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QSAR Study of Nitrophenyl Derivatives as Aldose Reductase Inhibitor

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Abstract
Aldose reductase (EC 1.1.1.21, ALR2) is an enzyme that plays a vital role in polyol pathway which catalyses the NADPH dependent reduction of glucose to sorbitol associated with chronic diabetic complications. Here, we report an attempt to elucidate the structural and physicochemical properties of Nitrophenyl analogs as inhibitors for Aldose reductase. QSAR Studies were performed on the set of nitrophenyl analogs as aldose reductase using VLife MDS 4.0 Software. The best model develops have predictive correlation coefficient (r^2_{pred}) of 0.8469. Model was developed, taking total 16 molecules of which 11 molecules are used for training set in the software and 5 molecules are used as test set to optimize the QSAR Model with co-relation coefficient (r^2) of 0.9352 and cross-validated correlation coefficient of (q^2) of 0.8639. Various sets of descriptors were analysed, each encoding different properties to develop a statistical model. The model was developed using multiple linear regression (MLR) technique, Partial Least Square (PLS) analysis and Principal Components Regression (PCR) analysis to predict the structural features of same set of nitrophenyl derivatives as aldose reductase inhibitors.

Keywords
Aldose reductase inhibitor, Diabetes, Nitrophenyl derivatives, QSAR.

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INTRODUCTION:
Aldose reductase (EC 1.1.1.21, ALR2) is the first enzyme of the polyol pathway that catalyses the NADPH dependent reduction of glucose to sorbitol [1, 2]. In mammalian cells, under normal glycaemia (3.8–6.1 mmol/L) [3], cellular glucose is predominantly phosphorylated into glucose 6-phosphate by hexokinase and enters the glycolytic pathway. Only trace amounts of non-phosphorylated glucose (about 3%) enter the polyol pathway [3]. However, under hyper glycaemic condition (>7 mmol/L), there is increased flux through the polyol pathway, accounting for greater than 30% of glucose metabolism [4, 5]. The rate limiting step of the polyol pathway is the reduction of glucose to sorbitol catalyzed by aldose reductase (AR), at the expense of reduced nicotinamide adenosine dinucleotide phosphate (NADPH) [6]. Sorbitol is, in turn, converted to fructose by sorbitol dehydrogenase (SDH) with the oxidized form of nicotinamide

adenine dinucleotide (NAD+) as a co-factor [5, 7] (Figure-1). The activation of polyol pathway is linked to the onset and progression of chronic diabetic complications viz. neuropathy, nephropathy, retinopathy, cataracts [5].

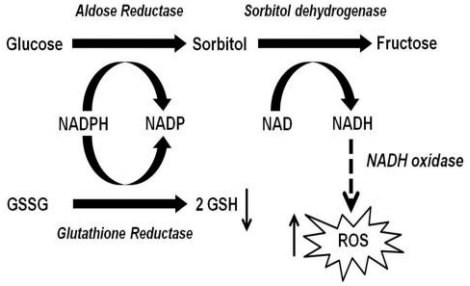


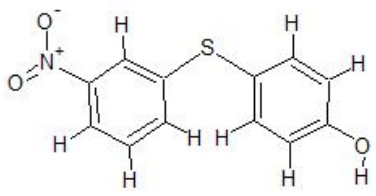
Figure 1

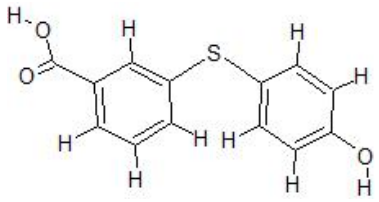
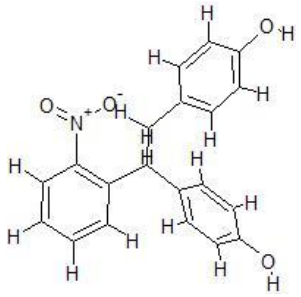
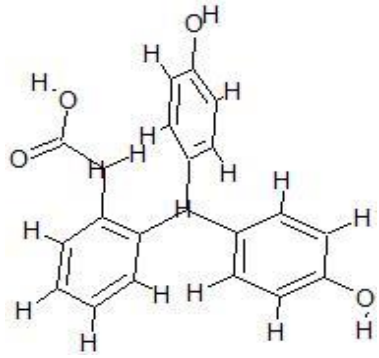
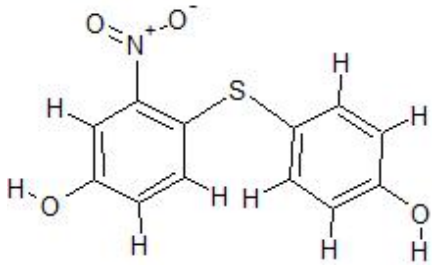
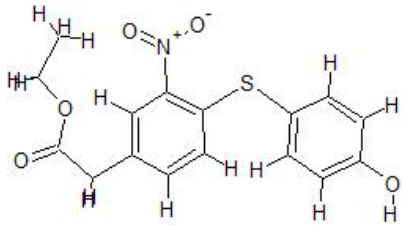
Excessive amount of glucose is shunted to the polyol pathway, where AR reduces glucose into sorbitol at the expense of NADPH. Since NADPH is essential for generation of GSH (intracellular antioxidant) from GSSG, the depletion of NADPH by the AR pathway may impair intracellular antioxidant defense. Sorbitol is then converted to fructose by SDH with the production of NADH, potentially leading to increased ROS via NADH oxidase. 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 [7, 8].

