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MODELING OF 5- OR 6- METHYL- 2-SUBSTITUTED BENZOXAZOLES / BENZIMIDAZOLES - A POTENT INHIBITOR OF FUNGAL INFECTION

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ABSTRACT

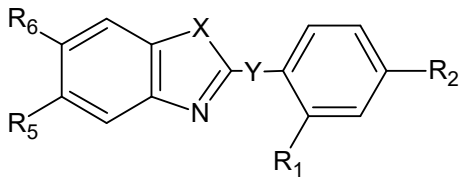
Benzoxazoles and its derivatives comprise an important class of therapeutic compounds which have gained much importance because of its wide applications in medicinal sector. A quantitative structure–activity relationships (QSAR) study using Multiple Linear Regression (MLR) methodology was performed for a series of 5- or 6- methyl- 2-substituted Benzoxazoles / Benzimidazoles , a potent inhibitor of fungal infection. QSAR models have been developed to predict the activities in terms of log 1/C using Dragon descriptors. A bi-parametric model containing MW and IP_1 is the best model for modeling antifungal activities of the present set of compounds. The model predictability was tested by cross validation parameters.

Key words: benzoxazoles, QSAR, MLR, anti-fungal, cross validation

INTRODUCTION

Studies have shown that fungal infection has increased tremendously in recent years. This may be because of greater use of antibiotics, acquired immunodeficiency syndrome epidemic, use of immunosuppressive drugs, intensive care low birth weight infants, use of catheters etc [1-13]. A major breakthrough was obtained in 1970 when azole drugs were developed for antifungal chemotherapy. Benzoxazoles and its derivatives comprise an important class of therapeutic compounds which have gained much importance because of its wide applications in medicinal sector. Now efforts were made to synthesize

different derivatives to make use of their potential profiles associated with diverse pharmacological activities such as analgesic, anti-tuberculosis [14], antibacterial [15], antifungal[16], anti-inflammatory, antioxidant and anthelmintic activity [17]. Recent observations suggest that substituted benzoxazoles and related heterocycles, possesses potential activity with lower toxicities in the chemotherapeutic approach in man. It was a common practice when the above objectives were fulfilled that these existing molecules be further modified. Benzoxazoles were found to be best antifungal agents and therefore the focus was on the modification of these molecules for better activity. The general structure of benzoxazoles is given below.



Benzoxazoles Structure

MATERIALS AND METHODS

QSAR analysis of some 5- or 6- methyl-2-substitutedbenzoxazoles/ benzimidazoles was studied for the antifungal activity against *C. albicans* using Hansch analysis. Prediction for the lead optimization in this QSAR analysis was attributed by the description of various hydrophobic, electronic, steric and structural parameters related to positions R_1, R_2, R_5, R_6, & Y. The cross validation method was also applied to the data set in order to prove the predictive power by using the NCSS statistical software. The resulting QSAR revealed that substitution at position Y with the CH_2 group was significant for the improved antifungal activity. Moreover, hydrophobic properties of the substituent at position R2 are indicative for the antifungal activity against *C. Albicans.* The position 2 and 5 are very important for the biological activity of these compounds [18-20]. Arpaci has reported the synthesis and in-vitro anti-fungal activity of different 5-or 6-methyl-2-substituted benzoxazoles or benzimidazoles against the fungus Candida albicans [21-23]. In this work an attempt has made to model the biological activity of a series of benzoxazoles and benzimidazoles using physico-chemical as well as topological indices.

The biological activity has taken in terms of minimum inhibitory concentration in the unit µg per ml while modeling the anti-fungal activity log 1/C has been used. The general structure of the molecule and their structural details are reported in Table 1.this table also contains activity value in terms of log 1/C. The physico- chemical parameters used for the present study are MW, MR, MV, P, IR,

and ST. These parameters have been calculated using ACD lab software [24]. The topological indices used in the present study are W. J_{hetz}, J_{hetm}, J_{hetv} and J_{hetp}. All these topological indices were calculated using Dragon software [25]. For modeling the activity and indicator parameter, IP_1 has been used. IP_1 has assigned a value of one if CH_2 is present at y, otherwise its value has been taken as zero. The data was subjected to regression analysis for modeling the biological activity of these compounds. The correlation matrix (Table 3) was obtained for understanding the co-relatedness of various parameters. It has been observed that no auto correlation exist among the parameters. However, IP_1 itself is competent in modeling antifungal activity of compounds used in the present study.

