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Qsar Modeling of Antibiacterial Activity of Some Benzimidazole Derivatives

Bhupendra Kumar Verma[1], Shailja Sachan[2], Balendra singh[1], Prabhanand Patel[1]
[1]*Department of Chemistry, A.P.S.University, Rewa-486003, India*
[2] *Department of Chemistry, Govt. M.S.GolvalkarCollege, Rewa-486001, India*

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ABSTRACT: Quantitative structure-activity relationship (QSAR) study fora training set of 12Benzimidazole derivatives is taken to correlate and predict the antimicrobial activity against Gram-negative bacteria Pseudomonas aeruginose. MLR is used to select the best descriptors and predict the activity of the model selected by cross validation. Our result is the based on the descriptor correlation between experimental and predicted inhibitory values got by the validation procedure. Using topological descriptors, the best model with r^2=0.9503,r^2cv=0.8907 and r^2adj=0.9317 higher values of regression coefficient indicate the validity of model and helpful to synthesize the new potent antimicrobial drugs.

Key words: Antimicrobial, Benzimidazole, molecular descriptor, QSAR.

I. INTRODUCTION

Benzimidazole is a bicyclic heteroatomic aromatic organic compound having an important antimicrobial properties specialy antifungal agent in medicinal chemistry. It is also an antitubercular, antioxidant, anticancer and antiallergic[1-5] compounds. Many benzimidazole derivatives are also effective inhibitors of the growth of HIV-virus. Albendazole, benzimidazole, fenbendazole, and their sulphoxide derivatives have a broadspectrum anthelmintic activity and used human as well as veterinary medicine. They act by binding to the fungal microbials and stopping hyphal growth. It also binds to the spindle microtubules and blocks nuclear division. They are used to cure many systemic parasitosis, including nematodoses,hidatidosis,teniasis diseases. Several benzimidazole derivatives have antiviral activity against HCV (Hepatitis C virus).[6-10]

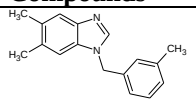
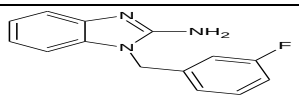
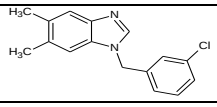
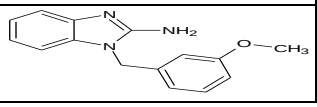
Other antimicrobial drugs which contain a benzimidazole group include etonitazene, galeterone, mavatrep, and dovitinib. Many dyes and fungicides (pesticides) are derived from benzimidazole.

QSAR method is used to estimate the characteristic of new drug molecules without the need of synthesis and test of them. It offers the possibility for screening a large number of compounds in a short time and at low cost[11-14]. It comprises three parts: the activity to be modeled and hence, predicted, data with which to model and third one a method to formulate the model. Purpose of QSAR in silico studies includes to predict biological activity and physico-chemical properties by rational means and to rationalize the mechanism of action within a series of compounds.

Presentation of data

In our present study, Table 1 represents the modeled compounds with their inhibitory activity[15]while Table 2 indicates the topological index: GNar, PW2, Psi-i-0, MLOGP2, DELS, Psi-i-1 with connectivity index X1sol.Table 3 shows the correlation matrix between the descriptors which are used in this study. Table 4 is cross Validation statistical parameters. Table 5 represents the calculated and observed inhibitory activity with residual.

Table 1. The structures of compounds studied and their antibacterial activity

S.No.	Structure of Compounds	log(1/C_{MIC})	S.No.	Structure of Compounds	log(1/C_{MIC})
1.		4.602	7.		3.981
2.		4.637	8.		3.704

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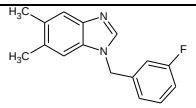
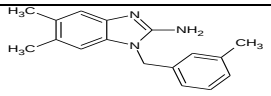
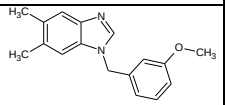
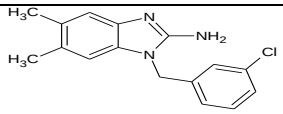
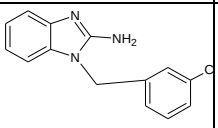
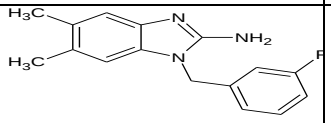
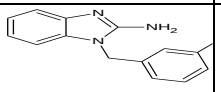
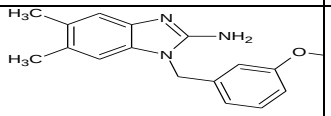
3.		4.609	9.		4.627
4.		4.328	10.		4.659
5.		4.278	11.		4.333
6.		4.314	12.		4.352

