The Antibacterial Activity of Benzimidazole Derivative and the Quantitative Structure-Activity Relationships

Shailja Sachan[#] , Aradhana Mishra[*], Santosh Tiwari[*], Vikash Pandey[*]
[#]Department of Chemistry,Govt. New Science College, Rewa-486001, India.
[*]Department of Chemistry, A.P.S.University, Rewa-486003, India

Abstract: A QSAR study on benzimidazole derivatives using several topological and indicator descriptors was performed and evaluated for their antibacterial activities. The correlation equations of these relationships which were designed according to the Hansch Analysis Method were given. The 5 best models were selected for the discussion. Initial regression analysis indicated that balaban index plays a dominating role in modeling the activity in all proposed models. Results are interpreted on the basis of multiple regression and cross-validation methodology. Furthermore, the domain of applicability which indicates the area of reliable prediction is defined.

Key words: Antibacterial, benzimidazole, Quantitative structure-activity relationship (QSAR)

***Corresponding Author**
E-Mail: santoshsonu_2007@rediffmail.com

Introduction

Benzimidazole is a heterocyclic aromatic organic compound. It is an important pharmacophore and a privileged structure in medicinal chemistry. This compound is bicyclic in nature which consists of the fusion of benzene and imidazole. Nowadays is a moiety of choice which possesses many pharmacological properties.

These heterocyclic systems nucleus is an important heterocyclic ring, and interest in the chemistry, synthesis and microbiology of this pharmacophore continues to be fuelled by its antifungal, antitubercular, antioxidant and antiallergic[1-5] properties. Other reports have revealed that these molecules are also present in a variety of antiparasitic and herbicidal agents. Albendazole, fenbendazole and their sulphoxide derivatives are methylcarbamate benzimidazoles with a broad spectrum anthelmintic activity, widely used in human and veterinary medicine. They are used against several systemic parasitoses, including nematodoses, hidatidosis, teniasis and others.[44] They are also used to treat microsporodial and cryptosporodial infections, which can cause lethal diarrhea in patients treated with immunosuppressive drugs, or infected with HIV Different substituted benzimidazolyl quinolinyl mercaptotriazoles are remarkably effective compounds both with respect to their virus inhibitory activity and their favourable antibacterial activity In recent years, benzimidazole derivatives have been attracted particular interest due to their antiviral activity against HCV (Hepatitis C virus).[6-10]

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 topological properties and biological activities. This is widely used for the prediction of topological properties in the chemical, pharmaceutical, and environmental spheres. This method included data collection, molecular descriptor selection, correlation model development, and finally model evaluation. QSAR studies have predictive ability and simultaneously provide deeper insight into mechanism of drug receptor interactions.[11]

Inhibitory Activity

The inhibitory activity[12] of benzimidazole is determined as µg/ml were first transformed to the negative logarithms of molar MICs (log 1/c mic), which was used as a dependent variable.

Presentation of Data

In present study, Table.1 shows the substitution with inhibitory activity while Table-2 represent the topological and indicator descriptor and Table-3 shows the correlation matrix between the descriptor which are used in the present study.Table-4 is the Regression statistical descriptor while table-5 is the cross-validated statistical description of developed models. Table-6 represents the calculated and observed inhibitory activity with residual. Fig.1 shows the graph plotted between the observed and calculated inhibitory activity while the Fig.2 is the graph plotted between the observed and residual to illustrate the systemic error and Fig.3 is the graph plotted with ridge regression to show the multicolinearty. In Table-2 the indicator IR_1 used when in R^2 substitution of compound if - CH3 is present then value put 1 otherwise it mention to 0 value; IR_2 used when if in R^2 substitution of compound –4 chloro COCH3 benzene is present then 1 value put otherwise it mention to 0 value.

Table1. The structures of the compounds studied and their antibacterial screening summary

