Exploring Structural Feature of Aldose-Reductase Inhibition by 5-[[2-(ω-Carboxyalkoxy)aryl]methylene]-4-oxo-2-thioxothiazolidine Derivatives Employing Fujita–Ban and Hansch Approach

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Designing of a highly selective, potent and safe inhibitor of aldose reductase (ALR) capable of potentially blocking the excess glucose flux through the polyol pathway that prevails under diabetic condition has been a long standing challenge. In our study, we did quantitative structure–activity relationship (QSAR) analysis, based on Fujita–Ban and classical Hansch approach, on 5-[[2-(ω-carboxyalkoxy)aryl]methylene]-4-oxo-2-thioxothiazolidine derivatives. Study gave structural insight into the binding mode of the molecules to the aldose reductase enzyme. The Fujita–Ban approach revealed that benzylidene thiazolidine nucleus is more potent as compare to naphthyl-methylene thiazolidine analogs. The bulkierness of naphthyl-methylene might be inquisitive with receptor. Hansch approach suggested that electron-withdrawing groups are conducive to aldose reductase inhibitory activity.

Key words aldose reductase; QSAR; Fujita–Ban analysis; Hansch analysis; 5-[[2-(ω-carboxyalkoxy)aryl]methylene]-4-oxo-2-thioxothiazolidine derivative

Diabetes mellitus has become pandemic and according to report, including a forecast by the World Health Organizations, there will be a sharp increase in the total number of cases by 2030, especially in the two most populous countries, China and India.[1,2] In fact, India could be bracing itself for the dubious distinction of becoming the diabetes capital of the world. This is an ominous forecast, because managing the long-term complication of diabetes, which includes nephropathy, neuropathy, retinopathy and cardiovascular complications, will have a serious impact on public health budgets.[3] The polyol pathway plays an important role in the development of degenerative complications of diabetes. The association between hyperglycemia and the development of long-term diabetic complications such as neuropathy, retinopathy and cataract is well documented.[4] Aldose reductase (alditol/$NADP^+$ oxidoreductase, E.C.1.1.1.21, ALR2) is the first enzyme of the polyol pathway, which reduces excess D-glucose into D-sorbitol with concomitant conversion of NADPH to $NADP^+$.[5—8] Aldose reductase inhibitors (ARIs) therefore offer the possibility of safely preventing or arresting the progression of long-term diabetic complications, with no risk of hyperglycemia.

Designing potent ARIs for inhibiting the ALR2 activity has been the target for many researchers. Both experimental studies and computer simulation have been carried out to find potent ARIs.[9—21] However, compounds that have been identified as potent ARIs in both *vitro* and *vivo* are few. All these found ARIs can be classified into several types such as flavonoids, spirohydantoins, substituted acetic acid and phenylsulfonylnitromethane derivations.

In our recent publication,[22] we have reported the QSAR analysis of 2,4-dioxo-5-(naphthylmethylene)-3-thiazolidineaceticacids and 2-thioxo analogues as aldose reductase inhibitors. Owing to our special interest in thiazolidine derivatives for the management of diabetes mellitus and in continuation with our previous work, we attempted to rationalize the title compound in terms of physicochemical and structural requirements. In present study, we have performed QSAR analysis of 5-[[2-(ω-carboxyalkoxy)aryl]methylene]-4-oxo-2-thioxothiazolidine derivatives[23] that combines Fujita–Ban[24] and Hansch approach[25,26] to design potent ARIs. Fujita–Ban approach is applied to determine the *de novo* contribution of substituents to the activity of the molecules. The series is subsequently subjected for Hansch approach. A quantitative model has been proposed for describing the factors influencing the affinity of the drug molecules towards the enzyme. These results could serve as a guideline in design of more potent and selective aldose reductase inhibitors.

