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MODELING ANTIBACTERIAL ACTIVITY OF 4-THIOZOLIDONE DERIVATIVES

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ABSTRACT: In the present work, efforts have been made to model the antibacterial activity of 4-thiazolidone derivatives against pathogenic bacteria *P. aeruginosa* by using QSAR (quantitative structure-activity relationship) methodology. Multivariate analysis gave excellent model which was tested using cross validation using leave one out method. The cross- validation method was applied to the data set in order to prove the predictive power of statistically significant QSAR models, which help to explore some expectedly potent compounds. The best model predicting the antibacterial activity indicated that the 2D auto-correlation, 3D and WHIM parameters such as MATS8p, RDF070u, RDF035e, Mor30v (3D) and E1u (WHIM Parameter) are very effective in describing the antibacterial activities of these compounds. The study revealed that E1u, MATS8p, RDF035e and RDF070u contribute positively whereas contribution of Mor30v contributes negatively to the antibacterial activity. The compounds with improved antibacterial potential can be successfully designed with selected quantitative structure activity relationship model.

INTRODUCTION: Heterocyclic compounds like thiazolidones, are very good antibacterial drugs. Thiazolidones and their derivatives are known to have antimicrobial, antiviral, antitumor, antihypertensive and anti-inflammatory properties [1-2]. 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 [3-7].

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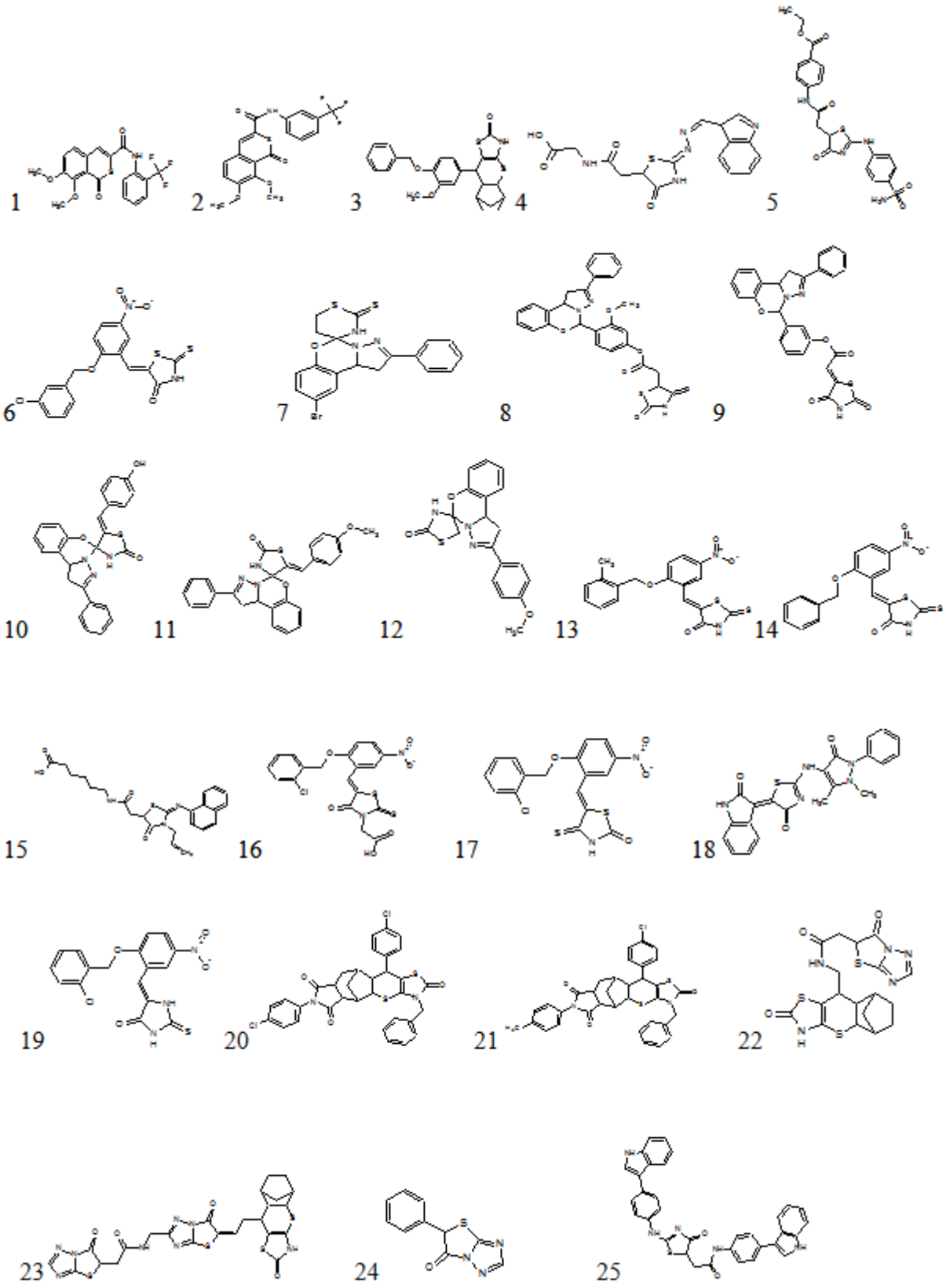
Computer technologies based on model development provide good insight for modification of molecular structures to get new organic molecules giving useful properties (including antibacterial activity). The present work is focused on the modeling of antibacterial activity of 4-thiazolidone derivatives.