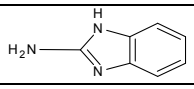
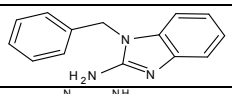
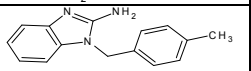
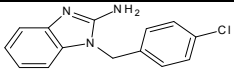
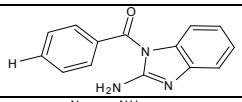
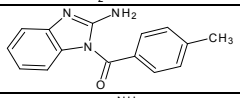
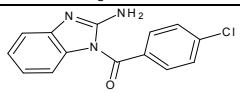
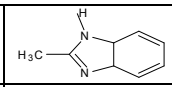
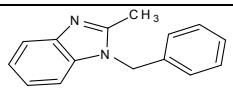
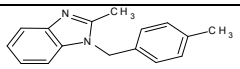
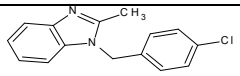
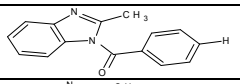
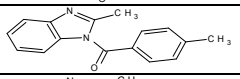
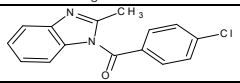
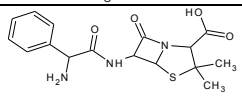
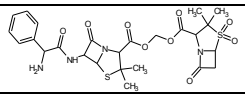
S.N0.	Structures of Compound	log1/ *c*MIC
1.		3.425
2.		3.951
3.		4.278
4.		4.615
5.		3.676
6.		4.303
7.		4.638
8.		3.121
9.		3.648
10.		3.975
11.		4.312
12.		3.373
13.		4.000
14.		4.33
15.		4.446
16.		5.787

Table 2. Calculated Topological Descriptors

S.No.	log1/*c* MIC	IR_1	IR_2	J	Jhetv
1	3.425	0	0	1.975	2.16
2	3.951	0	0	1.602	1.604
3	4.278	0	0	1.574	1.597
4	4.615	0	0	1.574	1.597
5	3.676	0	0	1.687	1.677
6	4.303	0	0	1.66	1.674
7	4.638	0	1	1.66	1.674
8	3.121	1	0	2.054	2.171

9	3.648	1	0	1.602	1.621
10	3.975	1	0	1.574	1.612
11	4.312	1	0	1.574	1.612
12	3.373	1	0	1.687	1.693
13	4	1	0	1.66	1.688
14	4.335	1	1	1.66	1.688
15	4.446	0	0	1.607	1.434
16	5.787	0	0	1.15	0.849

Result and Discussion

In the first step of the present study, different substituted benzimidazoles were evaluated for *in vitro* antibacterial activity against Gram-negative *Pseudomonas aeruginosa*. It is well known that there are three important components in any QSAR study: development of models, validation of models and utility of developed models.Base structure of benzimidazole derivatives compounds:

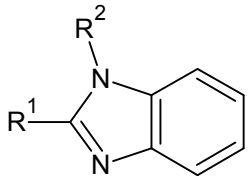


Table-3 Correlation Matrix of different discriptors

	log1/*c* MIC	**IR^1**	**IR^2**	**J**	**Jhetv**
log1/*c* *M*IC	1.0000				
IR^1	-0.4215	1.0000			
IR^2	0.2264	0.0476	1.0000		
J	-0.8403	0.2069	0.0331	1.0000	
Jhetv	-0.8466	0.2520	0.0462	0.9772	1.0000

In order to deduce the correlation of the observed antibacterial activity, a systemic QSAR has been carried out using the model proposed by Hansch et. al. Using the data of table-3, a correlation matrix was calculated as well as the colinearity between the descriptors. A high interrelationship was observed between J and Jhetv (r = 0.99) as well as the low interrelationship was observed between IR2 and J (r = 0.03). The data presented in Table-3 demonstrated the low colinearity between the parameters (r >0.8) except J. Model 1 is developed to predict the antibacterial activity.

log 1/c mic = 7.2038(±0.5257)-1.8738(±0.3148)-Jhetv

n = 16 R^2 = 0.7168 R^2A = 0.6966 F-Ratio = 35.441…….1

The developed QSAR model Eq.1 shows the importance of Jhetv which is negatively correlated with the antibacterial activity which indicate the topological descriptor Jhetv is inversely proportional with the antibacterial activity. The correlation coefficient between the descriptor and antibacterial activity is (r = 0.84) which is not sufficient.

log 1/c mic = 7.1867(±0.4726)+0.4955(±0.2382)IR1-1.9011(±0.2832)Jhetv

n = 16 R^2 = 0.7876 R^2A = 0.7549 F-Ratio = 24.096 ……2

The combination of the indicator descriptor IR^1 with topological descriptor Jhetv resulted in a very low increase in the r value i.e. r = 0.84 (eq.1) to r = 0.88 (eq.2) the interrelationships between the above parameters are very low r = 0.25. Looking at this interrelationship, it appears that there should be a significant increase in the r-value, where eq.2 does not represent the above fact. In an attempt to obtain still better regression expression we tried for some triparametric correlations which are

statistically significant. In doing so it has been observed that in all the three significant triparametric correlations obtained indicator parameter (IR_2) plays an important role, and the best triparametric model among them is as below:

