QSAR STUDY ON ANTIBACTERIAL EFFECTS OF BENZIMIDAZOLE AND IMIDAZOPYRIDINE DERIVATIVES

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A set of benzimidazole (*I*) and imidazopyridine (*II*) derivatives previously tested for their antibacterial activities against *Staphylococcus aureus (S. aureus)*, *Pseudomonas aeruginosa (P. aeruginosa)*, *Escherichia coli (E. coli)*, and *Bacillus subtilis (B. subtilis)* were analyzed by quantitative structure–activity relationship (QSAR) and the activity contributions for structural and substituent effects were determined using multiple regression procedure. The resulting QSAR revealed that for the activity contribution against *S. aureus* and *P. aeruginosa* the substituents of *p*-position on the phenyl moiety play important role, and besides the *p*-substituents the substituents in other positions improve the activity. For the potency against *E. coli*, the character of six membered ring of the fused ring system becomes important besides the substituents effects at the *p*-position of the phenyl group. It was also found that both the benzimidazole ring system and *p*-substituted benzyl moiety have significant structural effects besides the lipophilicity of the substituents at R^3 for the activity against *B. subtilis*.

The imidazole nucleus and its related structures are known to play a crucial role in the structure and functioning of a number of biologically important molecules. Among them, benzimidazole is one of the most important heterocyclic rings which showed different biological activities, for examples antibacterial[1–8], antifungal[2–10], antiparasitic[11–13], antiviral[14,15], anticancer[16] activities.

Over the last few years, Pedini et al.[2,5] studied the antibacterial and antimycotic activities of a series of 103 thienyl and furyl substituted benzimidazoles and benzoxazoles. They selected a set of 16 representative compounds, and used linear PLS modelling in order to establish quantitative relationships between the antibacterial activities of a number of benzimidazoles and benzoxazoles[17]. They obtained a straightforward interpretation of the structural features relevant to the activities and the prediction of a possible optimal structure. Most of the imidazo[4,5-*b*]- and [4,5-*c*]pyridines are bio-

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logically active. A number of their 2-alkyl derivatives showed herbicidal[18,19], antibacterial[20] and antihistaminic[21] activities.

In this work, the QSAR of the previously synthesized benzimidazoles[22,23] and imidazo[4,5-*b*]pyridines[24] against *S. aureus*, *E. coli*, *B. subtilis* and *P. aeruginosa* was analyzed.

The substituents R^1, R^2, and R^3 in the compounds are both electron donating and electron withdrawing groups. The antibacterial activity contributions for either ring systems or substituent effects have been determined from the correlation equations.

The Hansch approach has been widely used to understand drug action by analyzing the structure–activity relationships in various biological systems[25]. An important aspect of these studies is to find a relationship between biological properties of the molecules and their physicochemical factors governing the transport and drug–receptor interaction and also the structural and theoretical effects. These physicochemical parameters can be factored into electronic (E), hydrophobic (H) and steric (S) components. A general form of this assumption is given in Eq. (*1*).

$$\text{BA (biological activity)} = f_e(\text{E}) + f_s(\text{S}) + f_h(\text{H}) + f_i(\text{I}) \ldots \qquad (1)$$

EXPERIMENTAL

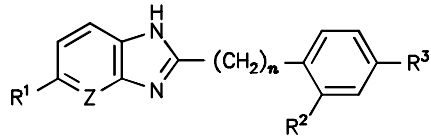
2-Phenyl (*Ia–Ij*) and 2-benzyl (*Ik–Iv*) benzimidazoles and 2-phenyl imidazopyridines (*II*) have been synthesized previously using the reported procedures[22–24]. IR, ^{1}H NMR spectra and elemental analyses were used to characterize these compounds.

Biological Activity

The antibacterial activities of the compounds *I* and *II* against *S. aureus*, *P. aeruginosa*, *E. coli* and *B. subtilis* were determined previously[23,24,26] using the tube dilution method[27] and given as minimum inhibitory concentration (MIC, μg/ml). The potency has been defined as log (1/*C*) in the QSAR analysis where *C* is the molar MIC value of the compounds and is used as the dependent variable in the study. The values of dependent variables which are appeared in the correlation equations are given in Table I.

