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RESEARCH ARTICLE

Exploration of QSAR modelling techniques and their combination to rationalize the physicochemical characters of nitrophenyl derivatives towards aldose reductase inhibition

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Abstract

The quantitative structure–activity relationship (QSAR) analysis of nitrophenyls active as aldose reductase inhibitors (ARIs) has been performed employing Fujita-Ban, classical Hansch approach and physicochemical properties. The multivariant regression expressions were developed using sequential multiple linear regression (SEQ-MLR) techniques considering adjustable correlation coefficient (r^2_{adj}). The statistical quality of SEQ-MLR equations were evaluated considering parameters like correlation coefficient (*r*), standard error of estimation (*SEE*), and variance ratio (*F*) at explicit degree of freedom (*df*). Orthogonality of the descriptors in SEQ-MLR was established through variance inflation factor (*VIF*).The QSAR analysis gave insight to some common important structural feature i.e. the hydroxyl group is crucial for hydrogen bond interaction with the receptor. Similarly electro-negative substitution is essential for polar interaction with charge region of the receptor. Moreover analysis inferred that diarylsulphides can be explored for optimization of the analogs.

Key Words: *Aldose reductase inhibitors; nitrophenyl derivatives; diabetes mellitus; QSAR; hansch analysis; fujita-ban analysis; inhibition*

Introduction

Aldose reductase (EC 1.1.1.21, ALR2) is the first enzyme of the polyol pathway (Figure 1) that catalyses the NADPH-dependent reduction of glucose to sorbitol. The activation of polyol pathway is linked to the onset and progression of chronic diabetic complications viz. neuropathy, nephropathy, retinopathy, cataracts.[1-7] Therefore, ALR2 has been considered as a target enzyme to develop drugs able to prevent the onset and to check the progression of diabetic complications, even in the presence of imperfect control of glycaemia. Over the last three decades numerous ALR2 inhibitors (ARIs) have been identified, most of which belong to the carboxylic acids (such as zopolrestat, ponalrestat, epalrestat) and hydantoins (such as sorbinil) classes of compounds.[1-4,8–11] Nevertheless, many of them have shown to be clinically inadequate because of adverse pharmacokinetics or toxic side-effects.[10] At present, epalrestat is the only ARI available on the market.[11]

In a search for potent inhibitors, many compounds of diverse structures have been identified. Kinetic studies suggest that these compounds appear to interact with the enzyme at a site independent of either substrate or nucleotide cofactor fold. Moreover, from the pioneering studies on sorbinil and alrestatin to recent investigation on zopolrestat and zenarestat, several compounds in clinical trials or in market for the treatment of the diabetic complications have been developed but they were withdrawn, suggesting that currently no "universally potent" inhibitor exists. Due to the shortage of drugs currently available for the treatment of diabetic complications, the search for new ARIs endowed with more

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favourable biological properties is still a major pharmaceutical challenge. In our recent publications [12-14] and many other researchers [15-17] have reported the QSAR analysis of different aldose reductase inhibitors. To gain insight into the structural and molecular requirements influencing the aldose reductase inhibitor activity, we herein describe QSAR analysis of nirophenyl derivatives. [18] The relevance of the best QSAR model obtained for the design of novel derivatives should be assessed not only in terms of predictivity, but also in terms of their ability to provide a chemical and structural explanation of their binding interaction. The results here obtained shall be useful for the designing of new aldose reductase inhibitors.

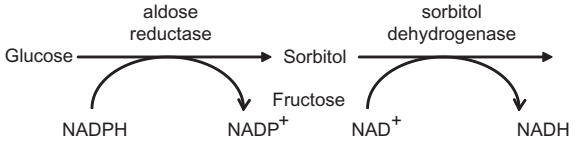
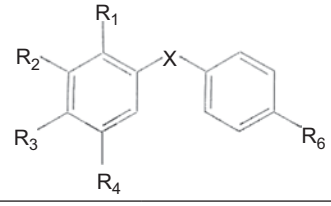


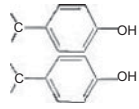
Figure 1. Polyol pathway.

