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Modelling of the Antibacterial Activity of Some Benzimidazole Derivatives

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Abstract

In this study, an attempt has been made to obtain the most significant QSAR model for modeling the logMIC activity of the benzimidazole derivatives as synthesized and reported by Seydal. For this purpose, some topological descriptors have been calculated using mol files created through Chemsketch software. The Dragon software has been used for the calculation of a pool of descriptors. Then stepwise regression analysis was done which resulted in statistically significant models. A two-parametric model has been found to be the best with R2 equal to 0.9487. The R2cv for the model comes out to be 0.94595 which confirms that the model may be accepted. The other tests for the proposed model e.g., VIF parameters and Ridge analysis also support the findings.

Keywords: Antibacterial Activity; Benzimidazole Derivatives; Topological Descriptors; QSAR Modeling; Cross Validation

Introduction

Benzimidazole is an aromatic heterocyclic chemical molecule. that forms with the union of the rings of the aromatic chemicals benzene and imidazole. Its commonly used substituted derivatives are generated by conducting condensation with aldehydes instead of formic acid, followed by oxidation. The United States Food and Drug Administration lists benzimidazole derivatives as one of the most used ring systems for small molecule medicines. Many medications in the benzimidazole class of chemicals operate as angiotensin II receptor blockers, benzimidazole fungicides, antihistamines, anthelmintics, and antipsychotics.

During the literature survey, it has been observed that many derivatives of benzimidazole have antibacterial properties and they show antimicrobial activities against Gram-positive and Gram-negative bacteria. This is primarily because due to the potential bioactivity of benzimidazole-based ligands [1-11]. Because of this reason, the incorporation of the imidazole and benzimidazole nuclei is an important synthetic strategy in drug discovery.

It has also been observed that benzimidazole has received much attention in the last two decades among those who are working in the field of drug discovery and synthesis. Since the position and type of the substituents on the benzimidazole ring play a responsible role in biological activities, they tried to change the substitution at different places to get new compounds. Therefore, various new benzimidazoles have been synthesized and investigated for therapeutic purposes.

To obtain better active molecule chemist synthesize derivatives by fusing another heterocyclic ring in benzimidazoles. Such yielded compounds have been found their diverse application as antioxidant [12,13], antifungal [14], antitubercular [15], anticancer [16,17], and antiallergic drugs [18]. In addition to the above some of the benzimidazoles have been found effective inhibitors of the

growth of HIV-virus [19,20].

In this study, an attempt has been made to develop the most significant QSAR model for the benzimidazole derivatives as synthesized and reported by Seydal [21].

Antibacterial Activity of Compounds

The compounds synthesized by Seydal [21] have been tested for their biological activities. They were evaluated for their in vitro growth inhibitory activity against the bacteria *Pseudomonas aeruginosa* (ATCC 27853).

Antibacterial activities were tested by the disc-diffusion method under standard conditions using Mueller-Hinton agar medium as described by NCCLS [22].

In addition, the minimum inhibitory concentration (MIC) experiment was carried out by the agar dilution method as per NCCLS standard M7-A5 [23].

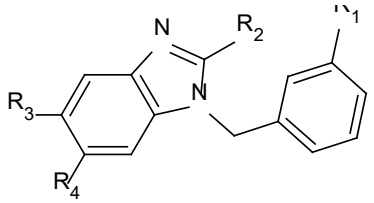
The MIC of tested benzimidazoles was defined as the lowest concentration of the compound at which no growth of the strain has been observed in a period and under specified experimental conditions.

To classify the antibacterial activity, they compared the activity with the antibacterial agents being used in therapeutic treatment. The MICs in the study were compared with Ampicillin and Gentamicin which were screened under similar conditions as reference drugs.

Agrawal, et al. [24-28] have used topological indices to correlate biological activities of man derivatives of sulfa compounds. QSAR studies have been published and widely cited by different workers in carrying out new synthesis.

Results and Discussion

In this study 12 benzimidazole derivatives have been taken from the work of [21]. The molecules were drawn using Chemsketch software [29]. The details of these structures along with their biological activities (logMIC) have been reported in Table 1. Molecular files (Mol) were prepared, and they were used for the calculation of topological parameters using Dragon software [30]. The calculated indices are summarized in Table 1.



