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Original Research Article

Quantitative evaluation of antibacterial activity of 4-thiozolidones

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Abstract

4-Thiazolidinone is a promising platform for the search of new potential antibacterial, antiviral, and anticancer agents etc. QSAR analysis of several potent compounds and different activities evaluation provide a solid background for the design of more potential drugs. Our present work is based on QSAR studies on 24 4-thiazolidinones against pathogenic bacteria Pseudomonas aeruginosa S. The data were divided into a training set and a test set, the former was used to develop the QSAR and the latter was used to evaluate the predictive capability of these developed models. In all the cases, the models were able to predict the test data set reasonably well. A four-parameter quantitative structure–activity relationship was derived (coefficient of determination, $r^2 = 0.8966$) for 19 training set compounds and internally validated (leave-one-out cross-validated coefficient of determination, $r^2_{cv} = 0.88$). External validation was carried out with the remaining 5 test set compounds (coefficient of determination for external validation, $r^2_{ext} = 0.9373$).
Key Words: Antibacterial activity, 4- thiazolidone, QSAR, external validation

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INTRODUCTION

Heterocyclic compounds like 4-thiazolidinone derivatives occupy an important place in medicinal chemistry as they show a variety of microbiological activity[1-2]. Therefore, an attempt was made to study the antibacterial activities of 4-thiazolidinone in present investigation. Quantitative structure-activity relationship (QSAR) studies are based on the fact that the biological activity of a compound is a function of its physicochemical properties. However, searching of more potent and efficient antibacterial agents is one of the major tasks of clinical practice due to the antibiotic resistant strains. Quantitative structure activity relationship (QSAR) analysis has been found to be a good tool for prediction of biological activity of novel compounds including antibacterial and antiviral agents[3-8].

Computational Details: QSAR method based on MLR of physico-chemical factors responsible for antimicrobial action along with their biological activity of 25 compounds were reported in the present work. Agrawal and coworkers have used many physicochemical and topological parameters to predict the antibacterial activity of many compounds[9-13]. The compounds used in the present study were taken from the literature[14]. The clinical isolates of the pathogenic bacteria *P. aeruginosa S* has been used as the test microorganisms. Dragon 6 software is used for the calculation of descriptors. The structural details of the compounds used along with the calculated descriptors from Dragon software are reported in Table 1. The parameters which have been calculated for the present study are WHIM descriptors (Molecular descriptors obtained as statistical indices of the atoms projected onto the 3 principal components obtained from weighted covariance matrices of the atomic coordinates), 2D autocorrelation by Moran (MATS) (Molecular descriptors calculated from molecular graph by summing the products of atom weights of the terminal atoms of all

the paths of the considered path length (the lag). The algorithms are calculated from lag 1 to lag 8 for 4 different weighting schemes) and GETAWAY R-indices (Descriptors calculated from the leverage matrix obtained by the centered atomic coordinates (molecular influence matrix, MIM). R and R+ descriptors are analogously obtained from the leverage/geometry matrix).[15-19]. The parameters used are L1v, MATS3e andR1u.

L1v: 1st component size directional WHIM index / weighted by atomic van der Waals volumes

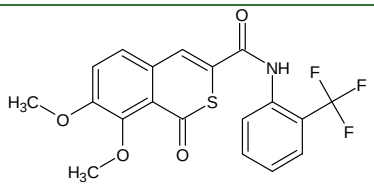
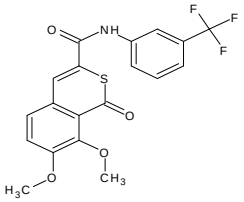
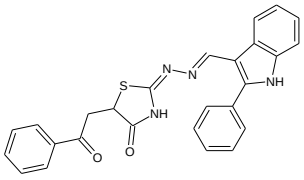
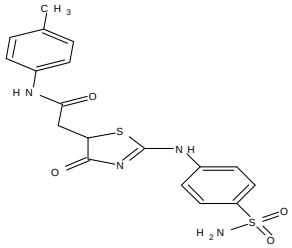
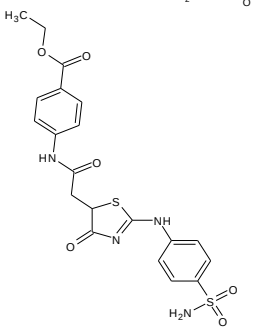
MATS3e: Moran autocorrelation of lag 3 weighted by Sanderson electronegativity