Experimental

The aldose reductase inhibitory activity data of nirophenyl derivatives was taken from the reported work of Constantino *et al* [18] (Table 1). The biological activity data (IC_{50} in μm) was converted to negative logarithmic mole dose (pIC_{50}) for quantitative structure activity relationship analysis. Initially series was subjected to Fujita-Ban analysis using regression technique in order to estimate the *de novo* contribution of substituents towards activity. Classical Hansch approach was carried out to establish correlations between ALR2 inhibitory activity and various substituent constants at position R_1 to R_6 and X of molecule (Figure 2). Values of the substituent constants like hydrophobic (π), steric (Molar refractivity or *MR*), hydrogen acceptor (*HA*), hydrogen donor (*HD*) and electronic descriptor (field effect or *F*, resonance effect or *R* and Hammett's constant or σ), were taken from the reported work of Hansch *et al* [19]. The indicator variable I_S and I_{OH} were included to account for structural variation due to presence and absence of substitution at position X and R_6. I_S considered as zero for triphenylmethanes while one for diarylsulphides. Similarly

Table 1. Structure and activity of nitrophenyles.



Comp No.	R_1	R_2	R_3	R_4	R_6	X	pIC_{50}
1.	H	NO_2	H	H	OH	S	5.310
2.	H	COOH	H	H	OH	S	4.678
3.	H	CH_2COOH	H	H	OH	S	4.854
4.	COOH	H	H	H	OH	S	4.108
5.	CH_2COOH	H	H	H	OH	S	4.456
6.	H	H	COOH	H	OH	S	4.745
7.	H	H	CH_2COOH	H	OH	S	4.658
8.	NO_2	H	H	H	OH		4.161
9.	CH_2COOH	H	H	H	OH		4.796
10.	NO_2	H	OH	H	OH	S	5.456
11.	NO_2	H	$COOC_2H_5$	H	OH	S	5.638
12.	NO_2	H	$CONH_2$	H	OH	S	5.629
13.	NO_2	H	NH_2	H	OH	S	5.458
14.	NO_2	H	COOH	H	OH	S	6.004
15.	NO_2	CH_3	H	H	OH	S	4.854
16.	NO_2	H	CH_3	H	OH	S	5.529
17.	NO_2	H	H	CH_3	OH	S	5.804
18.	NO_2	H			OH	S	5.620
19.	NO_2	H	H	H	OCH_3	S	4.699

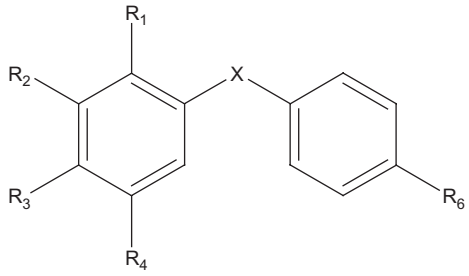


Figure 2. General structure for the present study.

I_{OH} considered as zero for methoxy substitution at R_6 while one for hydroxyl moiety.

The molecular modeling study was performed using CS ChemOffice [20] version 6.0, and Dragon [21] program while the regression analysis was carried out on VALSTAT [22]. Structures of all the compounds were sketched using builder module of the program. The sketched structures were subjected to energy minimization using molecular mechanics (MM2) until the RMS gradient value became smaller than 0.1kcal/mol Å. The energy minimized molecules were subjected to re-optimization via Austin model-1 (AM1) method until the RMS gradient attains a value smaller than 0.0001 kcal/mol Å using MOPAC. The geometry optimization of the lowest energy structure was carried out using EF routine. The descriptor values for all the molecules were calculated using "compute properties" module of program. The minimized molecule was saved as MOL file format. The MOL file was further used for calculation of various physicochemical properties using Dragon program. The *constitutional descriptor* and *3D-MoRSE descriptors* are computed for the present study.