Therefore presence of CH_2 group at **y** itself is very important in the exhibition of antifungal activity. The regression analysis yielded many significant models which are reported in Table 4. Interestingly physico- chemical parameters are best suited for modeling the anti fungal activity of these compounds as compared to topological indices. The mono-parametric and bi-parametric correlations obtained are reported in Table 4. As discussed earlier, when IP_1 was combined with physico-chemical parameters, then MV, MR and MW were found to be the only parameters which are useful. ST has not been useful in any combination obtained for modeling the activity. The three bi-parametric models are shown as below:

1. $Log1/C=0.0019\pm(0.0006)MV+0.3055\pm(0.0149)IP_1+3.6242$

$N=25, R^2=0.9511., R^2_A=0.9467, Se=0.0082, F=321.379, Q=118.9321$

2. $Log1/C=0.0071\pm(0.0015)\ MR+0.2906\pm(0.0119)\ IP_1+3.4848$

$N=25, R^2=0.9669, R^2_A=0.9639, Se=0.0067, F=321.379, Q=146.7628$

3. $Log1/C=0.2984(\pm0.0006)IP_1+0.0017(\pm0.0000)\ Mw+3.5778$

$N=25, R^2=0.9999, R^2_A=0.9999, Se=0.0004, F=113530.1, Q=2499.875$

RESULTS AND DISCUSSION

However, the one containing MW and IP_1 is the best for modeling the biological activity. The R^2 value for the model comes out as 0.9999 whereas the adjusted R^2 value also shows similar magnitude. The standard error of estimation is very low whereas the F value is very large. Just to confirm our result we have estimated log 1/C values of these compounds and found that they are in excellent agreement with the observed values. Such a comparison is given in Table 5. To confirm the result of observed and estimated activity using model 5, we have plotted a graph which has been demonstrated in figure 1. The predictive power of the model has come out to be 0.99 which is

further confirmed by cross validation parameters. The lowest PSE, S_{press} and PRESS/SSY value confirmed that the bi-parametric model containing MW and IP_1 is the best model for modeling antifungal activities of the present set of compounds. The cross validated R^2 value comes out to be 0.9999. This model is free from all defects as evident from ridge trace and VIF analysis given in Table 7. The parameters whose VIF value is greater than 10 will show co linearity. A perusal of this table shows that in all the cases VIF are less than 10 which mean that all the proposed models reported by us are free from co linearity. Similarly if λ (Eigen value) is found to be greater than 5 then the model will suffer from co linearity. The Table 7 shows that for all the parameters λ is less than 5. Therefore, from this point of view also proposed models are free from the defect of co linearity. Another test for co linearity is condition number (k) if its value is found to be >100 then the co linearity exists but the values reported in Table 7 indicates that the values are <100. Tolerance value (T) equal to1or less indicates absence of co linearity. Table 7 indicates that all the above mentioned parameters or models discussed in the study are free from multi co linearity.

Table 1: Compounds used in the present study along with observed log1/C values

Compd. no	R_1	R_2	R_5	R_6	X	Y	Obs.log1/C
1	Cl	H	CH_3	H	O	_	3.989
2	OCH_3	H	CH_3	H	O	_	3.980
3	NO_2	H	CH_3	H	O	_	4.007
4	Cl	Cl	CH_3	H	O	_	4.046
5	CH_3	CH_3	CH_3	H	O	_	3.977
6	OCH_3	OCH_3	CH_3	H	O	_	4.032
7	Cl	H	H	CH_3	O	_	3.989
8	OCH_3	H	H	CH_3	O	_	3.980
9	F	H	H	CH_3	O	_	3.958
10	NO_2	H	H	CH_3	O	_	4.007
11	Cl	Cl	H	CH_3	O	_	4.046
12	CH_3	CH_3	H	CH_3	O	_	3.977
13	OCH_3	OCH_3	H	CH_3	O	_	4.032
14	H	H	CH_3	H	O	CH_2	4.251
15	H	Br	CH_3	H	O	CH_2	4.383
16	H	NH_2	CH_3	H	O	CH_2	4.280
17	H	H	H	CH_3	O	CH_2	4.251
18	H	H	CH_3	H	NH	CH_2	4.249
19	H	Cl	CH_3	H	NH	CH_2	4.312
20	H	Br	CH_3	H	NH	CH_2	4.382
21	H	NH_2	CH_3	H	NH	CH_2	4.278
22	H	H	CH_3	H	O	CH_2O	3.980
23	H	H	CH_3	H	O	CH_2S	4.009
24	H	H	CH_3	H	NH	CH_2S	4.007
25	H	Cl	CH_3	H	NH	CH_2O	4.037

Table 2: Calculated values of physico-chemical and topological parameters of compounds used in the present study