Compd. No.	R_1	R_2	R_3	R_4	ATS2v	DBI	SNar	ATSC6p	ATSC8p	logMIC
1	CH_3	H	CH_3	CH_3	3.39	2.1	13.9	0.26	0.05	4.6
2	Cl	H	CH_3	CH_3	3.4	2.1	13.9	0.24	0.06	4.64
3	F	H	CH_3	CH_3	3.37	2.1	13.9	0.52	0.2	4.61
4	OCH_3	H	CH_3	CH_3	3.41	2.4	14.6	0.46	0.24	4.33
5	CH_3	NH_2	H	H	3.32	2	13.5	0.68	0.32	4.28
6	Cl	NH_2	H	H	3.32	2	13.5	0.7	0.34	4.31
7	F	NH_2	H	H	3.29	2	13.5	0.9	0.54	3.98
8	OCH_3	NH_2	H	H	3.33	2.2	14.2	0.85	0.56	3.7
9	CH_3	NH_2	CH_3	CH_3	3.42	2.2	14.3	0.16	0.03	4.63
10	Cl	NH_2	CH_3	CH_3	3.42	2.2	14.3	0.14	0.04	4.66
11	F	NH_2	CH_3	CH_3	3.4	2.2	14.3	0.37	0.17	4.33
12	OCH_3	NH_2	CH_3	CH_3	3.43	2.5	15	0.32	0.18	4.35

Table 1: Structural details of benzimidazoles used in present study.

To obtain a correlation matrix, the NCSS software [31] was used. The resulting correlation matrix showing intercorrelation among all the descriptors with activity is demonstrated in Table 2.

	logMIC	ATS2v	DBI	SNar	ATSC6p	ATSC8p
logMIC	1					
ATS2v	0.66	1				
DBI	0.07	0.78	1			
SNar	0.12	0.81	1	1		
ATSC6p	-0.85	-0.92	-0.48	-0.52	1	
ATSC8p	-0.94	-0.83	-0.3	-0.35	0.97	1

Table 2: Correlation matrix.

A perusal of Table 1 reveals that the compounds can be arranged in the following increasing order activity.

8 < 7 < 5 < 6 < 4 < 11< 12 < 1 < 3 < 9 < 2 <10

No conclusion could be drawn as why this change in the activity is observed. However, some of the reasons for this may be attributed to substitution of various groups at different positions. Even one may not be able to predict the activity by adding different substituents at various places. So, the QSAR analysis was preferred.

The data was subjected to regression analysis to get the best models. A perusal of correlation matrix suggests that the ATSC8p has the highest correlation with log MIC the next parameter which shows correlation value -0.8467 is ATSC6p and the third one is ATS2v which has a value of 0.6581. Other two parameters show poor correlation with activity.

Similarly, some parameters are highly correlated and some show moderate correlation. They are discussed as below:

- ATSC6p is highly correlated with ATS2v
- ATSC8p is highly correlated with ATSC6p
- SNar is highly correlated with DBI but moderately correlated with ATS2v
- ATSC8v is moderately correlated with ATS3v

It is well accepted fact that no two highly correlated parameters be used in multi-parametric correlation. Hence, they are generally not taken together. But according to Randic [32] different topological parameters contain different information hence their simultaneous use should not be restricted. Therefore, recommendation of Randic is being followed in obtaining best statistically significant models. However, the defect due to collinearity can be tested by Ridge analysis and obtaining VIF plots.

According to rule of Thumb [33] for 12 compounds one can go up to 4-parametric models. Therefore, in this analysis the best model will be restricted to that limit.

The systematic regression analysis [34] was carried out. The quality of statistical parameters is summarized in Table 3.

Model No.	Parameters	A_i (i=1,2,3)	C	Se	AdjR^2	R^2	F-Ratio	Q= R/Se
1	ATSC8p	-1.5018(± 0.1758)	4.71	0.11	0.87	0.88	72.96	8.81
2	ATSC6p	-0.9393 (±0.1866)	4.81	0.16	0.69	0.72	25.33	5.19
3	ATS2v	4.0476(± 1.4643)	-9.29	0.23	0.38	0.43	7.64	2.85
4	ATSC6p	1.2113(± 0.3475)	4.53	0.07	0.94	0.95	83.25	13.3
	ATSC8p	-3.1990 (±0.5016)						
5	DBI	-0.4826 (±0.1933)	5.79	0.09	0.91	0.93	58.69	11.16
	ATSC8p	-1.6145(± 0.1494)						
6	SNar	-0.1466 (±0.0601)	6.81	0.09	0.91	0.93	57.47	11.05
	ATSC8p	-1.6334 (±0.1536)						
7	ATS2v	-2.3621(± 1.0022)	12.80	0.09	0.91	0.93	55.88	10.9
	ATSC8p	-2.0121 (±0.2610)						
8	ATS2v	9.3556(± 0.9108)	-22.20	0.09	0.9	0.92	53.05	10.61
	DBI	-2.3006(± 0.3068)						