MATERIALS AND METHODS: QSAR has been widely used for years to provide a quantitative correlation between chemical structure and biological activity [8]. Agrawal and coworkers have used many physicochemical and topological parameters to predict the antibacterial activity of many compounds [9-12].

In the present study, 25 thiazolidone derivatives have been considered having biological activity in terms of its log values. The compounds are taken from the literature [13].

Dragon 6 software is used for the calculation of descriptors. The structural details of the compounds used in the present study are given in **Table 1**. The clinical isolates of the pathogenic bacteria *P. aeruginosa* has been used as the test microorganisms.

TABLE 1: STRUCTURES OF COMPOUNDS USED IN THE PRESENT STUDY



The calculated descriptors from Dragon software are reported in **Table 2**. Useful descriptors were selected by variable selection procedure and multiple regression analysis was performed using NCSS software [14]. The models obtained were subjected to cross validation by leave one out procedure [15]. The parameters which have been calculated for modeling are:

TABLE 2: CALCULATED VALUES OF PARAMETERS ALONG WITH THEIR BIOLOGICAL ACTIVITY

Mol ID	MATS8p	RDF070u	RDF035e	Mor30v	E1u	log BA
m-1	-0.097	16.86	14.2	0.18	0.566	0.813
m-2	-0.288	14.634	14.879	0.213	0.542	0.708
m-3	-0.021	28.143	25.506	0.49	0.521	0.763
m-4	-0.013	9.569	17.282	0.157	0.57	0.813
m-5	-0.016	17.013	16.407	0.237	0.574	0.839
m-6	0.141	11.937	13.932	0.34	0.525	0.724
m-7	-0.038	16.967	20.018	0.251	0.437	0.699
m-8	-0.158	32.736	25.099	0.406	0.456	0.699
m-9	-0.059	26.361	23.32	0.186	0.431	0.740
m-10	-0.134	26.763	28.588	0.363	0.456	0.740
m-11	-0.065	18.737	30.301	0.389	0.444	0.708
m-12	-0.133	12.862	30.674	0.303	0.466	0.740
m-13	-0.002	12.07	13.825	0.313	0.584	0.785
m-14	0.094	11.004	16.343	0.346	0.538	0.740
m-15	-0.122	13.397	12.736	0.201	0.553	0.740
m-16	0.014	16.025	15.293	0.41	0.512	0.695
m-17	-0.147	15.227	12.574	0.363	0.543	0.716
m-18	0.056	16.62	22.987	0.254	0.562	0.814
m-19	0.03	13.573	13.474	0.277	0.538	0.723
m-20	0.013	47.857	39.12	0.666	0.439	0.741
m-21	0.007	52.755	40.874	0.572	0.441	0.786
m-22	0.146	21.902	19.19	0.374	0.538	0.763
m-23	-0.157	15.774	22.249	0.449	0.546	0.724
m-24	0.072	2.142	8.353	0.033	0.515	0.732
m-25	0.052	18.879	28.528	0.521	0.642	0.845