Experimental

The aldose reductase inhibitory activity data of 5-[[2-(ω-carboxyalkoxy)-aryl]methylene]-4-oxo-2-thioxothiazolidine derivatives were taken from the reported work of Murata *et al.*[23] (Figs. 1, 2 and Tables 1, 2). The biological activity data (IC_{50} in nM) was converted to negative logarithmic mole dose (pIC_{50}) to reduce skewness of data set. Initially series was subjected to Fujita–Ban approach[24] using regression analysis in order to estimate the *de*

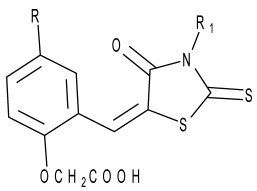

Fig. 1. General Structure of 5-(2-Carboxymethoxybenzylidine)thiazolidine Derivatives Used for the Present Study

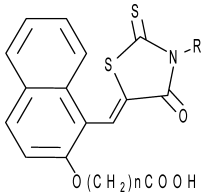

Fig. 2. General Structure of 5-[(2-ω-Carboxyalkoxy)naphthylmethylene]-thiazolidine Derivatives Used for the Present Study

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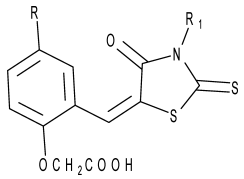
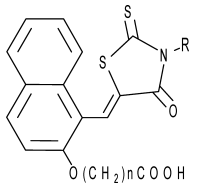
Table 1. Aldose Reductase Inhibitor Activity of 5-(2-Carboxymethoxybenzylidine)thiazolidine Derivatives



Compd. No.	Substituents		IC_{50} (nM)	pIC_{50}
	R	R_1		
1	H	H	560	6.252
2	H	CH_3	27	7.569
3	H	CH_2COOH	170	6.770
4	Br	H	17	7.770
5	Br	CH_3	16	7.796
6	Br	CH_2COOH	18	7.745
7	Cl	H	29	7.538
8	Cl	CH_3	18	7.745
9	Cl	CH_2COOH	21	7.678
10	CH_3O	H	38	7.420
11	CH_3O	CH_3	19	7.721
12	CH_3O	CH_2COOH	86	7.066

Table 2. Aldose Reductase Inhibitor Activity of 5-[(2-ω-Carboxyalkoxy)naphthylmethylene]thiazolidine Derivatives



Compd. No.	Substituents		IC_{50} (nM)	pIC_{50}
	n	R		
13	1	H	33	7.481
14	2	H	11	7.959
15	3	H	1100	5.959
16	1	CH_3	180	6.745
17	2	CH_3	630	6.201
18	3	CH_3	700	6.155

novo contribution of substituents to the activity of the molecules.

Hansch approach was carried out to establish correlations between ALR2 inhibitory activity and various substituent constants at position R and R_1 of molecule (Fig. 1). Values of the substituent constants like hydrophobic ($\sum \pi$), steric (molar refractivity or MR), hydrogen acceptor (HA), hydrogen donor (HD), electronic descriptor (field effect or $\mathcal{F}$, resonance effect or $\mathcal{R}$ and Hammett's constant or σ) and shape of each substituent (Verloop parameters L and B_1—B_3) were taken from the published literature.[25—27] In order to have a comparative study of 5-(2-carboxymethoxybenzylidine)thiazolidine derivatives an indicator variable I_V was included to account for structural variation due to presence and absence of substitution at position R_1. I_V was given 1 for compounds bearing *substitution* at R_1 position of thiazolidine ring and 0 for *unsubstituted* R_1 position.

Stepwise multiple linear regression analysis method was used to perform QSAR analysis employing in-house VALSTAT[28] program. The data was transferred to the statistical program in order to establish a correlation between physicochemical parameters as independent variables and aldose reductase inhibitory activity as dependent variable. The best model was selected from the various statistically significant equations on the basis of the observed squared correlation coefficient (r^2), the standard error of the estimate (*SE*), sequential Fischer test (*F*), inter-correlation among parameter (*ICAP*) and *Chance* statistics (evaluated as the ratio of the equivalent regression equations to the total number of randomized sets; a chance value of 0.001 corresponds to 0.1% chance of fortuitous correlation).