9	ATS2v	9.8287(± 1.0594)	-18.50	0.1	0.89	0.91	43.78	9.64
	SNar	-0.7304 (±0.1080)						
10	DBI	-0.8946 (±0.2932)	6.86	0.12	0.83	0.86	27.84	7.69
	ATSC6p	-1.1683 (±0.1570)						
11	SNar	-0.2750 (±0.0928)	8.80	0.12	0.82	0.86	26.89	7.56
	ATSC6p	-1.1938 (±0.1643)						

Table 3: Quality of statistical parameters for different models.

Here, best models obtained using one-, two-parametric models are reported.

One-Parametric Model

The best one-parametric model is obtained with ATSC8p as correlating parameter. The R^2 value for this model comes out to be 0.8795. The model is as below-

log MIC=4.7107-1.5018(± 0.1758) ATSC8p
N=12, SE=0.1065, R^2=0.8795, AdjR^2=0.8674, F-ratio=72.96, Q-value=8.805(1)

Here and here after, N refers to the number of data points used in the correlation, R^2 is the square of the correlation coefficient, SE is standard error of estimation, Adj R^2 is adjusted R^2 which takes care of added parameters, F is Fischer ratio and Q is Pogliani constant [36] which is R/SE.

Two-Parametric Model

When SNar is added to one-parametric model the value of R^2 changes from 0.8795 to 0.9274. The value of Adj R^2 changes from 0.8674 to 0.9112 which clearly indicates that addition of SNar to the one-parametric model is justified. The Q value also shows a high increment in this model. The model is given below:

log MIC= 6.8077 -1.6334 (±0.1536) ATSC8p-0.1466 (±0.0601) SNar
N=12, SE= 0.08717, R^2 =0.9274, AdjR^2 =0.9112, F-ratio= 57.465, Q-value= 11.047 (2)

To check whether a better R^2 may be obtained with other two-parametric combination, DBI is added to one-parametric model discussed above. This resulted into a better model in which the value of R^2 has been found to be 0.9288 which is better than what was obtained when SNar was added. This means that the model obtained is better than the two-parametric model in which ATSC8p and SNar were taken as correlating parameters. This is further confirmed when Adj R^2 values are compared. This value for the latter two-parametric model comes out to be 0.913 slightly better that previous two-parametric model Eq. (2). The Q value also show slight improvement. The model is given as below-

log MIC= 5.786-1.6145(± 0.1494) ATSC8p-0.4826 (±0.1933) DBI
N=12, SE= 0.08632, R^2= 0.9288, AdjR^2= 0.913, F-ratio= 58.69, Q-value= 11.164 (3)

Finally, the most favourable and significant two-parametric model is obtained when ATSC8p and ATSC6p are taken together. The R^2 value in this comes out to be 0.9487 which is highest among all the previous models discussed above. The Adj R^2 also is highest (0.9373) which suggests that this is the best two-parametric model. The Q value also changes from 0.11.164 to 13.297 suggesting that the two-parametric model given below is the best model for modelling the logMIC of present set of compounds. The model is reported below:
log MIC= 4.5328-3.1990 (±0.5016) ATSC8p+1.2113(± 0.3475) ATSC6p
N=12, SE= 0.07325, R^2= 0.9487, AdjR^2= 0.9373, F-ratio= 83.246, Q-value= 13.297 (4)

The three-parametric models were also tried but the improvement in regression parameters have very insignificant. Hence, they are not considered/ reported here.

Further confirmation of the model was obtained by estimating the logMIC values using best model (Eq.4). The observed and estimated values are reported in Table 4. They are in good agreement with each other confirming that the model represented in Eq.4 is the best among all the obtained models. A graph has been plotted against observed and estimated activity values to obtain the predictive power of the model. Such graph is demonstrated in Figure 1. The predictive power of the model comes out to be 0.948. This means that approximately 94% of the data can be explained by this model Figures 2 & 3.