log 1/c mic = 7.0987(±0.4316)-0.2889(±0.1490)IR1+0.5111(±0.2165)IR2-
1.7721(±0.2657)Jhetv

n = 16 R^2 = 0.8383 R^2A = 0.7978 F-Ratio = 20.730…….3

The developed QSAR model Eq.3 demonstrates the importance of indicator descriptors IR_1 and IR_2 with topological descriptor Jhetv. In this model Jhetv and IR_1 is negatively correlated with the antibacterial activity while IR_2 is positively correlated with the antibacterial activity. The correlation coefficient between the descriptors and antibacterial activity is r = 0.91 which is quite significant with the variance of 0.83. the PRESS/SSY is approximately 0.3 which is lower in all developed model shows that this model is best model the further addition of descriptor is prohibited due to rule of thumb according to which only one parameter is allowed for five compounds.

log 1/c mic = 8.5279(±0.6364)-0.3351(±0.1463)IR1+0.4943(±0.2149)IR2-
2.6314(±0.3910)J

n = 16 R^2 = 0.8406 R^2A = 0.8007 F-Ratio = 21.087…….4

The model Eq.4 is statistically significant model and demonstrates the importance of different combination of descriptors. In model eq.4 indicator descriptor IR2 is positively correlated while J and IR1 is negatively correlated with the antibacterial activity. The correlation coefficient between the descriptor and antibacterial activity r = 0.91 but the PRESS/SSY is slightly greater than the eq.3 indicate that this model is not best model. For the validation of developed model cross validation is applied with their descriptors is given below.

Table 4. Cross Validation Statistical parameters

Model	n	PRESS	SSY	PRESS/SSY	R^2_{cv}	S_{press}
1	16	2.1485	4.3461	0.49	0.6450	0.3664
2	16	1.9141	4.7748	0.40	0.6843	0.3548
3	16	1.5499	5.0822	0.30	0.7444	0.3112
4	16	1.7372	5.0961	0.34	0.7135	0.3295

We have under taken a cross-validation methodology for deciding the predictive power of the proposed model (Eq.1-Eq-4). This was needed because a model with good statistics may not have good predictive potential. The various cross-validated parameters, calculated for the proposed models are presented in table-4 and are discussed below. The predictivity of each was measured by the cross validated R^2_{CV}, PRESS, PRESS/SSY and S_{press}. PRESS appears to be an important cross validation parameter accounting for a good estimate of the real predictive error of the model. When its value is less than SSY, the model predicts better than by chance alone, and can be considered statistically significant. In our case (Table 4) PRESS<<SSY indicates that all models are not statistically significant. The model no.3 and 4 are only significant, it is because for the QSAR model to be considered reasonable, PRESS/SSY should be smaller than 0.4 and the data presented in Table 4 indicates that only model 3 are significant with highest R^2_{CV} = 0.74 and lowest S_{press} = 0.311 indicates that among all model, model no.3 is best and significant.

Finally, in order to confirm our findings, antibacterial activity of benzimidazoles derivatives log 1/c mic predicted by equation 3 were compared with the observed log 1/c mic value reported in **Table-5**. These comparisons are shown in **Table-5**. The values agree well within experimental error. The residual, is the difference between observed and calculated log 1/c mic.

Table 5. Antibacterial Screening Summary of Benzimidazole

Com. No.	Actual	Predicted	Residual
1	3.425	3.271	0.154
2	3.951	4.256	-0.305
3	4.278	4.269	0.009
4	4.615	4.269	0.346
5	3.676	4.127	-0.451
6	4.303	4.132	0.171
7	4.638	4.643	-0.005
8	3.121	2.963	0.158
9	3.648	3.937	-0.289
10	3.975	3.953	0.022
11	4.312	3.953	0.359
12	3.373	3.81	-0.437
13	4	3.819	0.181
14	4.335	4.33	0.005
15	4.446	4.558	-0.112
16	5.787	5.594	0.193