The data was transferred to the statistical program VALSTAT in order to establish correlation between physicochemical parameters as independent variables and aldose reductase inhibitory activity as dependent variable. The sequential multiple linear regression analysis (SEQ-MLR) method was employed. In sequential multiple regression the program searches for each permutation and combination sequentially for the data set. 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 (*SEE*), sequential Fischer test (*F*), chance statistics (*Chance*) and outliers (*Z-score value*).

Results and discussion

The *de novo* contributions of the predominant substituents were explored through Fujita-Ban analysis. Significant trivariant expression showed in Equation (1).

$$\begin{aligned} \mathrm{pIC}_{50} &= 0.683(\pm 0.209)[\mathrm{R}^1 NO_2] - 0.76 \\ &\quad (\pm 0.454)[R^6 OCH_3] + 0.644(\pm 0.323)[S] + 4.137 \\ n &= 18,\ r = 0.727,\ r^2 = 0.528,\ SEE = 0.429,\ F = 5.222 \end{aligned} \tag{1}$$

The Fujita-Ban analysis of the series suggested that nitro group (electro-negative in nature) substituent at R^1 position and presence of hydoxyl group (Polar and hydrogen acceptor) at R^6 is crucial for activity. Comparison of diarylsulphides and triphenylmethanes shows that diarylsulphides are more active as compared to triphenylmethanes.

Classical Hansch approach put forwards two significant tri-variant expressions (Equations 2 & 3) as,

$$\begin{aligned} \mathrm{pIC}_{50} &= 1.225(\pm 0.381)[\pi] + 0.426(\pm 0.283)[I_S] \\ &\quad + 0.037(\pm 0.023)\,[MR] + 3.413\ n = 18, \\ r &= 0.804,\ r^2 = 0.646,\ SEE = 0.371, \\ F &= 8.537, F_{(3,14\alpha 0.01)} = 6.68,\ \mathrm{ICAP} = 0.423 \end{aligned} \tag{2}$$

$$\begin{aligned} \mathrm{pIC}_{50} &= 1.502(\pm 0.352)[\pi] + 0.489(\pm 0.286)[I_S] \\ &\quad + 0.554(\pm 0.389)[I_{OH}] + 3.204 \\ n &= 18,\ r = 0.799,\ r^2 = 0.638,\ SEE = 0.376, \\ F &= 8.210,\ F_{(3,14\alpha 0.01)} = 6.68,\ \mathrm{ICAP} = 0.152 \end{aligned} \tag{3}$$

Equations (2) and (3) showed correlation coefficient value ≅ 0.8. The value of sequential Fischer test suggested more than 99% internal statistical significance as it exceeded the tabulated value $F_{(3,14\ \alpha\ 0.01)}$=6.68. The inter correlation among the parameters (ICAP) was significantly low (0.423 & 0.152) suggested that parameter contributed individually and independently to the equations. Z-score analysis suggested absence of outlier in the series. This analysis indicates that equation is able to explain structural diversity in the congeners. Randomized biological activity data test (*Chance* <0.001) revealed that the result was not based on chance correlation. 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. The Calculated pIC_{50} using Fujita-Ban Model, Equations (2) and (3) has been given in Table 2. Both expressions supported the presence of sulfide linkage as compare to mono substituted methelene bridge. This finding indicates that bulkier substitution might be unfavorable as compare to simple bridging. In Equation (2), Molar refractivity (*MR*) which is representative of molar volume and polarizability of the substituents play crucial role at R position of the scaffold and suggested that bulkier group with optimum polarizability is favorable. The substituted group might be interacting significantly at hydrophobic area of the active site. Similarly in equation 3, *Swain Lupton field constant* (F) contributed positively and suggested that electronic interaction is crucial for inhibition of aldose reductase enzyme. The substitution of the phenolic hydroxy group with a methoxy group leads to a less active compound and it might be due to loss of hydrogen bond interaction.