Model N0	Descriptors used	N	PRESS	SSY	PRESS/ SSY	R^2_{CV}	PSE	S_{PRESS}
1	ATSC8p	12	0.11	0.83	0.14	0.86	0.1	0.11
2	ATS2v, ATSC8p	12	0.07	0.87	0.08	0.92	0.08	0.09
3	Snar, ATSC8p	12	0.07	0.87	0.08	0.92	0.08	0.09
4	DBI, ATSC8p	12	0.07	0.87	0.08	0.92	0.07	0.09
5	ATSC6p, ATSC8p	12	0.05	0.89	0.05	0.95	0.06	0.07

Table 4: Cross validated parameter for the proposed models.

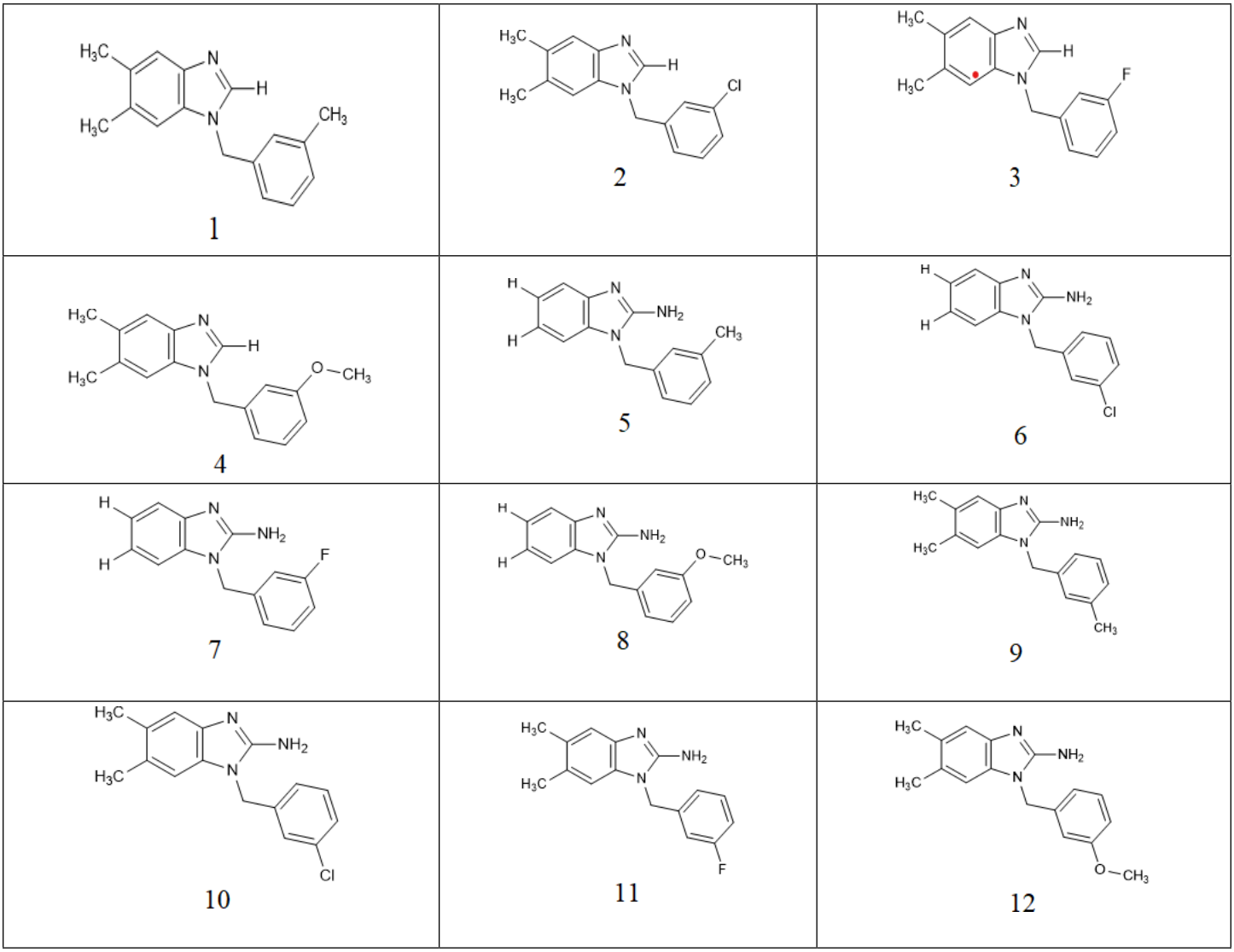


Figure 1: Molecular Structures used in the present study.