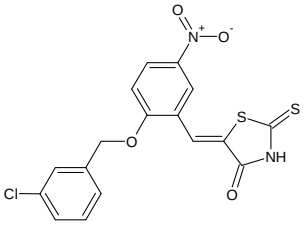
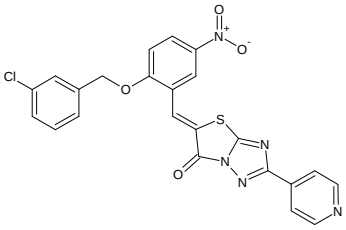
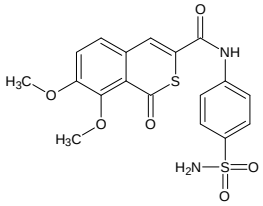
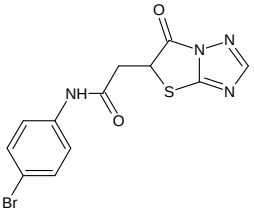
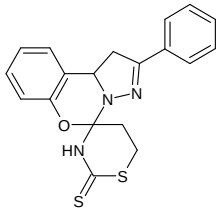
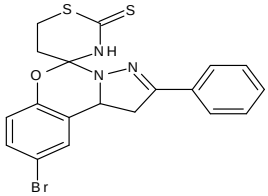
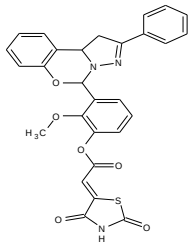
R1u: R autocorrelation of lag 1 / un-weighted

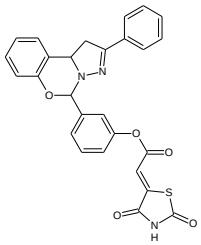
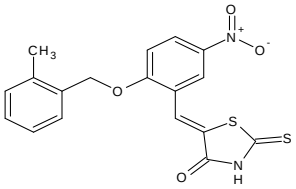
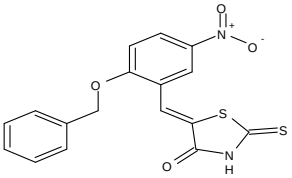
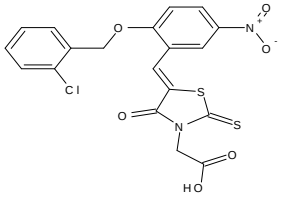
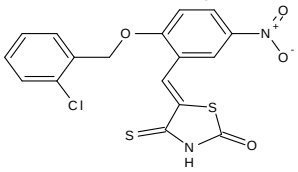
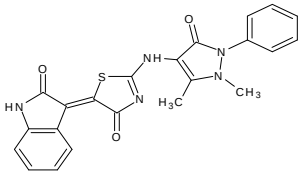
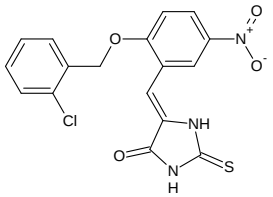
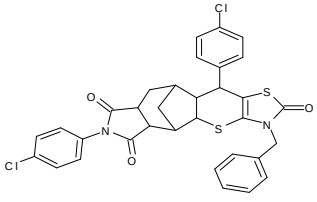
The data were divided into a training set and a test set, the former was used to develop the QSAR and the latter was used to evaluate the predictive capability of these developed models. In all the cases, the models were able to predict the test data set reasonably well. The useful descriptors were selected by variable selection procedure and multiple regression analysis was performed using NCSS software[20]. The models obtained were subjected to cross validation by leave one out procedure[21].

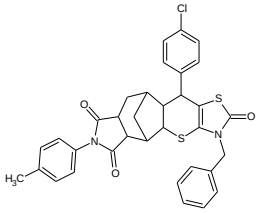
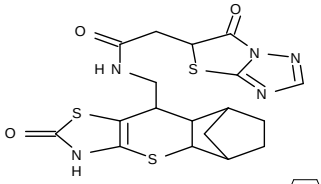
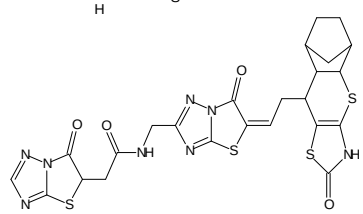
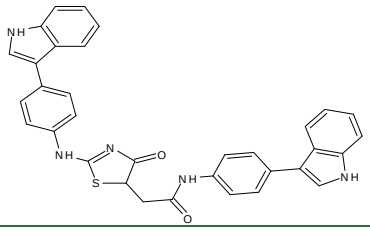
RESULTS AND DISCUSSION

Table 1: Calculated values of parameters along with structure of compounds and biological activity