Followed by classical Hansch analysis series was subjected to QSAR analysis in order to explore the three dimensional properties of the molecule which are responsible for the interaction of molecule with aldose reductase enzyme.

Table 2. Calculated pIC_{50} (C) and Z-score value (Z) using Fujita-Ban Model, Equations (2) and (3).

Comp. No.	ObservedpIC_{50}	Fujita-Ban Model		Equation (2)		Equation (3)	
		C	Z	C	Z	C	Z
1	5.310	4.781	1.357	5.044	0.790	5.253	0.168
2	4.678	4.781	−0.265	4.611	0.198	4.742	−0.187
3	4.854	4.781	0.187	4.765	0.264	4.682	0.505
4	4.108	4.781	−1.728	4.611	−1.493	4.742	−1.856
5	4.456	4.781	−0.835	4.765	−0.917	4.682	−0.661
6	4.745	4.781	-0.093	4.611	0.397	4.742	0.009
7	4.658	4.781	−0.316	4.765	−0.318	4.682	−0.070
8	4.161	4.820	−1.691	4.618	−1.355	4.764	−1.766
9	4.796	4.137	1.691	4.339	1.355	4.193	1.766
10	5.456	5.464	−0.021	5.466	−0.029	5.688	−0.680
11	5.638	5.464	0.446	6.051	−1.226	5.748	−0.323
12	5.629	5.464	0.423	5.660	−0.092	5.613	0.047
13	5.458	5.464	−0.016	5.229	0.678	5.283	0.514
14	6.004	5.464	1.386	5.665	1.007	5.748	0.749
15	4.854	5.464	−1.566	5.198	−1.019	5.192	−0.991
16	5.529	5.464	0.167	5.198	0.983	5.192	0.986
17	5.804	5.464	0.872	5.198	1.799	5.192	1.791
19	4.699	4.699	0.000	5.044	-1.022	4.699	0.000

Energy minimized structural properties was correlated with inhibitory activity. The multivariant expressions were developed on the basis of adjustable correlation coefficient (r^2_{adj}). This parameter tells us regarding the statistical significance of incorporated physicochemical descriptor in SEQ-MLR. Adjustable r^2 takes into account of adjustment of conventional correlation coefficient (r^2). Therefore, if a physicochemical descriptor is added that does not contribute its fair share, the r^2_{adj} will actually decline. Adjustable correlation coefficient is a measure of the % explained variation in the dependent variable that takes into account the relationship between the number of cases and the number of independent variable in the regression model. Whereas r^2 will always increase when an independent variable is added, r^2_{adj} will decrease if the added variable does reduce the unexplained variation enough to offset the loss of degrees of freedom. The SEQ-MLR furnished uni and bi-variant expression with increasing correlation coefficient (Equations 4 and 5) and also the r^2_{adj} value is increasing significantly from uni to bi-variant expression.

$$\begin{aligned} &pIC_{50} = 3.028(\pm 0.706)[MS] - 3.127 \\ &n = 19,\ r = 0.721,\ r^2 = 0.519,\ r^2_{adj} = 0.491, \\ &SEE = 0.404,\ F = 18.376,\ q^2 = 0.446 \end{aligned} \quad (4)$$

$$\begin{aligned} &pIC_{50} = 4.268(\pm 1.045)\,[Mor28v] + 2.552(\pm 0.342) \\ &\quad [Mor18e] + 7.090\, n = 19,\ r = 0.883,\ r^2 = 0.779, \\ &r^2_{adj} = 0.751, SEE = 0.283,\ F = 28.195,\ q^2 = 0.655 \end{aligned} \quad (5)$$

Therefore we plan to move for higher variant expression like tri-variant. In case of tri-variant expression adjustable r^2 value significantly improved, hence these expressions (explained variance ~ 85%) were further explored for QSAR study.