Results and Discussion

Two subsets of the series were subjected to Fujita–Ban approach in order to estimate the *de novo* contribution of substituents to the activity of the molecules as

$$pIC_{50} = 6.686 + 0.907[Br] + 0.790[Cl] + 0.539[MeO] + 0.463[Me] + 0.070[CH_2COOH]$$
$$n = 12,\ r = 0.871,\ r^2 = 0.759,\ SE = 0.322,\ F = 3.786 \quad (1)$$

Contributions of parameters to model are: [Br] : [Cl] : [MeO] : [Me] : [CH_2COOH]::[9.771] : [8.514] : [5.808] : [6.650] : [1]

$$pIC_{50} = 6.440 - 0.766[Me] + 1.056[N_1] + 1.022[N_2]$$
$$n = 6,\ r = 0.842,\ r^2 = 0.708,\ SE = 0.691,\ F = 1.621 \quad (2)$$

Contributions of parameters to model are:
[Me] : [N_1] : [N_2]::[1.124] : [1.033] : [1]

The subsets were combined to find out the significance of benzylidine/naphthylmethylene ring system.

$$pIC_{50} = 7.055 + 0.906[Br] + 0.789[Cl] + 0.538[MeO] + 0.049[Me] - 0.137[CH_2COOH] + 0.199[Ring] - 0.361[N_1] - 1.023[N_3]$$
$$n = 18,\ r = 0.812,\ r^2 = 0.660,\ SE = 0.538,\ F = 2.183 \quad (3)$$

Contributions of parameters to model are:
[Br] : [Cl] : [MeO] : [Me] : [CH_2COOH] : [Ring] : [N_1] : [N_3] ::[7.953] : [9.232] : [4.726] : [1] : [1.608] : [6.993] : [14.785] : [5.985]

The multivariant regression expression, Eq. 1, account for more than 75.9% variance in activity with *de novo* contribution of substituents to the activity of the molecules. Here descriptor [N_1], [N_2] and [N_3] are the number of methylene group present at n position of the naphthylmethylene ring. [N_1] when number of methylene group is 1, [N_2] when number of methylene group is 2, [N_3] when number of methylene group is 3. The Fujita–Ban analysis of first subset of the series, suggested that electro-negative substituents at R position *i.e.* Br and Cl group is crucial for activity. At R position, these groups might be imparting for the electronic interaction with the receptor. The less favorable effect of MeO may be attributed to electron-releasing nature of it. Comparison of subset of equations revealed that, benzylidine thiazolidine derivatives might be having the optimum shape and size in comparison to the naphthylmethylene thiazolidine derivatives for the interaction with the receptor.

The combined model (Eq. 3) depicted that benzylidine ring is favorable for the activity. *De nova* contribution of groups also help in understanding of binding of ARI with aldose reductase by means of possible hydrogen bond interaction in between acetate chain of thiazolidine and polar positive charge region of ALR active site and the hydrophobic interaction of aromatic ring substitution and lipophilic pocket of ALR. The calculated activity of the series employing Eqs. 1 and 3 has been shown in Table 3.

The series was subjected to stepwise multiple linear regression analysis, in order to develop 2D-QSAR model between inhibitory activity of aldose reductase inhibitors as dependent variable and different afore-mentioned substituent constants as independent variables. All the regression coefficients were significant at 95% confidence interval. The repre-

sentative QSAR model's regression coefficients with pertinent statistical parameters are described below.

$$pIC_{50}=6.867(\pm0.412)+2.000(\pm1.258)[\mathcal{F}]$$
$$n=12,\ r=0.751,\ r^2=0.564,\ SE=0.335,\ F=12.939 \quad (4)$$

Equation 4 has moderate correlation coefficient (r=0.751). The t-value (t=3.597) exceeds the critical value (3.581), making the model more reliable. The value of Sequential Fischer test (F=12.939), which exceeds the tabulated value ($F_{1,10\alpha0.01}$=12.8) explain the fitness of Model. The positive contribution of $\mathcal{F}$, field effect, reveled that electronegative substitution at benzylidene ring is essential for the aldose reductase inhibitory activity.

$$pIC_{50}=6.690(\pm0.505)+2.000(\pm1.232)[\mathcal{F}]+0.266(\pm0.455)[I_V]$$
$$n=12,\ r=0.798,\ r^2=0.637,\ SE=0.322,\ F=7.907 \quad (5)$$