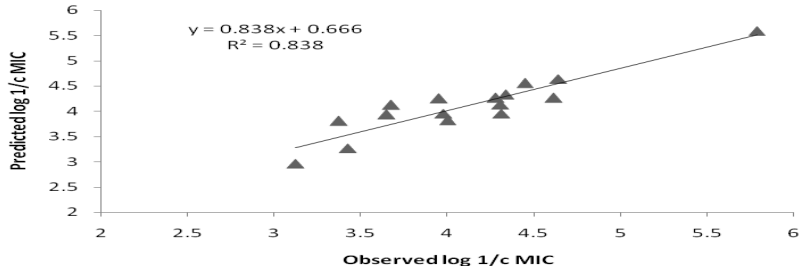


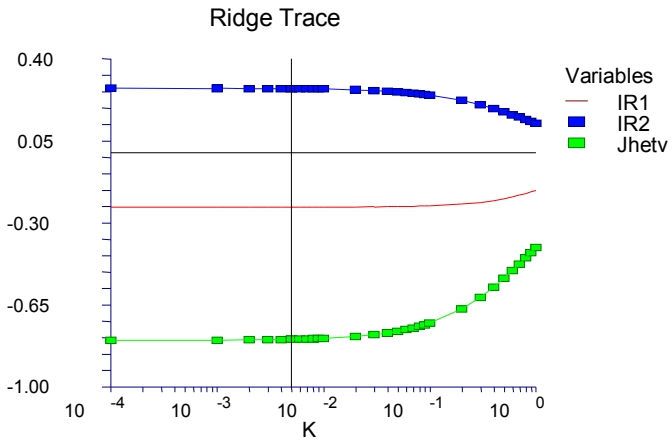
Fig 1: Graph showing Relation between Observed and Predicted Antibacterial activity

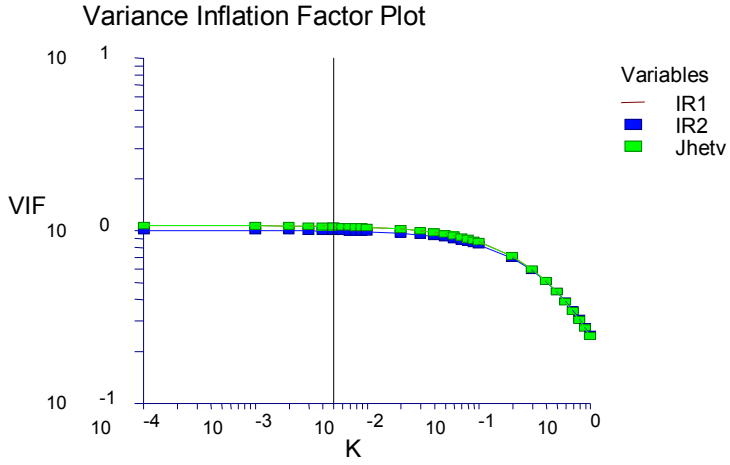
To realize the effect of multicolinearity between the descriptors which affect the variance of model we proceed the ridge trace the graph is given below which show that there is no problem of multicoliearity in the developed model.

By observing both the graph we conclude that there is no problem of multicoliearity during the process of model development.

Conclusion

- In this study topological indices namely Jhetv play an important role which is negatively correlated with the antibacterial activity therefore as the value of Jhetv decreases the antibacterial activity increases.
- Indicator descriptor IR^1 indicates that as the methylation decreases the antibacterial activity increases.
- The $ClCOCH_3$ at 4 position effects positively with antibacterial activity.





References

1. P. R. Patel, C. Ramalingan, Bioorg. Med. Chem. Lett., 17 (2007) 6610-6614.
2. R. Kharb, P.C. Sharma, M.S. Yar, J. Enz. Inhib. Med. Chem., in press
3. P. C. Sharma, S. Jain, Acta Pol. Pharm. Drug Res., 65(5) (2008) 551-586.
4. P.C. Sharma, S.V. Sharma, A. Sharma, B Suresh, Ind. J. Pharm. Sci., 70(2) (2008) 154-158.
5. P.C. Sharma, S.V. Sharma, S. Badami., Ind J. Pharm. Educ. Res., 41(2) (2007) 140-145.
6. P.C. Sharma, S.V. Sharma, S. Jain, S. Singh, Acta Pol. Pharm. Drug Res., 66(1) (2009) 101-104.
7. A. Sharma, V. Kumar, S. Jain, J. Enz. Inhib. Med. Chem. In press.
8. P.C. Sharma, S. Yadav, R. Pahwa, Med Chem Res, in press.
9. World Health Organisation (1999). Report on infectious diseases: removing obstacles to healthy development. Geneva, Switzerland.
10. P.C. Sharma, S. Jain, Acta Pharm. Sciencia, 50 (2008) 35-40.
11. R. Chawla, U. Sahoo, A. Arora, Acta Pol. Pharm. Drug Res., 67 (2010) 55-61.
12. C.G. Almeida, C.G. Diniz, V.L. Silva, Med. Chem., 5 (2009) 1-3.