of prediction (SDEP =0.098) suggested good predictive ability of the activity. The robustness and wide pragmatism of the equation was further supported by r^2bs=0.891, chance< 0.01. At per value of bootstrap squared correlation coefficient (r^2bs) with conventional squared correlation coefficient (r^2), suggested that the model is a proper representative of analogs.

The overall high value r value and low standard error of estimate prove it to be the best model describing the activity. The high value of Q^2 (0.816) is fairly high making it to be the best predictive model. Predicted activity values were calculated using the correlation developed and a comparison was made with the observed values (Table **9**). The absence of any serious multicollinearity between the descriptors present in the model was confirmed by the calculation of correlation matrix (Table **10**).

The developed QSAR model can be utilized for the further development of new molecules belonging to the class of 4-oxothiazolidines and 5-arylidines to exhibit good anti-inflammatory activity, as it reveals the various physicochemical parameters that play important roles in exhibiting potential anti-inflammatory activity.

CONCLUSIONS

The present study provides important structure insights in designing better lipoxygenase inhibitors. The analysis also revealed that steric (MR and CAA) and topological parameters (BI, MTI, CC and TVC) play an important role in lipoxygenase inhibitory activity. Bulky substituents in the

Table 9. Observed, Calculated, Residual, Predicted and Predicted Residual Activities of Compounds for Lipoxygenase Inhibitory Activities in Model-4

No	Observed Activity	Calculated Activity	Residual	Predicted	Predicted Residual activity
1	-1.4435	-1.4801	0.0366	-1.4847	0.0412
2	-1.59	-1.4749	-0.1151	-1.4596	-0.1304
3	-1.4854	-1.4697	-0.0157	-1.4674	-0.018
4	-1.6478	1.5468	-0.101	1.5324	-3.1804
5	-1.5228	-1.5416	-3.1894	-1.5445	0.0217
6	-1.6197	-1.5364	-0.0833	-1.5225	-0.0972
7	-1.3996	-1.4233	0.0237	-1.4430	0.0434
8	-1.4435	-1.4312	-0.0123	-1.4258	-0.0177
9	-1.0457	1.2156	-2.2613	1.2509	-2.2966
10	-0.9208	*	*	*	*
11	-1.1426	-1.2205	0.0779	-1.2390	0.0964
12	-1.4854	-1.5067	0.0213	-1.5116	0.0262
13	-1.5228	-1.4919	-0.0309	-1.4862	-0.0366
14	-1.4435	1.4770	0.0335	1.4832	-2.9267
15	-1.59	1.6396	0.0496	1.6523	-3.2423
16	-1.5576	-1.6247	0.0671	-1.6399	0.0823
17	-1.6197	-1.6099	-0.0098	-1.6078	-0.0119
18	-1.2219	-1.2691	0.0401	-1.3016	0.0797
19	-1.2886	-1.2356	-0.053	-1.1359	-0.1527
20	-1.0457	-0.9851	-0.0606	-0.9596	-0.0861
21	-1.1426	-1.0323	-0.1103	-0.9696	-0.173
22	-0.9208	-0.9662	0.0454	-0.9897	0.0689

*Compound removed as outlier.

Table 10. Correlation Matrix for Model-4

	CAA	MR	CC	TVC
CAA	1.0000			
MR	0.4537	1.0000		
CC	0.0561	0.0783	1.0000	
TVC	0.0327	0.3467	0.4632	1.0000

thiazolidine nucleus will decrease the binding affinity of 4-oxothiazolidines derivatives towards lipoxygenase indicated by negative contribution of molar refractivity and connolly accessible area. The positive contribution of topological parameters illustrates that increase in branching and presence of heteroatom is favorable for lipoxygenase inhibitory activity. Our study supplements the previous SAR studies and provides the necessary physico-chemical requirements at the substituents position for better lipoxygenase inhibitory activity.

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