The addition of second descriptor I_V, Indicator Variable, in Eq. 4 is statistically significant. Equation 5 accounts for more than 63% variance in the aldose reductase inhibitory activity. The Eq. 5 has high correlation coefficient (r=0.798) and low standard error of the estimate (SE=0.322). The inter-correlation among the parameters is also less ($ICAP$=0.000). The correlation matrix for the parameter employed in Hansch approach has been shown in Table 4. The value of Sequential Fischer test (F=7.907), which exceeds the tabulated value ($F_{2,09\alpha0.05}$=5.71) explain the fitness of Model. The Eq. 5, considered as model, is used for the internal predictivity of the series (Table 5). Randomization test (*chance*<0.015) in randomize biological activity data revealed that the result were not based on chance correlation. The positive contribution of I_V demonstrates the possible hydrophobic interaction of substitution of the aromatic ring with the aldose reductase. The positive coefficient of I_V suggests that substitution at nitrogen atom of thiazolidine ring is conducive to aldose reductase inhibitory activity. The substituted analogues are more active as compare to un-substituted thiazolidine analogues.

In conclusion, the present study provides important structural insight in the binding mode of the molecules to the aldose reductase enzyme. The Fujita–Ban approach revealed that benzylidene thiazolidine nucleus is more potent as compare to naphthyl-methylene thiazolidine analogs. The bulkierness of naphthyl-methylene might be inquisitive with receptor. Hansch approach suggested that electron-withdrawing groups are conducive to aldose reductase inhibitory activity.

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Table 3. Calculated Activity of the Series Using Fujita–Ban Approach

Compd. No.	Eq. 1		Eq. 3	
	Calculated pIC_{50}	Z-value	Calculated pIC_{50}	Z-value
1	6.686	−1.827	6.893	−1.638
2	7.149	1.767	6.942	1.600
3	6.755	0.059	6.756	0.035
4	7.593	0.745	7.800	−0.077
5	8.055	−1.092	7.848	−0.134
6	7.662	0.347	7.662	0.211
7	7.476	0.260	7.682	−0.370
8	7.939	−0.816	7.731	0.035
9	7.545	0.557	7.545	0.339
10	7.225	0.822	7.432	−0.030
11	7.688	0.141	7.481	0.614
12	7.294	−0.963	7.294	−0.585
13	—	—	7.483	−0.004
14	—	—	7.055	2.307
15	—	—	6.032	−0.188
16	—	—	6.743	0.004
17	—	—	7.104	−2.307
18	—	—	6.081	0.188

Table 5. Calculated and Predicted (by LOO Method) Activities of Series Using Hansch Approach

Compd. No.	Calculated pIC_{50}	Z-value	Predicted pIC_{50}(LOO)
1	6.690	−1.501	7.065
2	6.956	2.100	6.645
3	6.956	−0.639	7.051
4	7.570	0.685	7.475
5	7.836	−0.138	7.846
6	7.836	−0.313	7.859
7	7.510	0.095	7.498
8	7.776	−0.107	7.783
9	7.776	−0.337	7.797
10	7.210	0.721	7.139
11	7.476	0.841	7.441
12	7.476	−1.407	7.535

Table 4. Correlation Matrix of Substituent Constants Employed for Hansch Analysis

	$\Sigma\pi$	HA	MR	$\mathcal{F}$	$\mathcal{R}$	σ	L	B_1	B_2	B_3
$\Sigma\pi$	1.000									
HA	0.587	1.000								
MR	0.523	0.367	1.000							
$\mathcal{F}$	0.838	0.058	0.864	1.000						
$\mathcal{R}$	0.264	0.936	0.660	0.297	1.000					
σ	0.958	0.348	0.700	0.956	0.003	1.000				
L	0.429	0.479	0.976	0.844	0.757	0.650	1.000			
B_1	0.938	0.269	0.776	0.973	0.087	0.992	0.716	1.000		
B_2	0.052	0.839	0.802	0.492	0.977	0.215	0.880	0.298	1.000	
B_3	0.549	0.355	0.979	0.909	0.661	0.748	0.990	0.805	0.806	1.000

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