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QSAR STUDIES ON 5-BENZYLIDENE-1,3-THIAZOLIDINE-2,4-DIONES AS POTENTIAL α-GLUCOSIDASE INHIBITORS

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Abstract: A linear quantitative structure-activity relationship (QSAR) model is presented for modeling and predicting the α-glucosidase inhibitory activity. The model was produced by using the multiple linear regression (MLR) technique on a twenty one compound database that consists of newly discovered 2,4-thiazolidinediones. The major conclusion of this study is that molecular weight, wiener index, andrews affinity and polar surface area affect significantly the α-glucosidase inhibitory activity by 2,4-thiazolidinediones. The selected QSAR descriptors serve as a primary guidance for the design of novel and selective α-glucosidase inhibitors.

Keywords: α-Glucosidase inhibitory activity, QSAR

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INTRODUCTION

QSAR studies are useful tools in the rational search for bioactive molecules. The main success of the QSAR method is the possibility to estimate the characteristics of new chemical compounds without the need to synthesize and test them. This analysis represents an attempt to relate structural descriptors of compounds with their physicochemical properties in the chemical, pharmaceutical and environmental spheres. This method includes data collection, molecular descriptor selection, correlation model development, finally model evaluation. QSAR studies have predictive ability and simultaneously provide deeper insight into mechanism of drug receptor interactions [1-20].

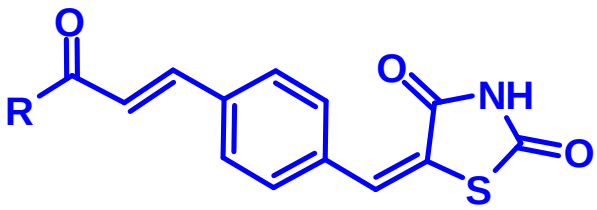
EXPERIMENTAL SECTION

MATERIALS AND METHODS

Data set

In this QSAR study, biological and chemical data of 2,4-thiazolidinediones (Table 1) were used, which have been reported in the work of Subhash et al. [21] In order to model and predict the biological effect of the specific compounds as potential α-glucosidase inhibitors, some physicochemical constants, molecular and topological descriptors were calculated using Chem3D ultra 10.0. [22-25]

Table 1. Molecular structures of 2,4-thiazolidinediones used for the QSAR study.



Code	R	Code	R
5a	2-MeC_6H_4	**5l**	3-$NO_2C_6H_4$
5b	3-MeC_6H_4	**5m**	2-ClC_6H_4
5c	2-$OMeC_6H_4$	**5n**	2,4-diClC_6H_3
5d	3-$OMeC_6H_4$	**5o**	2-FC_6H_4
5e	3-OHC_6H_4	**5p**	2,4-diFC_6H_3
5f	3,5-diOHC_6H_3	**5q**	Furan-2yl
5g	4,5-diOHC_6H_3	**5r**	Thiophen-3-yl

5h	2-Me,5-OHC_6H_3	**5s**	Pyrrol-2yl
5i	2-$NH_2C_6H_4$	**5t**	Pyridin-4-yl
5j	3-$NH_2C_6H_4$	**5u**	Naphthalen-3-yl
5k	2-$NO_2C_6H_4$		

Molecular Modeling

The molecular structures of 2,4-thiazolidinediones were modeled using Chemdraw ultra 10.0 (Cambridge software), and then modeled structure is copied to Chem3D ultra 10.0 to create a 3D model and, finally subjected to energy minimization using molecular mechanics (MM2). The minimization was executed until the root mean square gradient value reached a value smaller than 0.001kcal/mol. Such energy minimized structures are considered for generating QSAR descriptors. [26-30]

Multiple linear regression (MLR) model development-variable selection

The separation of the data into training and validation (test) sets was performed using random selection process. The complete MLR analysis was carried out using software Molegro Data Modeler v 2.0 (www.molegro.com) the values of descriptors selected for developing MLR model are presented in the Table 2. QSAR models were generated using MLR based on manual selection method and were correlated to biological activity. α-Glucosidase inhibitory activity (-log IC_{50} µg/mL) was taken as the dependent variable. Leave-one-out (LOO) method is used to validate the results. Multiple Linear Regression (MLR) based best QSAR models of 2,4-thiazolidinediones for the prediction of α-glucosidase inhibitory activity was given as follows. [31]

Best QSAR Model

(-logIC_{50}) = (0.000259889 X (Molecular Weight) + 9.54402e-05 X (Polar surface area) - 0.00233215 X (Andrews affinity) - 8.33044e-05 X (Wiener index) - 3.39367).

Cross validation of QSAR models

The test sets of 2,4-thiazolidinediones were considered to evaluate the influence of descriptors molecular weight, wiener index, andrews affinity and polar surface area and their reliability on developed QSAR model. The predicted α-glucosidase inhibitory activity obtained for validation set of 1,5-benzothiazpines are shown in Table 2. The experimental and predicted activities of 2,4-thiazolidinediones (Training and Test sets) calculated using best QSAR MLR model indicating an excellent quality of correlation.

Table 2. Molecular descriptors used in the regression analysis, observed and predicted activity values for 2,4-thiazolidinediones (Training and Test sets).