Table 2. Calculated Topological Descriptors

Comp.	log(1/C_{MIC})	GNar	PW2	Psi-i-0	MLOGP2	DELS	X1sol	Psi-i-1
1	4.602	2.081	0.591	12.333	14.981	19.092	9.131	9.703
2	4.637	2.081	0.591	12.379	17.127	18.367	9.42	9.738
3	4.609	2.081	0.591	12.24	16.142	22.754	8.737	9.63
4	4.328	2.077	0.583	12.868	10.908	19.318	9.669	10.009
5	4.278	2.12	0.581	11.705	9.851	16.303	8.737	9.129
6	4.314	2.12	0.581	11.751	11.605	15.56	9.026	9.165
7	3.981	2.12	0.581	11.611	10.755	20.033	8.343	9.056
8	3.704	2.113	0.573	12.24	6.754	16.513	9.275	9.436
9	4.627	2.048	0.596	12.884	13.186	25.192	9.542	10.202
10	4.659	2.048	0.596	12.93	15.204	24.351	9.83	10.237
11	4.333	2.048	0.596	12.79	14.276	29.197	9.148	10.129
12	4.352	2.045	0.588	13.418	9.557	25.468	10.08	10.508

II. RESULT AND DISCUSSION

In the present study different derivatives of benzimidazoles were evaluated for in vitro antimicrobial activity against Gram-negative Pseudomonas aeruginosa. QSAR works with three important components: development of models, validation of models and utility ofdeveloped models. The result of antimicrobial studies of 1-benzylbenzimidazoles against Escherichia coli are summarized in table 5. A set of 12 compounds were used for MLR model, generation using QSAR Hansch approach on benzimidazole derivatives.

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Table 3.Correlation Matrix of different descriptors

	log(1/C_{MIC})	**GNar**	**PW2**	**Psi-i-0**	**MLOGP2**	**DELS**	**X1sol**	**Psi-i-1**
log(1/C_{MIC})	1.0000							
GNar	-0.5953	1.0000						
PW2	0.8438	-0.8288	1.0000					
Psi-i-0	0.3748	-0.9205	0.5565	1.0000				
MLOGP2	0.8468	-0.4306	0.8025	0.1334	1.0000			
DELS	0.3675	-0.8661	0.7659	0.7072	0.3396	1.0000		
X1sol	0.3144	-0.7208	0.3367	0.8893	0.0059	0.3632	1.0000	
Psi-i-1	0.4803	-0.9685	0.6760	0.9882	0.2564	0.7725	0.8509	1.0000

In order to find the correlation between observed and predicting antimicrobial activity, a systemic QSAR has been carried out using the model proposed by Hansch et.al. By using the data of table 2, a correlation matrix as well as the multicollinearity between the descriptors was calculated. By the table 3.A high interrelationship between Psi-i-0 and Psi-i-1 (r=0.9882) as well as the low interrelationship between MLOGP2 and X1sol (r=-0.0059) was observed.

log (1/C_{MIC}) = 3.3726 + 0.795(MLOGP2) ……1

N = 12 R^2 = 0.7170 R^2A=0.6887, F-Ratio=25.338

The developed QSAR model eq.1 shows the importance of topological descriptor MLOGP2 which is positively correlated with the antibacterial activity which indicate that topological descriptor MLOGP2 is directly proportional to the antibacterial activity. The correlation coefficient between the descriptor and antibacterial activity (r=0.84) is not sufficient.

log (1/C_{MIC}) = -26.0471 + 53.4210(PW2) - 0.0457(DELS) ……2

N = 12 R^2=0.9000 R^2A=0.8778, F-Ratio=40.497

The combination of the topological descriptors PW2 and DELS resulted mild increase of the r value i.e. r=0.84 to r=0.94.Eq.1 indicate that the importance of DELS is negatively correlated with the antibacterial activity which means the topological descriptor DELS is inversely proportional to the antibacterial activity. The interrelationships between the above parameters r=0.7659 is medium (Table 3).Watching at this inter relationship, it seems that there is insufficient increase in the r-value. Equ. 2 does not represent the significant r value. So far the addition of more descriptors needed for development of QSAR model.