1. **E1u:** 1st component accessibility directional WHIM index / unweighted [16-20]. WHIM descriptors are based on the statistical indices calculated on the projections of atoms along principal axes. They are built in such a way as to capture relevant molecular 3D information regarding the molecular size, shape, symmetry and atom distribution with respect to invariant reference frames. The algorithm consists of performing a Principal Components Analysis on the centered Cartesian coordinates of a molecule by using a weighted covariance matrix obtained from different weighing schemes for the atoms.

The following weighting schemes are used for computing the weighted covariance matrix, S^w:

- Unweighted (u), that is the weight $w_i = 1$ for each i.
- Atomic masses ($w_i = m_i$)
- Atomic van der waals volumes ($w_i = v_i$)
- Atomic Sanderson electronegativities ($w_i = e_i$)
- Atomic polarizabilities ($w_i = p_i$)
- Atomic electro topological states ($w_i = s_i$)

2. **MATS8p:** Moran autocorrelation of lag 8 weighted by polarizability [21-22]. Moran Autocorrelation Descriptors is labeled as MATS. The symbol for each of the autocorrelation descriptors is followed by two indices *d* and *w* where *d* stands for the lag and *w* stands for the weight. The lag is defined as the topological distance *d* between pairs of atoms. The topological distance between a pair of atoms (*i, j*) is given in the ij^{th} entry in the Topological Level Matrix. The lag can have any value from the set {0, 1, 2, 3, 4, 5, 6, 7, 8}.The weight can be *m* (relative atomic mass), *p* (polarizability), *e* (Sanderson electronegativity) and *v* (Van der Waals volume). *Relative mass* is defined as the ratio of atomic mass of an atom to that of carbon. Similarly, the other three weights *p*, *e* and *v* are scaled by the corresponding values for Carbon.

Let *n* be the number of atoms in the molecule. For any chosen value for lag *d* and any chosen weight *w*, we compute the Autocorrelation Descriptors using the following formulae.

$$ATSdw = \sum_{i=1}^{\pi}\sum_{j}^{\pi} \delta_{ij}\left(w_i w_j\right)$$

Where, w_i and w_j are the weights of the atoms *i* and *j*, $\omega\epsilon\{m,p,e,v\}$, and δ_{ij} is Kronecker delta, that is, δ_{ij} =1 if the ij^{th} entry in the Topological Level Matrix is = *d*, and δ_{ij} = 0 otherwise.

3. **RDF035e:** Radial Distribution Function-035 /weighted by Sanderson electronegativity

4. **RDF070u:** Radial Distribution Function - 070 / unweighted [23]. The radial distribution function (RDF) descriptors are based on the distance distribution in the molecule. The radial distribution function of an ensemble of *n* atoms can be interpreted as the probability distribution of finding an atom in a spherical volume of radius *R*. A typical RDF descriptor is denoted by *RDFsw* where *s* and *w* take the values $10 \leq s \leq 155$ in units of 5 and $\in \{u,m,v,e,p\}$, and it is defined as follows:

$$RDF(R,W) = f\sum_{i-1}^{n-1}\sum_{j-i+1}^{n} w_i w_j e^{-\beta(R-\gamma u)^2}$$

Where, *f* is a scaling factor, r_{ij} is the Euclidean distance between the atoms *i* and *j*, w_i and w_j are the weights of the atoms *i* and *j* respectively, *n* is the total number of atoms, β is the smoothing parameter which defines the probability distribution of the individual inter-atomic distance. β can be interpreted as the temperature factor that defines the movement of the atoms.