$$\begin{aligned} &pIC_{50} = 4.080(\pm 0.797)[Mor28v] + 0.921(\pm 0.259) \\ &\quad [Mor14e] + 3.271(\pm 0.329)[Mor18e] + 7.694 \\ &n = 19,\ r = 0.938,\ r^2 = 0.880,\ r^2_{adj} = 0.856, \\ &SEE = 0.215,\ F = 36.723,\ q^2 = 0.788 \end{aligned} \quad (6)$$

Equation (6) showed better correlation coefficient (r=0.938), which accounted for ~85% of the explain variance in the activity calculated as $r^2_{adj} = r^2\,(1\text{-}1/F)$ that accounts in percentage when multiplied by 100. The data showed overall internal statistical significance level better than 99.9% as the calculated variance ratio i.e. Fischer value (F) exceeded the tabulated $F_{(3,15}\,\alpha_{\,0.001)} = 10.8$. The P value of each substituent constant is less than 0.05, suggests linear relationship between the descriptors and activity. The orthogonality of the substituent in SEQ-MLR was established through variance inflation factor values (*VIF* value) [23,24]. *VIF* values larger than 10 indicates that the information of the descriptors may be hidden by the correlation of the descriptors [25]. VIF is less than 2 for all the contributing descriptors revealed that the descriptors are fairly independent to each others (*Mor28v*=1.243, *Mor14e*=1.806, *Mor18e*=1.982).

The model was further analyzed for the outlier by the Z-score method (*Z-value*). The best QSAR model should not have any outlier. The *Z-value* for individual compounds lies within the specific range (<|2.5|), indicated absence of outliers. Test revealed that the model is able to explain the structurally diverse analogs and is helpful in designing more potent compounds using these physiochemical descriptors.

The chance of fortuitous correlation were checked with the help of randomized biological activity test (*Chance*), the value of Chance in model 1 is less than 0.001 suggested that the results were not based on prospective correlation.

To further access the robustness and statistical confidence of the model, bootstrapping analysis was performed. The bootstrapping analysis gives an overview about contribution of individual molecules to the QSAR model. The r^2_{bs} is average squared correlation coefficient calculated during the validation procedure which is computed from a subset of compounds used one at a time for the validation procedure while S_{bs} is the standard deviation in multiple run of a given data set. If the value of r^2_{bs} is at par to conventional r^2 and S_{bs} is low than the model is robust and promising. In our study both values (r^2_{bs}= 0.893 & S_{bs}=0.055) fall within the agreement.

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)' method. In this, model was built with N-1 compounds and the Nth compound is predicted (Table 3). Each compound is left out from the model derivation and predicted in turn. The value of q^2 is the basic requirement for declaring a model to be a valid one is q^2>0.5 [26]. The consistency of the model supported by q^2=0.788, S_{PRESS} = 0.286 and S_{DEP} =0.254 values (Figure-3). Further robustness was confirmed through leave n out method, where the value of n is 3. The value of leave n out cross validation squared correlation coefficient (q_n^2), leave n out standard error of prediction (SnPRESS) and leave n out standard deviation of prediction (S_{nDEP}) are 0.776, 0.271 and 0.261 respectively. Leave multiple out method suggested robustness of the model.