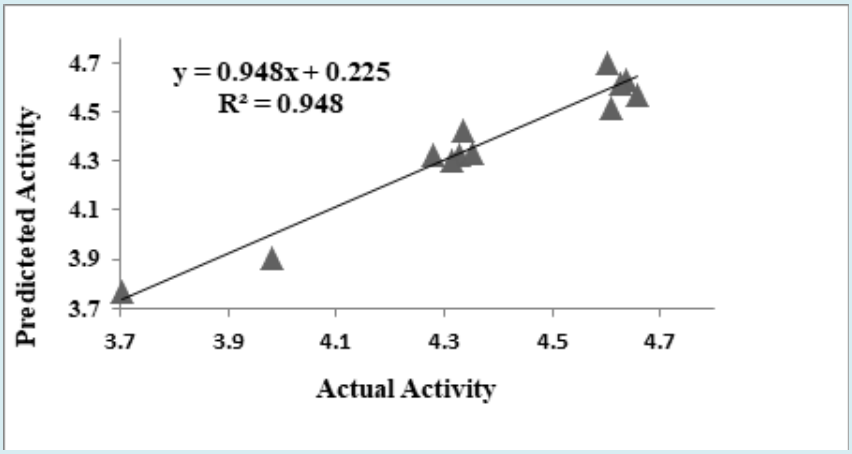


Figure 2: Plot between observed and estimated log MIC using best model.

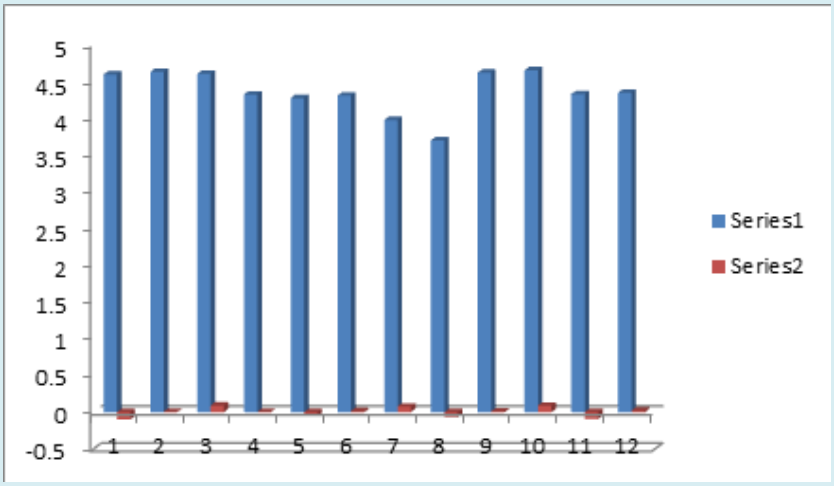


Figure 3: Residual plot using best model for the activity.

Compd. No.	Observed Log MIC	Estimated Log MIC	Residual
1	4.6	4.7	-0.1
2	4.64	4.63	0.01
3	4.61	4.52	0.09
4	4.33	4.32	0.01
5	4.28	4.33	-0.05
6	4.31	4.3	0.01
7	3.98	3.9	0.08
8	3.7	3.77	-0.07
9	4.63	4.62	0.01
10	4.66	4.57	0.09
11	4.33	4.43	-0.09
12	4.35	4.33	0.02

Table 5: Observed and Estimated log MIC values for the present set of compounds.

Calculation of cross validated parameters [36] are also important method for deciding whether the proposed model is best or not. Therefore, the calculation of cross validated parameters for the proposed models were calculated. They are reported in Table 5. The highest R^2_{CV} value obtained relates to two-parametric model represented by Eq. 4 above.

The ratio PRESS/SSY can be used to get suitable confidence intervals for prediction of new compounds. When the ratio of PRESS/SSY is less than 0.4 (PRESS/SSY < 0.4), then the QSAR model is significant and reasonable. When the value of PRESS/SSY is less than 0.1 (PRESS/SSY <0.1), that indicates that the model is excellent. The other cross validated parameters, as per the above values, are also in favour of this model.

To check whether the model obtained suffers due to collinearity or not, Ridge analysis has been performed. The plot obtained is demonstrated in the form of Figures 4 & 5.