5. **Mor30v:** 3D-MoRSE descriptors Weighted by van der Waals volume [24-26]. 3D MoRSE descriptors (3D Molecule Representation of Structures based on Electron diffraction) are derived from Infrared spectra simulation using a generalized scattering function (Soltzberg and Wilkins, 1977). A typical MoRSE descriptor is denoted by *M orsw* where *s* and *w* take the values $1 \leq s \leq 32$ and $w \in \{u,m,v,e,p\}$, where, *u* is unweighted, *m* is weighted by mass, *v* is weighted by van der Waals volume, *e* is weighted by electronegativity and *p* is weighted by polarizability

The MoRSE descriptor is defined as follows:

$$Mor(s,w) = I(s,w) = \sum_{i-2}^{n}\sum_{j-1}^{i-1} w_i w_j sin(sr_{ij})/(sr_{ij})$$

Where, r_{ij} is the Euclidean distance between the atoms *i* and *j*, and w_i and w_j are the weights of the atoms *i* and *j* respectively.

RESULTS AND DISCUSSION: The parameters calculated have been summarized in Table 2 which includes MATS8p, RDF070u, RDF035e, Mor30v and E1u. A correlation matrix has been obtained which shows correlation among the selected parameters and activity and is reported in **Table 3**. This table reveals that E1u is the only parameter which may be useful in one-parametric modeling. However, the combination of different parameters may result better models. The data was subjected to regression analysis and many statistically significant models have been obtained which are summarized in **Table 4**.

TABLE 3: CORRELATION MATRIX

	log BA	MATS8p	RDF070u	RDF035e	Mor30v	E1u
log BA	1.0000					
MATS8p	0.3085	1.0000				
RDF070u	0.0356	-0.0472	1.0000			
RDF035e	0.1031	-0.0549	0.8166	1.0000		
Mor30v	-0.0298	0.1026	0.7266	0.7264	1.0000	
E1u	0.5859	0.1806	-0.5405	-0.5336	-0.2090	1.0000

TABLE 4: REGRESSION PARAMETERS AND QUALITY OF CORRELATIONS

Model No.	Parameters used	Ai= (1……5)	B	Se	R^2	R^2_A	F-ratio	Q=R/Se
1	E1u	0.4621(±0.1333)	0.5125	0.0490	0.3432	0.3147	12.020	11.9558
2	E1u MATS8p	0.4323(±0.1340) 0.0898(±0.0728)	0.5309	0.0485	0.3857	0.3298	6.906	12.8051
3	E1u RDF070u	0.6743(±0.1387) 0.0020(±0.0007)	0.3643	0.0429	0.5185	0.4748	11.847	16.7848
4	E1u RDF035e	0.7068(±0.1281) 0.0031(±0.0009)	0.3212	0.0399	0.5849	0.5471	15.497	19.1676
5	E1u MATS8p RDF035e	0.6759(±0.1279) 0.0793(±0.0588) 0.0030(±0.0008)	0.3410	0.0391	0.6179	0.5633	11.320	20.1040
6	E1u Mor30v RDF070u	0.7771(±0.1321) -0.1573(±0.0643) 0.0037(±0.0009)	0.3297	0.0388	0.6253	0.5718	11.682	20.3804
7	E1u Mor30v RDF035e	0.8288(±0.1072) -0.1942(±0.0524) 0.0059(±0.0010)	0.2633	0.0317	0.7488	0.7129	20.869	27.2975
8	E1u Mor30v RDF035e RDF070u	0.9343(±0.0969) -0.2595(±0.0492) 0.0047(±0.0010) 0.0022(±0.0007)	0.2132	0.0268	0.8292	0.7951	24.276	33.9778
9	E1u MATS8p Mor30v RDF035e RDF070u	0.9059(±0.0772) 0.1161(±0.0324) -0.2826(±0.0395) 0.0048(±0.0008) 0.0023(±0.0006)	0.2342	0.0213	0.8981	0.8713	33.488	44.4921

Here some statistically significant models having R^2 more than 0.7 have been discussed.