Diabetes mellitus (DM) is characterized by chronic hyperglycaemia and disturbances of carbohydrate, fat, and protein metabolism resulting from an absolute or relative deficiency of insulin (Diagnosis and classification of diabetes mellitus, 2007). Increased oxidative stress is thought to play an important role in the pathogenesis of diabetic complications, as supported by increased levels of oxidized DNA, proteins, and lipids [9, 10]. The induction of oxidative stress in DM can result from multiple mechanisms. Excessive levels of glucose can disrupt the electron transport chain in the mitochondria, leading to overproduction of superoxide anions [11]. High glucose can also stimulate oxidative stress via the auto-oxidation of glucose [12] and through non-enzymatic glycation [13].

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. Due to the shortage of drugs currently available for the treatment of diabetic complications, the search for new ARIs endowed with more favourable biological properties is still a major pharmaceutical challenge [14, 15]. To gain insight into the structural and molecular requirements influencing the aldose reductase inhibitor activity, we herein describe QSAR analysis of nitrophenyl derivatives (Table-1 and Table-2). 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.

Table-1: Structures, Experimental and Predicted Activity of Nitrophenyl Derivatives Used in Training set for Aldose Reductase Inhibition.

Sr. No.	Mol No.	Structure	IC_{50} Value	pIC_{50} Value		Residual
				Experimental	Predicted	
1	Mol 1		04.90	5.310	5.051	0.259

2	Mol 2		21.00	4.678	4.828	(-0.150)
3	Mol 8		69.00	4.161	4.228	(-0.067)
4	Mol 9		16.00	4.796	4.763	0.033
5	Mol 10		03.50	5.456	5.559	(-0.103)
6	Mol 11		02.30	5.638	5.431	0.207

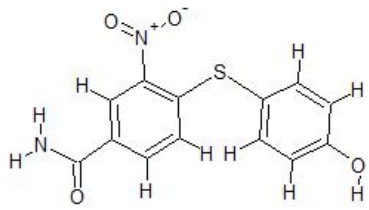
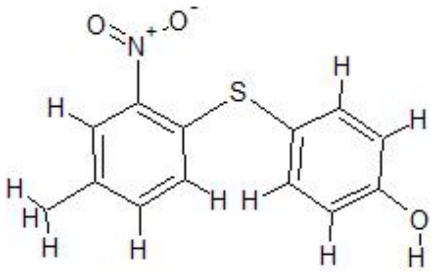
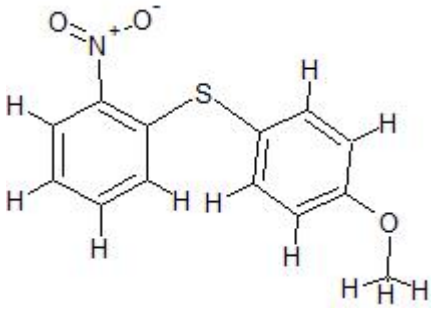
7	Mol 12		02.35	5.629	5.827	(-0.198)
8	Mol 14		00.99	6.004	5.971	0.033
9	Mol 16		02.96	5.529	5.433	0.096
10	Mol 18		02.40	5.620	5.673	(-0.053)
11	Mol 19		20.00	4.699	4.750	(-0.051)

Table-2: Structures, Experimental and Predicted Activity of Nitrophenyl Derivatives Used in Test set for Aldose Reductase Inhibition.