Mol. ID	Structure of compounds used	L1v	MATS3e	R4u	Biological Activity
M-2		14.915	-0.012	1.195	7.5
M-5		15.182	-0.019	1.237	7
M-8		28.679	-0.028	1.288	7.3
m-14		28.845	-0.216	1.321	7.3
m-15*		30.348	-0.214	1.146	6.5

m-17		14.698	-0.115	1.185	6.5
m-18		25.91	-0.053	1.312	8
m-19		13.305	-0.087	1.173	5.5
m-22		15.357	-0.198	1.104	5.5
m-24*		9.275	-0.095	1.502	6.1
m-25		9.863	-0.15	1.337	5
m-29		20.324	-0.094	1.36	7.3

m-30		9.579	-0.032	1.388	5.5
m-51		14.263	-0.056	1.231	6.1
m-53*		13.398	-0.056	1.191	5.5
m-57		16.568	-0.087	1.435	6.23
m-58		12.965	-0.106	1.172	6.56
m-59		26.427	0.023	1.145	7.52
m-60		13.343	-0.095	1.272	6.54
m-61*		19.961	-0.038	1.867	9.55

m-62		21.392	-0.024	1.935	9.43
m-63		13.081	0.01	1.886	8.9
m-64		45.54	0.058	1.86	12.5
m-66*		42.037	-0.11	1.334	8.8

*Training Set

Table 2: Observed estimated and residual biological activity values using eqn. 3

Mol. ID	Observed biological activity	Estimated biological activity	Residual
M-2	7.50	6.57	0.93
M-5	7.00	6.68	0.32
M-8	7.30	8.23	-0.93
m-14	7.30	7.26	0.04
m-15*	6.50	6.92	-0.42
m-17	6.50	5.92	0.58
m-18	8.00	7.86	0.14
m-29	5.50	5.90	-0.40
m-22	5.50	5.28	0.22
m-24*	6.10	6.38	-0.28
m-25	5.00	5.65	-0.65
m-29	7.30	7.16	0.14
m-30	5.50	6.44	-0.94
m-51	6.10	6.35	-0.25
m-53*	5.50	6.14	-0.64
m-57	6.23	7.02	-0.79
m-58	6.56	5.75	0.81
m-59	7.52	7.86	-0.34
m-60	6.54	6.15	0.39
m-61*	9.55	8.94	0.62
m-62	9.43	9.37	0.06
m-63	8.90	8.53	0.37
m-64	12.50	12.22	0.28
m-66	8.80	9.33	-0.53

Table 3: Cross validation parameters for proposed models (eqn. 1, 2, 3)

Model No.	Parameters used	PRESS	SSY	PRESS/SSY	R^2CV	S_{PRESS}	PSE
1	L1v	20.742	33.089	0.63	0.37	1.10	1.0
2	L1v MATS3e	12.907	40.924	0.32	0.68	0.90	0.8
3	L1v MATS3e R1u	5.566	48.265	0.12	0.88	0.61	0.5

Table 4: Ridge analysis for three variable model (eqn. 3)

Independent variables	Variance Inflation Factor (VIF)	Tolerance (T)	Eigen Value (λ)	Condition Number (k)
MATS3e	1.33	0.75	1.77	1
L1v	1.20	0.84	0.69	2.57
R1u	1.35	0.74	0.54	3.32

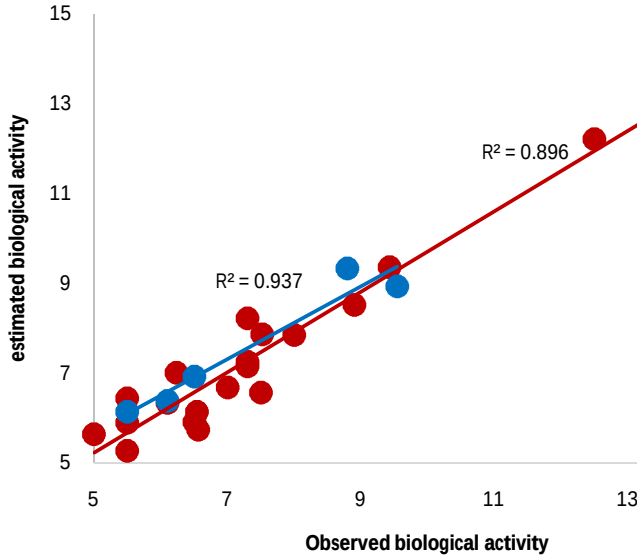


Figure 1: Correlation between observed and estimated biological activity values using eqn. 3