Three variable model: When Mor30v and RDFo35e is added with Elu a three parametric model is resulted with R^2 = 0.7488. The adjusted R^2_A (0.7129) for this model also shows significant improvement. The model is as below:

log BA =0.8288(±0.1072) E1u-0.1942(±0.0524) Mor30v+0.0059(±0.0010) RDF035e+0.2633

N=25, R^2 = 0.7488, R^2_A= 0.7129, Se = 0.0317, F=20.869, Q = 27.2975

Addition of RDF070u to above model yielded a four parametric model with better statistics. The R^2 value changes from 0.7488 to 0.8292 and R^2_A change from 0.7129 to 0.7951. Change in adjusted R^2 clearly indicates that the added parameter has its fair share in the model. The model is as below:

Four variable model: log BA =0.9343(±0.0969) E1u-0.2595(±0.0492) Mor30v+0.0047(±0.0010) RDF035e+0.0022(±0.0007) RDF070u+ 0.2132

N=25, R^2 = 0.8292, R^2_A= 0.7951, Se= 0.0268, F=24.276, Q = 33.9778

Further improvement was observed when E1u, MATS8p, Mor30v, RDF035e and RDF070u have been taken together resulting into a five-parametric model (model 9, Table 4). The values of R^2 and R^2_A have come out to be 0.8981 and 0.8713 and the Q value [27-28] has come out to be 44.4921. The model is as under:

Five variable model: log BA =0.9059(±0.0772) E1u+0.1161(±0.0324) MATS8p-0.2826(±0.0395) Mor30v+0.0048(±0.0008) RDF035e+0.0023(±0.0006) RDF070u+ 0.2342

N=25, R^2 = 0.8981, R^2_A= 0.8713, Se= 0.0213, F=33.488, Q = 44.4921

No higher order model is permitted as Rule of Thumb restricts that (No of compounds are 25 hence maximum permitted no of parameters is 5.) Therefore, the five parametric model is the best model for modeling the anti-bacterial activity (log BA) of compounds used in the present study. Further confirmation is 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 0.8981. The biological activity (log BA) of all the compounds have been estimated using model- 9 (**Table 5**). The estimated log BA values are in good agreement with the observed values showing that the proposed model is best suited for estimating log BA values of present set of compounds.

To validate the model cross validation parameters have been calculated and they are reported in **Table 6**. We know that PRESS is a good estimate of the real predictive power of the model. If this value is smaller than SSY, the model predicts better than chance and can be considered statistically significant. Table 6 shows that all the proposed models are better than chance and are statistically significant. The ratio PRESS / SSY can be used to calculate the approximate confidence interval of the prediction of new compounds. If this ratio should be smaller than 0.4 the model is reasonably good. In the proposed model, this ratio is smaller than 0.4 and therefore, the model-9 has excellent predictive power.

TABLE 5: OBSERVED AND ESTIMATED BIOLOGICAL ACTIVITY AND RESIDUAL VALUES USING MODEL 9

Compd. No.	Observed biological activity log BA	Estimated biological activity log BA	Residual log BA
m-1	0.813	0.792	0.021
m-2	0.708	0.737	-0.029
m-3	0.763	0.753	0.011
m-4	0.813	0.81	0.003
m-5	0.839	0.803	0.035
m-6	0.724	0.725	0
m-7	0.699	0.69	0.009
m-8	0.699	0.71	-0.011
m-9	0.74	0.738	0.002
m-10	0.74	0.728	0.012
m-11	0.708	0.708	0
m-12	0.74	0.733	0.008
m-13	0.785	0.769	0.016
m-14	0.74	0.739	0.002
m-15	0.74	0.756	-0.016
m-16	0.695	0.694	0.001
m-17	0.716	0.702	0.014
m-18	0.814	0.827	-0.013
m-19	0.723	0.743	-0.02
m-20	0.741	0.743	-0.002
m-21	0.786	0.791	-0.005
m-22	0.763	0.775	-0.012
m-23	0.724	0.727	-0.003
m-24	0.732	0.745	-0.013
m-25	0.845	0.855	-0.01

TABLE 6: CROSS VALIDATION PARAMETERS FOR PROPOSED MODELS

Model No.	Parameters used	PRESS	SSY	PRESS/SSY	R^2CV	S_{PRESS}	PSE
1	E1u	0.0312	0.0163	1.9141	-0.9141	0.0368	0.0353
4	E1u RDF035e	0.0197	0.0278	0.7086	0.2914	0.0299	0.0281
7	E1u Mor30v RDF035e	0.0119	0.0356	0.3343	0.6657	0.0238	0.0218
8	E1u Mor30v RDF035e RDF070u	0.0081	0.0394	0.2056	0.7944	0.0201	0.0180
9	E1u MATS8p Mor30v RDF035e RDF070u	0.0048	0.0427	0.1124	0.8876	0.0159	0.0139