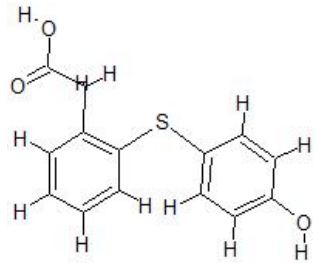
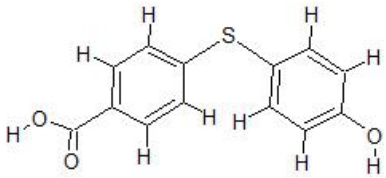
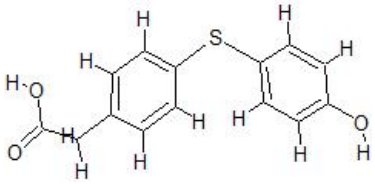
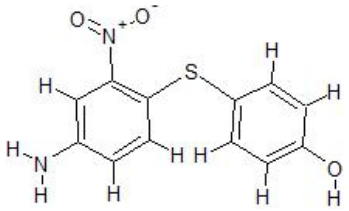
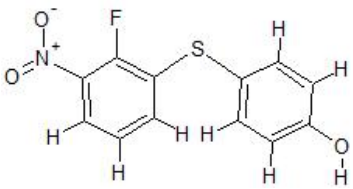
Sr. No.	Mol No.	Structure	IC_{50} Value	pIC_{50} Value		Residual
				Experimental	Predicted	
12	Mol 5		35.00	4.456	4.680	(-0.224)
13	Mol 6		18.00	4.745	4.828	(-0.083)
14	Mol 7		22.00	4.658	4.861	(-0.203)
15	Mol 13		03.48	5.458	5.443	0.015
16	Mol 20		00.90	8.050	8.173	(-0.123)

Table-3: Potential Molecular Descriptors Used in Present Study [16, 17].

Descriptors	Description
2D Descriptors: Use the atoms and connections information of the molecule for the calculation.	
Extended Topochemical Atom (ETA) based descriptor:	
DeltaEpsilonC	This descriptor signifies a measure of contribution of electronegativity.
Cluster based Descriptor:	
chiV3Cluster	This descriptor signifies valence molecular connectivity index of 3rd order cluster.
Estate Contribution based Descriptor:	
Sss CH2E-index	This descriptor signifies Electrological state indices for number of –CH2 group connected with two Single bonds.
Distance based Topological Descriptor:	
MomInertiaZ	This descriptor signifies moment of inertia at Z-axis.

MATERIALS AND METHODS:

Softwares required:

The molecular modelling was performed using ACD / ChemSketch 2012 (https: // www.acdlabs.com/ resources /freeware / chemsketch /), QSAR modelling was performed using VLife MDS 4.0 by VLife sciences (http: // vlifesciences.com /), Openbabel GUI by BABEL (https://openbabel.org/docs/dev/GUI/GUI.html) was used to transform chemical structures and files into working formats.

Computational Methods:

QSAR Studies:

All computational work was performed using VLife MDS 4.0 [18] Software developed by Nova Lead Pharma division, 2014. A total of 15 compounds [14] and biological activity data (IC_{50}) were taken for the present study (Table-1 and Table-2). IC_{50} in µm were converted to negative logarithmic mole dose (pIC_{50}) for quantitative structure activity relationship analysis. All the structure was drawn in ChemSketch 2012 by ACD Soft wares and then subjected to conformational 3-D optimization [19]. All the chemical structures were converted to their working formats (from .sk2 to. mol) according to VLife MDS 4.0 software to perform further studies [20]. Energy Minimization using Force Field Batch Minimization tool of VLife MDS software with RMS Gradient of 0.001 and iteration limit 10000 employing MMFF94 force field has been performed [19]. A set of physicochemical descriptors were calculated using 2-D QSAR's Calculate Descriptors function [18]. A set of Potential descriptors used for present study along with their functions are shown in Table-3.

The data was transferred to QSAR sheet provided by software to establish correlation between physicochemical parameters as independent variables and Aldose reductase inhibitory activity (pIC_{50}) as dependent variable [21]. The QSAR model was developed using multiple linear regression analysis (MLR) method, Principal Components Regression (PCR) method and Partial Least Square (PLS) method employed with Sphere exclusion auto-scaling technique [21]. Further Active molecule Mol 20 was added in the test series to understand predictivity of the models developed. The best model was selected from the various statistically significant equations on the basis of the observed squared correlation coefficient (r^2), cross-validated correlation coefficient of (q^2) and predictive correlation coefficient (r^2_{pred}) [22].

RESULTS AND DISCUSSION:

QSAR Models:

A set of 15 molecules used for evaluation, encompassed a wide range of structures to validate the model [21]. Further 1 active molecule (Mol 20) was included in the test series to understand the predictivity of the models developed and to show the interaction between ligand and receptor molecule. Correlation of pIC_{50} between experimental values and the predicted values in test set by considering different models developed by training set using different techniques are shown below:

Model-1:

[Multiple Linear Regression (MLR) analysis]

pIC_{50}= (-18.1000) (±2.7003) [DeltaEpsilonC] + 3.9492 (±0.4478) [chiV3Cluster] +

(-1.0911) (±0.0880) [SssCH2E-index] + 1.0180

n=11 _____ (Model-1)

[r^2= 0.9352, q^2= 0.8639, F_test= 33.6571, Degree of freedom= 7, pred_r^2= 0.8469.]

