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2D QSAR STUDIES ON 1,5-BENZOTHIAZEPINES AS POTENTIAL CYTOTOXIC AGENTS

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Abstract: A linear quantitative structure-activity relationship (QSAR) model is presented for modeling and predicting the cytotoxicity. The model was produced by using the multiple linear regression (MLR) technique on a twenty two compound database that consists of newly discovered 1,5-benzothiazepines. The major conclusion of this study is that molecular weight, wiener index, andrews affinity and polar surface area affect significantly the cytotoxicity (brine shrimp lethality) by 1,5-benzothiazepines. The selected QSAR descriptors serve as a primary guidance for the design of novel and selective cytotoxic agents.

Keywords: Cytotoxicity, QSAR

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INTRODUCTION

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

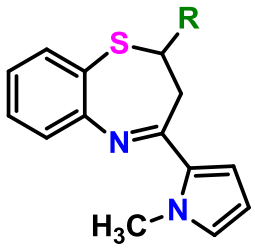
Experimental Section

Materials and Methods

Data set

In this QSAR study, biological and chemical data of 1,5-benzothiazepines (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 cytotoxic agents, some physicochemical constants, molecular and topological descriptors be calculated using Chem3D ultra 10.0. [22-25]

Table 1. Molecular structures of 1,5-benzothiazepines used for the QSAR study.



Code	R	Code	R
4a	C_6H_5	4l	4-FC_6H_4
4b	4-MeC_6H_4	4m	4-ClC_6H_4
4c	4-$NMe_2C_6H_4$	4n	2,4-diClC_6H_3
4d	3-$OMeC_6H_4$	4o	3-BrC_6H_4
4e	3,4-di$OMeC_6H_3$	4p	4-BrC_6H_4
4f	3,4,5-tri$OMeC_6H_2$	4q	2-OH,3-Br,5-ClC_6H_2
4g	2-OHC_6H_4	4r	4-Allyl-OC_6H_4
4h	4-OHC_6H_4	4s	Styren-yl

4i	3-OMe,4-OHC$_6$H$_3$	**4t**	Pyridin-3-yl
4j	3-NO$_2$C$_6$H$_4$	**4u**	Indol-3-yl
4k	4-NO$_2$C$_6$H$_4$	**4v**	Anthracen-9-yl

Molecular Modeling

The molecular structures of 1,5-benzothiazepines were modeled using Chemdraw ultra 10.0 (Cambridge software), and then represented is copied to Chem3D ultra 10.0 to create a 3D model and,in conclusion 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 whole 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. Cytotoxicity (-log ED_{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 1,5-benzothiazepines for the prediction of cytotoxicity was given as follows. [31]

Best QSAR Model

(-logED_{50}) = (-0.000531205 X (Molecular weight) - 0.00211013 X (Polar surface area) - 0.0105001 X (Andrews affinity) - 6.8519e-05 X (Wiener index) - 2.77791).

Cross validation of QSAR models

The test sets of 1,5-benzothiazepines 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 cytotoxicity obtained for validation set of 1,5-benzothiazpines are shown in Table 2. The experimental and predicted activities of 1,5-benzothiazepines (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 1,5-benzothiazepines (Training and Test sets).

Code	Molecular weight	Polar Surface Area	Andrews affinity	Wiener index	-log(ED_{50})[a] (observed)	-log(ED_{50})[a] (predicted)	-log(ED_{50})[a] (predicted)
(Training set)							
4a	318	86.518	9.23429	4251	-3.62849	-3.61835	-3.61725
4b	332	87.065	9.60073	4233	-3.62665	-3.63297	-3.63443
4c	361	86.614	9.161	3801	-3.5799	-3.5795	-3.57947
4d	348	87.632	9.52744	3784	-3.57795	-3.59518	-3.59848
4e	378	93.291	9.23429	4251	-3.62849	-3.62412	-3.62306
4f	408	93.245	9.60073	4233	-3.62665	-3.63748	-3.63956
4g	334	86.251	9.23429	4251	-3.62849	-3.61779	-3.61662
4h	334	87.433	9.60073	4233	-3.62665	-3.63375	-3.63536
4i	364	85.547	5.78975	2301	-3.36192	-3.38162	-3.38739
4j	363	76.893	5.86304	2051	-3.31197	-3.34935	-3.35842
4k	363	77.14	7.47538	3423	-3.53441	-3.48293	-3.4726
4l	336	77.155	7.84182	2807	-3.44824	-3.4403	-3.43884
4m	352	76.652	8.42812	2998	-3.47683	-3.46593	-3.4634
4n	387	77.056	13.3384	5643	-3.75151	-3.76867	-3.80141
4o	397	85.483	8.35483	3621	-3.55883	-3.53929	-3.53803
4p	397	76.958	8.42812	3314	-3.52035	-3.50338	-3.50117
4q	447	78.045	6.0829	2218	-3.34596	-3.36213	-3.3657
(Test set)							
4r	374	77.927	6.44934	2218	-3.34596	-3.37658	-3.38148
4s	344	89.572	8.42812	3314	-3.52035	-3.51968	-3.51945
4t	319	77.286	12.6055	7455	-3.87245	-3.89422	-4.01284
4u	357	76.922	9.38086	3600	-3.5563	-3.5512	-3.54969