In the model *3D-MoRSE Code* [27-30] contributed positively to the inhibitory activity. *Mor28v, Mor14e* and *Mor18e* are 3D molecular representation of structure based on electron diffraction code (3D-MoRSE Code) was calculated by summing atom weights viewed by a different angular scattering function. The values of these code functions were calculated at 32 evenly distributed values of scattering angle(s) in the range of 0-31 Å^{-1} from the three dimensional atomic co-ordinates of a molecule. The 3D-MoRSE code was calculated using the following expression;

$$I(s) = \sum_{i=2}^{N} \sum_{j=1}^{i-1} A_i A_j \frac{\sin sr_{ij}}{sr_{ij}}$$

Where, s is scattering angle,

r_{ij} is interatomic distance of ith and jth atom

A_i and A_j are atomic properties of ith and jth atom respectively including atomic number, atomic mass, partial atomic charges, residual electro-negativities, and atom polarizability. In MoRSE Code, *v* notation after digital value used for the atom weights was contributed by especially through atomic volumes and similarly *e* notation after digital value contributed by especially through residual electro-negativities. *Mor14e* and *Mor18e* are responsible for the polar interaction of inhibitors with charge region of receptor. Similarly *Mor28v* might be crucial for accommodation of bulkier group in lipophilic pocket of ALR.

Remarkably, the results of the Hansch approach are in full agreement with the Fujita-Ban approach. The QSAR analysis gave insight to some common important structural feature i.e. hydroxyl group at R_6 position is crucial for hydrogen bond interaction with receptor. *MR* favored hydrophobic interaction of the substituted group with receptor. Similarly MoRSE code of the model also supports hydrophobic interaction with lipophilic pocket of the receptor. *Swain Lupton field constant* ($\mathcal{F}$) and residual electro- negativities contribution of MoRSE code suggested electro-negative substitution is essential for polar interaction with charge region of receptor. Study inferred that diarylsulphides can be explored for optimization of the analogs. In conclusion,

Table 3. Calculated (C), calculated leave one out (Cl), pIC_{50} and Z-score value (Z) obtained from Equation (6) with used physiochemical properties.

	Physiochemical properties			pIC_{50}		
Comp. No.	Mor28v	Mor14e	Mor18e	C	Z	Cl
1	0.064	0.017	−0.889	5.063	1.257	5.045
2	0.056	0.074	−0.939	4.920	−1.232	4.940
3	0.128	0.273	−1.006	5.178	−1.650	5.207
4	0.044	−0.162	−0.999	4.457	−1.780	4.563
5	0.158	0.409	−1.412	4.097	1.828	3.937
6	0.129	0.355	−1.172	4.714	0.156	4.710
7	0.064	0.515	−1.134	4.721	−0.320	4.742
8	0.071	0.126	−1.125	4.420	−1.323	4.464
9	0.109	0.000	−1.049	4.708	0.448	4.697
10	0.168	−0.042	−0.849	5.564	−0.552	5.587
11	0.070	0.075	−0.802	5.426	1.082	5.404
12	0.189	0.147	−0.888	5.696	−0.344	5.713
13	0.097	0.215	−0.876	5.423	0.179	5.419
14	0.200	0.202	−0.837	5.959	0.231	5.939
15	0.179	0.129	−1.178	4.691	0.833	4.653
16	0.180	0.135	−0.896	5.622	−0.477	5.642
17	−0.061	0.126	−0.562	5.723	0.412	5.618
18	0.003	−0.756	−0.471	5.470	0.767	5.182
19	0.026	0.219	−1.039	4.604	0.485	4.585

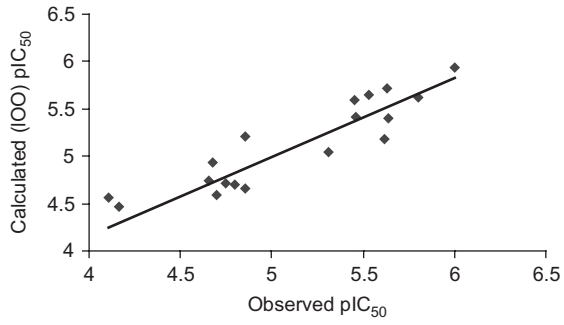


Figure 3. A plot between observed and calculated (loo) pIC_{50} data obtained from Equation (6).

we found a qualitative agreement between the Fujita-ban and Hansch approach; the results here obtained would be useful for the designing of new ARIs.

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