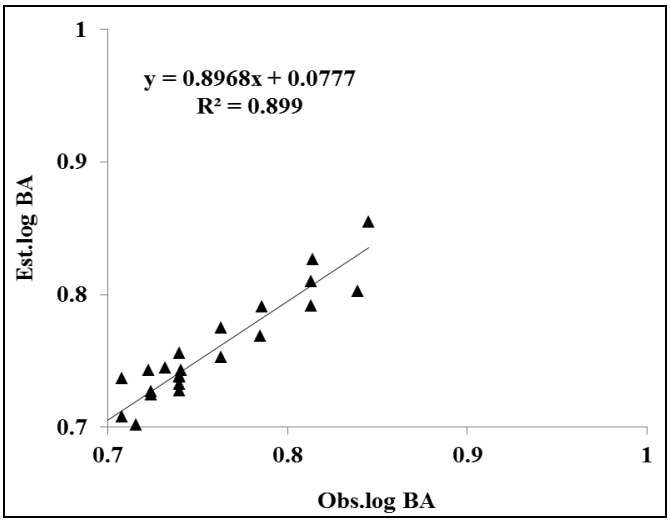


FIG. 1: CORRELATION BETWEEN OBSERVED AND ESTIMATED BIOLOGICAL ACTIVITY VALUES USING MODEL 9

The developed models are cross-validated by leave-one-out method. Another cross-validated parameter related to uncertainty of prediction, the PSE, has also been calculated. The lowest value of PSE for model 9 supports its highest predictive potential (power).

The low value of PSE and S_{PRESS} and high value of R^2_{CV} suggest that the five-parametric model is most appropriate in predicting the log BA values of present set of compounds.

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 9 (**Table 7, figures 2 and 3**).

TABLE 7: RIDGE ANALYSIS FOR FIVE VARIABLE MODEL (MODEL 9)

Independent variables	VIF	T	λ	k
MATS8p	1.07	0.94	2.83	1.00
RDF070u	3.88	0.26	1.13	2.51
RDF035e	3.82	0.26	0.68	4.17
Mor30v	2.96	0.34	0.19	15.01
E1u	1.79	0.56	0.18	15.47

VIF= Variance inflation factor; T= Tolerance; λ = Eigen value; k= Condition number