Compd.	J_{hetZ}	J_{hetm}	J_{hetv}	J_{hetp}	W	Mw	MR	MV	P	IR	ST	IP_1

No.												
1	2.45	2.45	1.80	1.71	505	243.68	68.79	193	506.1	1.63	47.2	0
2	2.42	2.42	1.69	1.59	592	239.27	70.58	205.1	526.9	1.60	43.5	0
3	2.46	2.46	1.71	1.59	681	254.24	70.44	192.9	525.7	1.65	55	0
4	2.456	2.46	1.80	1.73	599	278.13	73.69	205	541.9	1.64	48.8	0
5	2.36	2.36	1.80	1.71	599	237.30	73.55	213.6	545.5	1.60	42.4	0
6	2.385	2.38	1.63	1.52	809	269.30	77.26	229.1	583.5	1.59	42	0
7	2.434	2.44	1.74	1.65	505	243.69	68.79	193	506.1	1.63	47.2	0
8	2.402	2.40	1.64	1.54	592	239.27	70.58	205.1	526.9	1.60	43.5	0
9	2.407	2.41	1.68	1.57	505	227.23	63.89	185.3	477.3	1.61	44	0
10	2.446	2.45	1.67	1.55	681	254.24	70.44	192.9	525.7	1.65	55	0
11	2.439	2.44	1.75	1.67	599	278.13	73.69	205	541.9	1.64	48.8	0
12	2.344	2.34	1.75	1.66	599	237.30	73.55	213.6	545.5	1.60	42.4	0
13	2.37	2.37	1.59	1.48	809	269.30	77.26	229.1	583.5	1.59	42	0
14	1.973	1.97	1.55	1.47	545	223.27	68.62	195.2	507.9	1.62	45.8	1
15	1.973	1.97	1.55	1.49	650	302.17	76.31	211.4	558.4	1.64	48.6	1
16	1.941	1.94	1.53	1.46	650	238.28	72.86	197.5	533.7	1.66	53.3	1
17	1.961	1.96	1.51	1.43	545	223.27	68.62	195.2	507.9	1.62	45.8	1
18	1.939	1.94	1.65	1.58	545	222.29	70.75	190.7	513.5	1.66	52.5	1
19	1.932	1.93	1.64	1.58	650	256.73	75.65	202.7	549.4	1.67	53.9	1
20	1.941	1.94	1.65	1.59	650	301.18	78.44	206.9	564	1.68	55.1	1
21	1.909	1.91	1.62	1.56	650	237.30	74.99	193	539.3	1.70	60.9	1
22	1.949	1.95	1.17	1.08	672	239.27	70.47	200.5	525.6	1.62	47.2	0
23	2.235	2.24	1.48	1.54	672	255.33	76.56	205.6	563.8	1.67	56.4	0
24	2.193	2.19	1.57	1.65	672	254.35	78	203.1	569.9	1.69	62	0
25	1.91	1.91	1.22	1.14	793	272.73	77.5	208	567.1	1.67	55.2	0

IP_1 (Indicator parameter) =When Y=CH_2, IP_1=1

Table 3: Correlation matrix

	log1/C	J_{hetm}	Mw	MV	ST	IP_1
log1/C	1					
J_{hetm}	-0.7753	1.0000				
Mw	0.2181	0.0183	1.0000			
MV	-0.1072	0.1366	0.5124	1.0000		
ST	0.3337	-0.4172	0.1928	-0.3737	1.0000	
IP_1	0.9659	-0.7986	-0.0416	-0.2458	0.2860	1.0000

Table 4: Regression parameters and quality of correlation

Model No.	Parameters used	Ai=(1……2)	B	Se	R^2	R^2_A	F-ratio	Q=R/Se
1	Mw	0.0014±(0.0013)	3.7400	0.0354	0.0476	0.0062	1.1490	6.1631
2	IP_1	0.2951±(0.0165)	4.0031	0.0094	0.9331	0.9301	320.584	102.7629
3	MV IP_1	0.0019±(0.0006) 0.3055±(0.0149)	3.6242	0.0082	0.9511	0.9467	321.379	118.9321
4	MR IP_1	0.0071±(0.0015) 0.2906±(0.0119)	3.4848	0.0067	0.9669	0.9639	321.379	146.7628
5	Mw IP_1	0.0017±(0.0000) 0.2984±(0.0006)	3.5778	0.0004	0.9999	0.9999	113530.1	2499.875