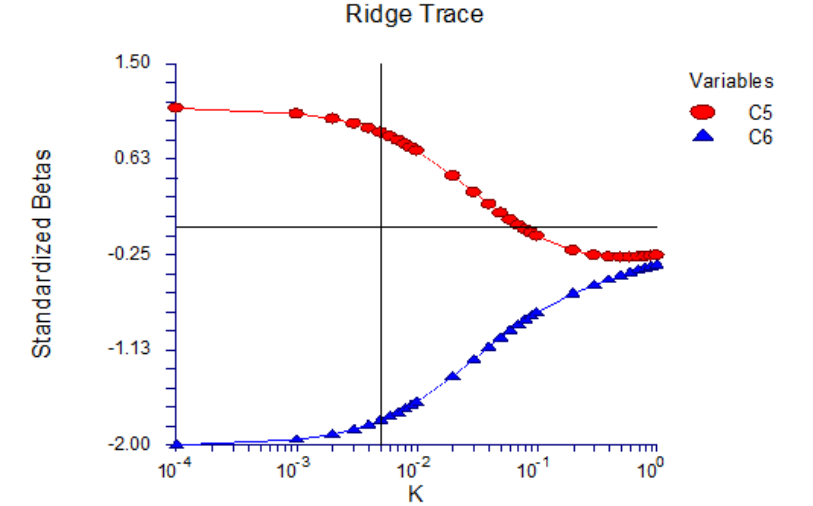


Figure 4: Ridge Trace for the bi-parametric model containing ATSC6p (C5), ATSC8p(C6) as correlating parameters.

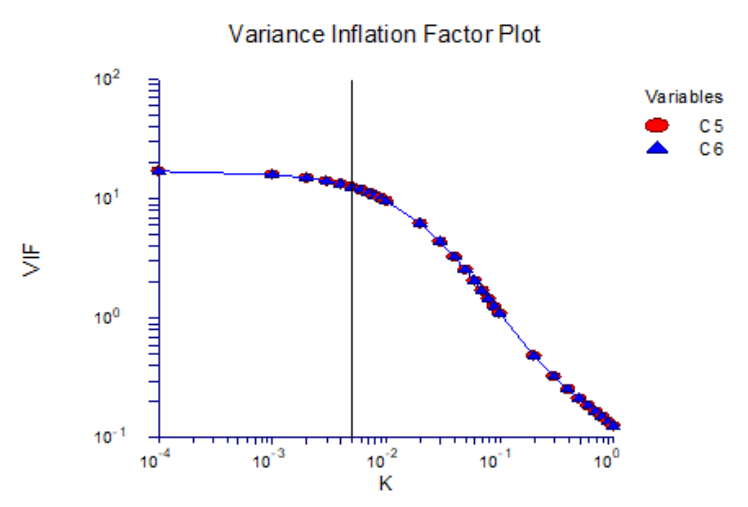


Figure 5: VIF Trace for the bi-parametric model containing ATSC6p (C5) ATSC8p(C6) as correlating parameters.

Table 6 is related to Ridge analysis, based on which we discuss the defect of co-linearity in models. The parameters reported in table 6 are Variance Inflation Factor (VIF), Tolerance (T), Eigen values (λ_i), and Condition Number (k). These values are reported for all the independent parameters used in the proposed model. The model with a parameter whose VIF value is greater than 10 will show co-linearity (Fig.5). But in our proposed models the VIF value is always less than 10, which means that all the proposed models are free from the defect of co-linearity.

Model No.	Parameters Used	VIF	λ_i	K
4	ATSC6p	17.217	1.9705	1
	ATSC8p	17.217	0.0295	66.85

Table 6: Ridge Regression parameters for the best obtained models.

The Tolerance value T equal to 1 or less than 1 indicates that the model is free from co-linearity. The values for T in Table 6, are less than 1. Therefore, from this point of view also proposed models are free from the defect of co-linearity.

Another test for collinearity is λ_i. The parameter of the model whose λ_i value is greater than 5 will suffer from co-linearity. Since, every value of λ_i is less than 5, which means all the proposed models are free from co-linearity defects. Also, if the value of condition number k is greater than 100, then the collinearity exists but in our case from this point of view, the proposed models are well acceptable.

Therefore, based on the above discussion, it is clear that all the parameters shown in table 6 are free from collinearity or more precisely multi co-linearity.

Conclusions

- Topological parameters are useful in modelling the antibacterial activity of benzimidazole derivatives considered in this study.
- Two-parametric model using ATSC8p and ATSC6p as correlating parameters gave excellent results thus accepted as best QSAR model.
- The parameter ATSC8p has a negative coefficient indicating that the higher value of this parameter will reduce the pMIC value. Thus, it has a retarding role towards the biological activity.
- The parameter ATSC6p has a positive coefficient which shows that it has a positive role towards the activity.
- The best two-parametric model is free from collinearity defect.
- This model can be used in further modification of molecular structure to get more potent compounds.

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