log (1/C_{MIC})=-206.3594+57.1618(GNar) + 112.4254(PW2) + 2.6154(Psi-i-1)……....3

N = 12 R^2 = 0.9430 R^2A = 0.9216 F-Ratio = 44.101

The developed QSAR model (eq .3) Demonstrate the importance of topological descriptors GNar, PW2 and Psi-i-1. The correlation coefficient between the descriptors and antibacterial activity is r=0.9711 which is quite sufficient with the variance of 0.94 the PRESS/SSY is approximately 0.1199 and F-Ratio value in not enough. For better regression expression we tried for some triparametric model.

log (1/C_{MIC})=-207.8132+52.9057(GNar)+135.0909(PW2)+1.8262 (Psi-i-0)……...4

N = 12 R^2 = 0.9503 R^2A = 0.9317 F-Ratio = 51.013

The developed QSAR model (eq.4) indicate the importance of descriptors and is significant model because all the three descriptors like GNar, PW2 and Psi-i-0 are positively correlated with the antibacterial activity. The correlation coefficient between the descriptors and antibacterial activity r=0.9748 which is quite significant with the R^2=0.9503.The PRESS/SSY is approximately 0.1093 which is the lowest value in all developed model, showed that this model is the best.

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Table 4: Cross Validation Statistical parameters

Model	N	PRESS	SSY	PRESS/SSY	R^2_{CV}	S_{press}
1	12	0.4149	0.9417	0.4406	0.5594	1.8975
2	12	0.1936	0.9417	0.2056	0.7945	1.2735
3	12	0.1122	0.9417	0.1191	0.8809	0.9301
4	12	0.1029	0.9417	0.1093	0.8907	0.9293

Table 5: Antibacterial Screening Summary of Benzimidazole

Compound	Actual	Predicted	Residual
1	4.602	4.644	-0.042
2	4.637	4.728	-0.091
3	4.609	4.475	0.134
4	4.328	4.329	-0.001
5	4.278	4.210	0.068
6	4.314	4.294	0.020
7	3.981	4.038	-0.057
8	3.704	3.736	-0.032
9	4.627	4.580	0.047
10	4.659	4.664	-0.005
11	4.333	4.409	-0.076
12	4.352	4.316	0.036

To realize the effect of multicolinearity between the descriptors which affects the activity of model we proceed the ridge trace the graph which show that there is mild multicolinearity problem does not affect the variance of developed model.

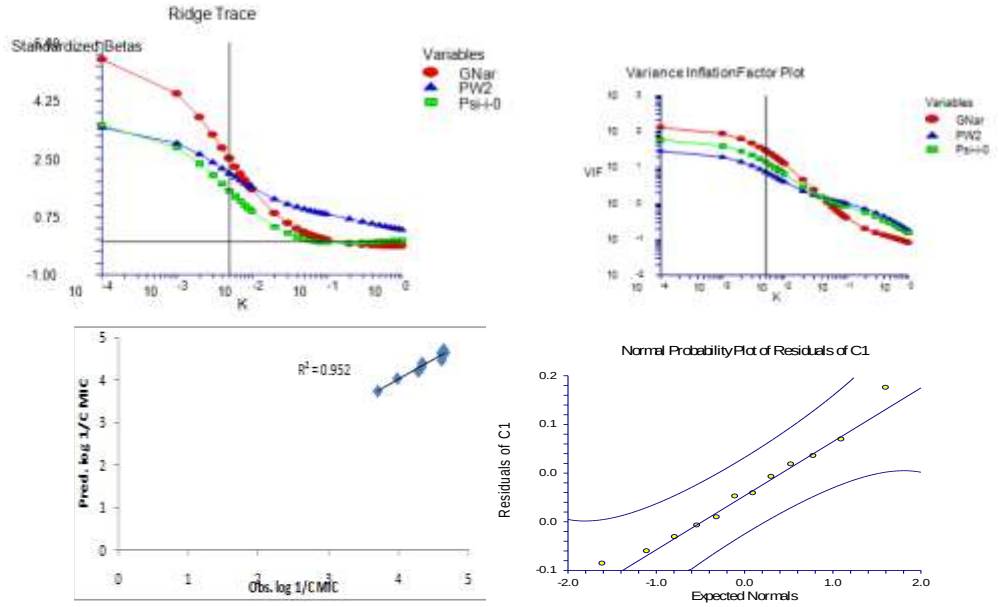

Fig 1: Graph showing relation between observed and predicted antibacterial activity

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III. CONCLUSION

In view of result and discussions, we conclude that topological descriptor GNar, PW2 and Psi-i-0 can be successfully used for modeling benzimidazole derivatives as antimicrobial drugs. These results will help in pharmaceutical science for design and prediction of new benzimidazoles drugs exhibiting better activities than these reported in this result.

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