Following Statistical measures were used to correlate biological activity and molecular descriptors; N= Number of samples, r^2= coefficient of correlation, q^2= cross validated coefficient of correlation, r^2_pred= coefficient of correlation of predicted data set, F test, Degree of Freedom.

Model-1 developed has a correlation coefficient (r^2) of 0.9352 and cross validated (q^2) of 0.8639.

Correlation plot of observed values in comparison with predicted values is depicted in Figure-2. And has a prediction of 86.3% variance. The model developed validated by an external set of compounds with a predictive correlation of coefficient of 0.8469. Results comparing observed and predicted pIC_{50} along with residual values and model evaluated with test set of compounds are shown in Table-1 and Table-2.

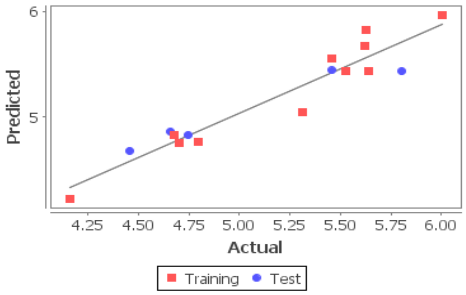


Figure-2

Model-2:

[Partial Least Square (PLS) analysis]

pIC_{50}= (-18.6869) [DeltaEpsilonC] + 4.0062 [chiV3Cluster] + (-0.6507) [SssCH2E-index] + (-0.000) [MomInertia Z] n=11 _____ (Model-2)

[r^2= 0.9556, q^2= 0.6126, F_test= 86.0726, Degree of freedom= 8, pred_r^2= 0.7917]

Model-2 developed has a correlation coefficient (r^2) of 0.9556 and cross validated (q^2) of 0.6126. Correlation plot of observed values in comparison with predicted values is depicted in Figure-3. And has a prediction of 61.2% variance. The model developed validated by an external set of compounds with a predictive correlation of coefficient of 0.7917.

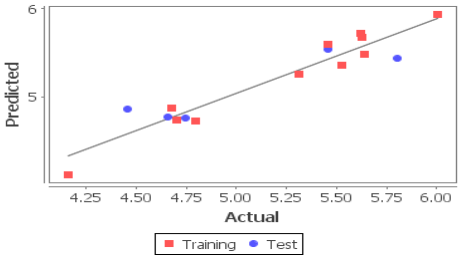


Figure-3

Model-3:

[Principal Components Regression (PCR) analysis]

pIC_{50}= (-16.4408) [DeltaEpsilonC] + 2.9867 [chiV3Cluster] + 1.5515 [SsssCHE-index] n=11 _____ (Model-3)

[r^2= 0.8677, q^2= 0.6549, F_test= 26.2291, Degree of freedom= 8, pred_r^2= 0.7152]

Model-3 developed has a correlation coefficient (r^2) of 0.8677 and cross validated (q^2) of 0.6549. Correlation plot of observed values in comparison with predicted values is depicted in Figure-4. And has a prediction of 65.4% variance. The model developed validated by an external set of compounds with a predictive correlation of coefficient of 0.7152.

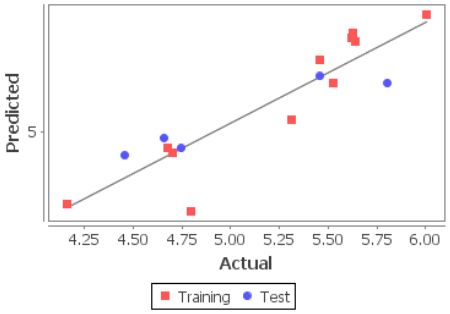


Figure-4

CONCLUSION:

Models developed to predict the structural features of nitrophenyl derivatives to inhibit aldose reductase reveals useful information about the structural features required for the molecules. In all 3 models developed, Electronegativity of atoms, Valence molecular connectivity index of 3rd order cluster, Electrological state indices for number of $-CH_2$ group connected with two single bonds and Moment of inertia at Z-axis were the major contributing descriptors. Descriptor values obtained helps us to understand the structural features required by ATP binding site of nitrophenyl derivatives. Out of all three models, the first model developed using Multiple Linear Regression (MLR) analysis with Stepwise-Forward algorithm has good predictive correlation coefficient (r^2_ pred) of 0.8469. Model was developed, taking total 16 molecules of which 11 molecules are used for training set in the software and 5 molecules are used as test set to optimize the QSAR model with correlation coefficient (r^2) of 0.9352 and cross-validated correlation coefficient (q^2) of 0.8639.

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