4v	418	85.083	8.35483	3621	-3.55883	-3.53844	-3.53721

[a]ED_{50} values in µg/mL.

RESULTS AND DISCUSSION

The successful results of statistical analysis (Table 3) led to the conclusion that activity of 1,5-benzothiazepines as cytotoxic agents 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 statistics 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)	0.97	0.95	-	-
		4 (Test set)	0.88	0.93	-	-
	Leave one out (LOO)	4 (Training set)	0.93	0.95	0.03	0.91
		4 (Test set)	0.99	0.99	0.002	0.99

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

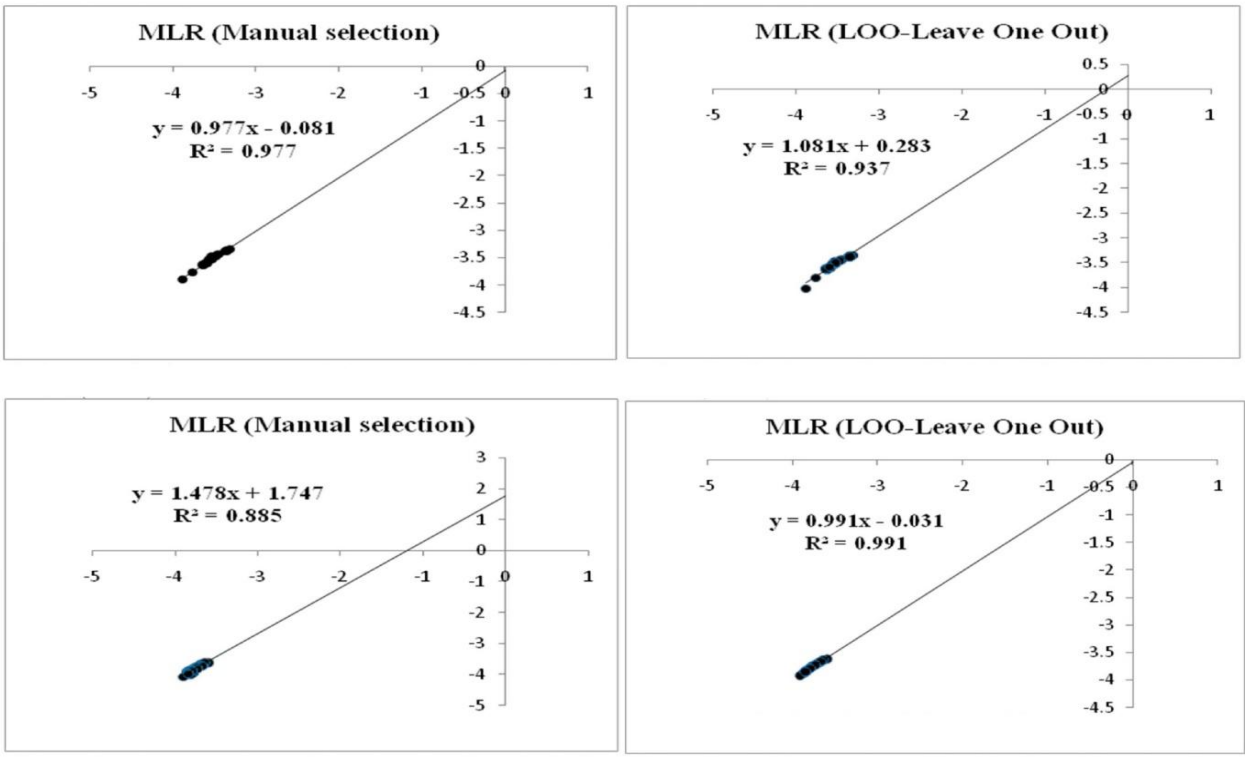


Figure 1. Plots of predicted versus observed biological activity of 1,5-benzothiazepines (Training and Test sets).

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