Table 5: Observed and estimated values of log1/C using model 5

Compd. No	Obs.log1/C	Est.log1/C	Residual
1	3.989	3.988	0.001
2	3.980	3.981	-0.001
3	4.007	4.006	0.001
4	4.046	4.046	0.000
5	3.977	3.977	0.000
6	4.032	4.031	0.001
7	3.989	3.988	0.001
8	3.980	3.981	-0.001
9	3.958	3.961	-0.003
10	4.007	4.006	0.001
11	4.046	4.046	0.000
12	3.977	3.977	0.000
13	4.032	4.031	0.001
14	4.251	4.252	-0.001

15	4.383	4.385	-0.002
16	4.280	4.278	0.002
17	4.251	4.252	-0.001
18	4.249	4.251	-0.002
19	4.312	4.309	0.003
20	4.382	4.384	-0.002
21	4.278	4.276	0.002
22	3.980	3.981	-0.001
23	4.009	4.008	0.001
24	4.007	4.006	0.001
25	4.037	4.037	0.000

Table 6: Cross validation parameters of proposed models

Model No.	Parameters used	PRESS	SSY	PRESS/SSY	R^2_{CV}	S_{PRESS}	PSE
1	Mw	0.4836	0.0241	20.0664	-19.0664	0.1450	0.1391
2	IP_1	0.0339	0.4738	0.0715	0.9285	0.0384	0.0368
5	Mw IP_1	0.0000492	0.5077	0.0001	0.9999	0.0015	0.0014

Table 7: Variance inflation factor (VIF), Eigen Values (λ), Tolerance (T), Condition number (k) values for the proposed models.

Names of Independent variable	Variance inflation	Eigen value	Condition no.	Tolerance
Mw	1.0017	0.0416	1.0000	0.9983
IP_1	1.0017	0.9584	1.0900	0.9983

