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.
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\textsubscript{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

\((-\log(C_{50})) = (0.000259889 \times \text{Molecular Weight}) + 9.54402e-05 \times \text{Polar surface area} - 0.00233215 \times \text{Andrews affinity} - 8.33044e-05 \times \text{Wiener index} - 3.39367.\)

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).

<table>
<thead>
<tr>
<th>Code</th>
<th>Molecular weight</th>
<th>Polar Surface Area</th>
<th>Andrews affinity</th>
<th>Wiener index</th>
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<th>-log(I\textsubscript{C50})\textsuperscript{a} (predicted)</th>
<th>-log(I\textsubscript{C50})\textsuperscript{a} (predicted)</th>
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\(^a\)IC\textsubscript{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.

<table>
<thead>
<tr>
<th>QSAR Models</th>
<th>(MLR) Method</th>
<th>No. of descriptors</th>
<th>( R^2 )</th>
<th>( P )</th>
<th>PRESS</th>
<th>( Q^2 )</th>
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</thead>
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<td>MLR Model-1</td>
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<td>0.99</td>
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<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4</td>
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<td>0.95</td>
<td>-</td>
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<tr>
<td></td>
<td>Leave one out (LOO) (Training set)</td>
<td>4</td>
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<td>0.99</td>
<td>0.001</td>
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<tr>
<td></td>
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<td>0.64</td>
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<td>0.003</td>
<td>0.59</td>
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</tbody>
</table>

\( R^2 \) (correlation coefficient), \( P \) (spearman rank correlation coefficient), PRESS (predicted error sum of squares), \( Q^2 \) (cross validated correlation coefficient)
Figure 1 Plots of predicted versus observed biological activity of 2,4-thiazolidinediones (Training and Test sets).

REFERENCES