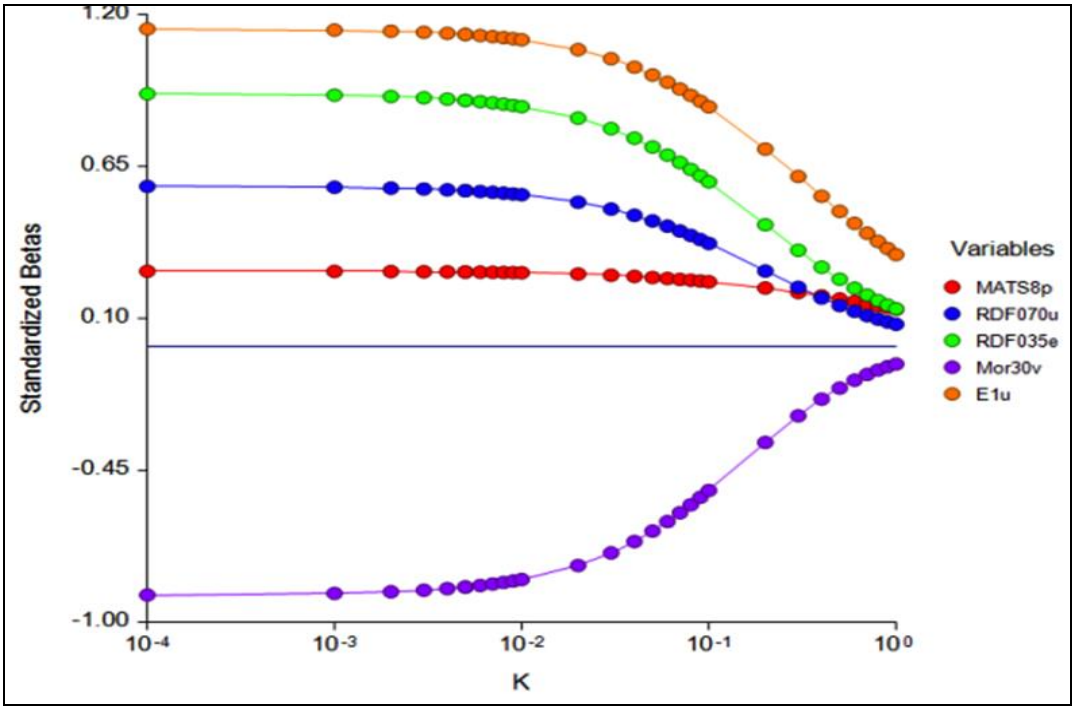


FIG. 2: RIDGE TRACE FOR FIVE VARIABLE MODEL (MODEL 9)

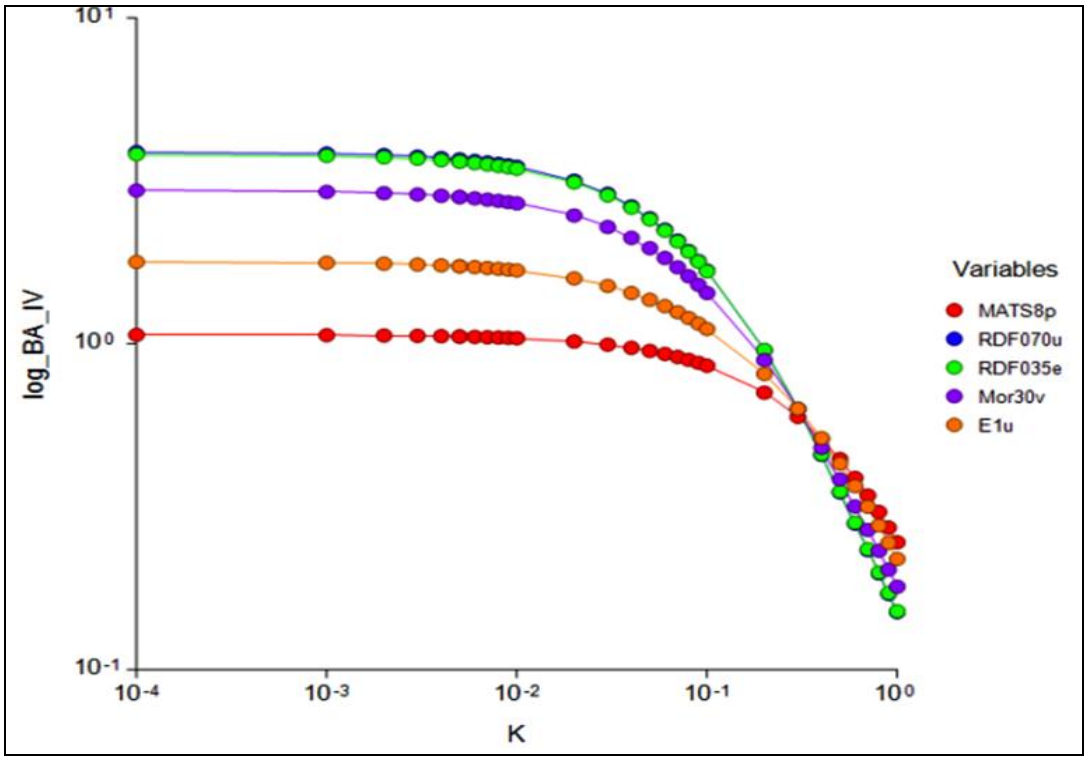


FIG. 3: VIF PLOT FOR FIVE VARIABLE MODEL (MODEL 9)

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

1. E1u along with MATS8p, RDF035e, RDF070u and Mor30v are suitable parameters for modeling the anti-bacterial activity of present set compounds
2. Coefficients for E1u, MATS8p, RDF035e and RDF070u are positive suggesting that higher value of these parameters will favour the biological activity. Negative coefficient of Mor30v suggests that it has retarding effect towards log BA values, hence in future designing of potent compounds its lower value will give better results.

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