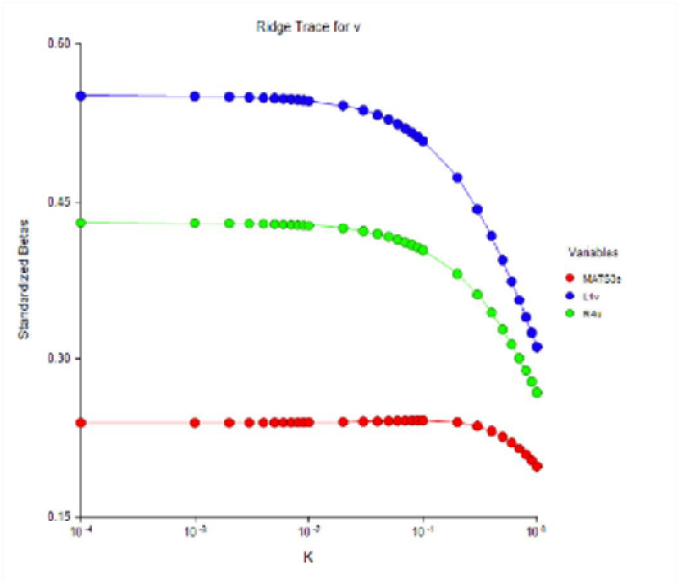


Figure 2: Ridge Trace for three variable model (eqn. 3)

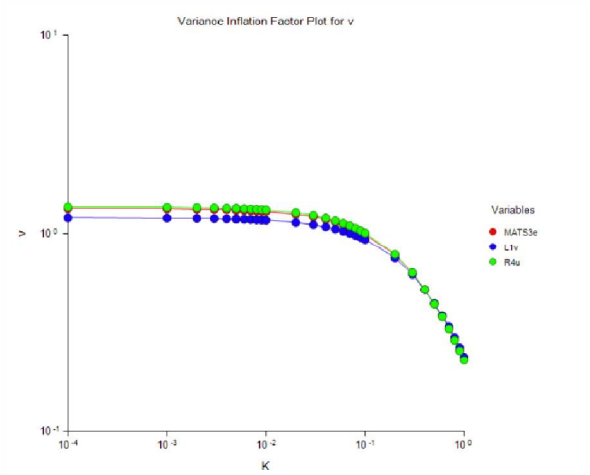


Figure 3: VIF plot for three variable model (eqn. 3)

The attempt to obtain multi-linear mathematical models using different molecular descriptors led to improvement of correlation coefficients and of other statistic parameters were given below

One variable model: BA = 0.1534(±0.0295) L1v +4.2576

N=19, R^2= 0.6147, R^2_A= 0.5920, Se=0.1541, F=27.12, Q= 5.09

Two variable model: BA = 0.1269 (±0.0254) L1v + 9.7788 (±3.1378) MATS3e +5.4201

N=19, R^2= 0.7602, R^2_A= 0.7303, Se=0.1253, F= 12.907, Q= 6.96

Three variable model: BA = 0.1077 (±0.0178) L1v +5.7640 (±2.3116) MATS3e +2.9364 (±0.6601) R1u +1.5215

N=19, R^2= 0.8966, R^2_A= 0.8759, Se=0.0850, F= 43.360, Q= 11.14 No mono-parametric correlation is capable of modeling the antibacterial activity of present set of compounds; however combination of three parameters as permitted by Rule of Thumb are the most suitable for modeling the antibacterial activity of compounds used in the present study. The predictive potential of this model has been obtained by plotting observed activity against estimated activity and such a comparison is demonstrated in figure 1. The predictive power of the model comes out to be 0.8966. To validate the best model cross validation parameters have been calculated and is reported in Table 3. It is an established fact that PRESS is a good estimate of the real predictive power of the model. If PRESS is smaller than SSY, the model predicts better than chance and can be considered statistically significant. To be a reasonably good QSAR model, this ratio of PRESS and SSY should be smaller than 0.4. The best model proposed by us are having this ratio smaller than 0.4 and therefore, the model 3 has excellent predictive power. The developed model is cross-validated by leave-one-out

method. Another cross-validated parameter related to uncertainty of prediction, the PSE, has also been calculated. The low value of PSE for model 4 supports its highest predictive potential (power). The low value of PSE and S_{PRESS} and high value of R^2_{CV} suggest that the tree-parametric model is most appropriate in predicting antibacterial activity of present set of compounds. This model was further validated by estimation of antibacterial activity value for the test set. The correlation potential for the test set is found to be 0.9373, as shown in Fig 1.There is no colinearity among the used parameters which has been established by ridge analysis as well as various inflation factors calculated from the model 4 (Table 4, figures 2 and 3).

CONCLUSIONS

On the basis of above discussion following conclusions can be drawn.

1. L1v, MATS3e andR1u are suitable parameters for modeling the anti-bacterial activity of present set compounds
2. The positive coefficients for L1v, MATS3e and R1u suggest that higher value of this parameter will favour the biological activity, hence in future designing of potent compounds their higher values will give better results.

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