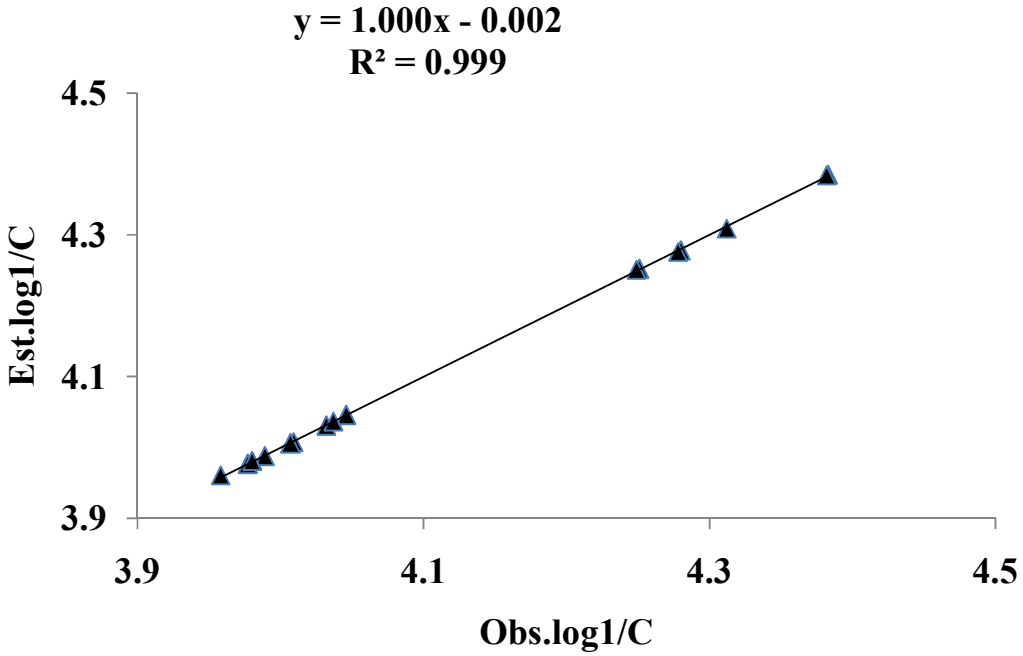


Fig 1: Correlation between observed and estimated log1/C using model 5

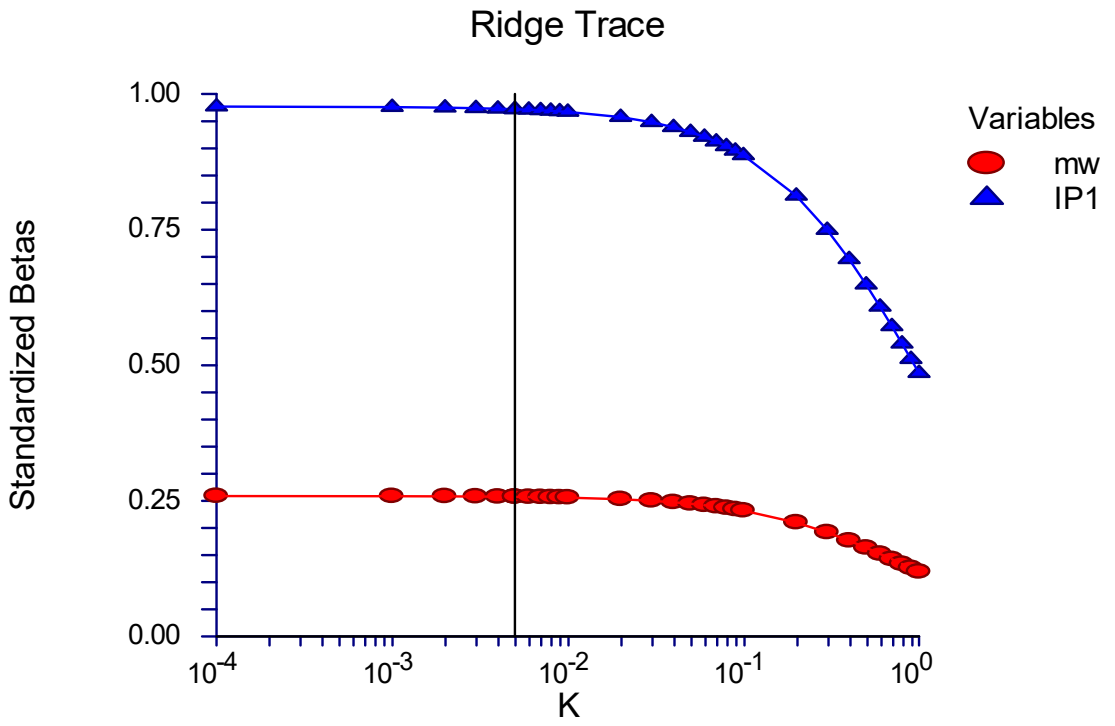


Fig.2

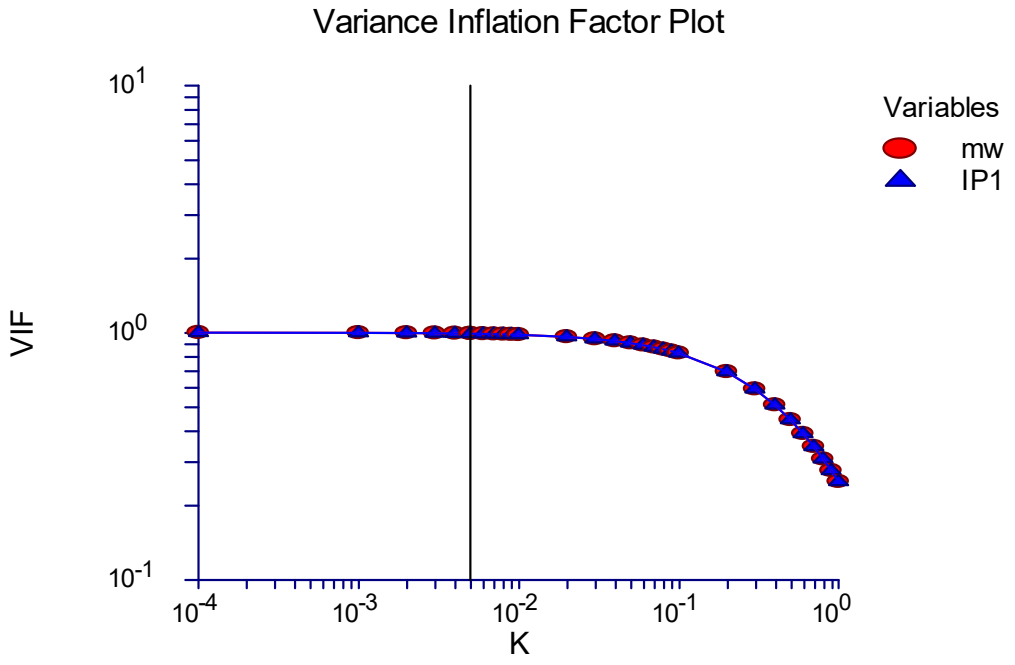


Fig.3

CONCLUSION

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

For modeling the activity an indicator parameter, IP1 has been used. Since the indicator parameter has positive coefficient, presence of CH2 group at y itself is very important in the exhibition of antifungal activity of the present set of compounds. Coefficient for MW is also positive suggesting that a higher value of MW will favour the log 1/C activity. Therefore, while designing new antifungal agents of this series High value of MW and presence of CH2 group at y will certainly give better potent anti-fungal drugs.

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