Code	Molecular weight	Polar Surface Area	Andrews affinity	Wiener index	-log(IC_{50})[a] (observed)	-log(IC_{50})[a] (predicted)	-log(IC_{50})[a] (predicted)
(Training set)							
4a	349	93.245	9.60073	3784	-3.47683	-3.61835	-3.63536
4b	349	86.251	9.23429	4251	-3.75151	-3.63297	-3.38739
4c	365	87.433	9.60073	4233	-3.62665	-3.5795	-3.35842
4d	365	85.547	13.3384	5643	-3.5799	-3.59518	-3.4726
4e	351	76.893	8.35483	4251	-3.57795	-3.62412	-3.43884
4f	367	77.14	8.42812	4233	-3.62849	-3.63748	-3.63536
4g	367	77.155	6.0829	4251	-3.62665	-3.61835	-3.38739
4h	365	76.652	9.60073	4251	-3.62849	-3.63297	-3.35842
4i	350	77.056	9.23429	4233	-3.62665	-3.5795	-3.4726
4j	350	85.483	9.60073	3801	-3.36192	-3.59518	-3.43884
4k	380	76.958	13.3384	3784	-3.31197	-3.62412	-3.63536
4l	380	78.045	8.35483	4251	-3.53441	-3.63748	-3.38739
4m	369	93.245	8.42812	4233	-3.44824	-3.61835	-3.35842
4n	404	86.251	6.0829	5643	-3.47683	-3.63297	-3.4726
4o	353	87.433	9.60073	3621	-3.75151	-3.5795	-3.43884
4p	371	85.547	9.23429	3314	-3.55883	-3.50338	-3.63536
4q	325	76.893	9.60073	2218	-3.34596	-3.36213	-3.38739
(Test set)							
4r	341	76.893	8.35483	3314	-3.34596	-3.34596	-3.63536
4s	324	77.927	8.42812	2218	-3.52035	-3.52035	-3.38739
4t	336	89.572	6.0829	3314	-3.87245	-3.87245	-3.35842
4u	385	77.286	8.35483	7455	-3.5563	-3.5512	-3.4726

[a]IC_{50} values in µg/mL.

RESULTS AND DISCUSSION

The successful results of statistical analysis (Table 3) led to the conclusion that activity of 2,4-thiazolidinediones as α-glucosidase inhibitors can be successfully modeled with molecular descriptors (molecular weight, wiener index, andrews affinity and polar surface area). Molecular weight is an important parameter that signifies the size of the molecule. Wiener index is a topological index of a molecule, defined as the sum of the numbers of edges in the shortest paths in a chemical graph between all pairs of non-hydrogen atoms in a molecule related to molecular branching. Andrews's affinity defines the functional group contributions to drug-receptor interactions. The polar surface area (PSA) is defined as the surface sum over all polar atoms, (usually oxygen and nitrogen), including also attached hydrogens. PSA is a commonly used medicinal chemistry metric for the optimization of cell permeability.[32-36]

Table 3. Comparative statistical measures for developed QSAR models using different (MLR) Multiple Linear Regression Techniques.

QSAR Models	(MLR) Method	No. of descriptors	R^2	P	PRESS	Q^2
MLR Model-1	Manual selection	4 (Training set)	0.99	0.99	-	-
		4 (Test set)	0.99	0.95	-	-
	Leave one out (LOO)	4 (Training set)	0.98	0.99	0.001	0.98
		4 (Test set)	0.64	0.55	0.003	0.59

R^2 (correlation coefficient), **p** (spearman rank correlation coefficient), **PRESS** (predicted error sum of squares), **Q2** (cross validated correlation coefficient)

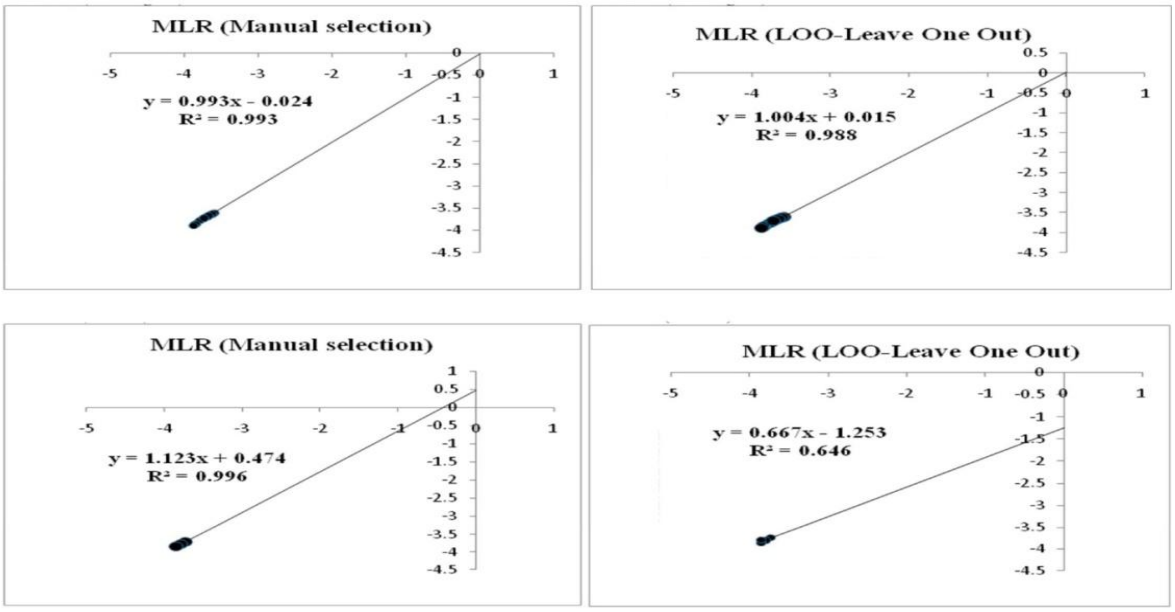


Figure 1 Plots of predicted versus observed biological activity of 2,4-thiazolidinediones (Training and Test sets).

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