Calculations

The multiple regression analysis which involves finding the best fit of a dependent variable (microbiological activity) to a linear combination of independent variables by the least square method was used. Stepwise regression procedure was applied for the selection of descriptors. Correlation and regression analysis were performed using SPSS computer program package[28]. The probability of *F* value of each variable to enter in the regression was choosen as $p \leq 0.05$ and that to remove from the equation was choosen as $p > 0.05$ to develop the best fitted model of correlation equations. In order to judge the validity of the predictive power of the QSAR, cross-validation method was applied to the original data set. For this purpose PRESS (Predictive Residual Sum of Squares) was calculated according to Eq. (*2*) (refs[29,30]).



I, II

	R^1	R^2	R^3	Z	*n*
Ia	CH_3	OCH_3	OCH_3	CH	0
Ib	Cl	CH_3	CH_3	CH	0
Ic	NO_2	CH_3	H	CH	0
Id	H	H	CH_3	CH	0
Ie	H	OCH_3	H	CH	0
If	CH_3	OCH_3	CH_3	CH	0
Ig	NO_2	CH_3	CH_3	CH	0
Ih	H	H	OCH_3	CH	0
Ii	Cl	H	H	CH	0
Ij	CH_3	H	OCH_3	CH	0
Ik	H	H	NO_2	CH	1
Il	H	H	Cl	CH	1
Im	Cl	H	Br	CH	1
In	Cl	H	CH_3	CH	1
Io	Cl	H	NH_2	CH	1
Ip	Cl	H	Cl	CH	1
Iq	NO_2	H	OCH_3	CH	1
Ir	NO_2	H	OC_2H_5	CH	1
Is	NO_2	H	NO_2	CH	1
It	CH_3	H	CH_3	CH	1
Iu	CH_3	H	OCH_3	CH	1
Iv	CH_3	H	OC_2H_5	CH	1
IIa	H	H	H	N	0
IIb	H	H	Cl	N	0
IIc	H	H	CH_3	N	0
IId	H	H	C_2H_5	N	0
IIe	H	H	$C(CH_3)_3$	N	0
IIf	H	H	F	N	0

TABLE I
Observed (obs.) and calculated (calc.) values of biological activities of compounds *I* and *II*

Compound	*S. aureus*		*P. aeruginosa*		*E. coli*		*B. subtilis*	
	obs.[a]	calc.[b]	obs.[a]	calc.[b]	obs.[a]	calc.[b]	obs.[a]	calc.[b]
Ia	4.08	4.11	4.08	4.03	3.78	3.76	4.08	4.04
Ib	4.01	4.04	4.01	3.90	4.01	3.95	–	–
Ic	4.06	4.09	4.06	4.11	3.76	3.76	4.06	4.05
Id	4.29	4.07	3.99	4.02	3.99	3.95	4.29	4.34
Ie	–	–	4.02	4.00	3.71	3.76	4.02	4.05
If	4.36	4.33	4.06	4.02	–	–	–	–
Ig	4.39	4.31	4.08	4.14	–	–	4.39	4.35
Ih	4.02	3.85	4.02	4.03	3.71	3.76	4.02	4.04
Ii	–	–	4.03	3.99	3.72	3.76	–	–
Ij	3.74	3.74	–	–	3.74	3.76	–	–
Ik	3.40	3.34	3.70	3.77	3.70	3.71	3.70	3.78
Il	–	–	3.69	3.73	3.69	3.70	–	–
Im	3.81	3.75	–	–	3.81	3.81	4.41	4.39
In	4.01	3.95	4.01	4.02	–	–	4.31	4.23
Io	3.41	3.59	–	–	3.71	3.74	–	–
Ip	–	–	3.74	3.73	3.74	3.70	4.35	4.31
Iq	4.05	3.99	4.35	4.26	3.75	3.76	4.06	3.92
Ir	4.07	4.10	–	–	4.07	4.02	4.08	4.14
Is	3.36	3.47	4.02	4.00	3.72	3.71	3.72	3.78
It	3.95	3.96	3.95	4.02	3.95	3.95	–	–
Iu	3.98	3.74	3.98	4.03	–	–	3.98	3.92
Iv	3.71	3.85	4.01	4.05	–	–	4.01	4.14
IIa	3.89	3.86	–	–	3.89	3.92	–	–
IIb	3.81	3.85	3.81	3.73	3.81	3.87	3.81	3.89
IIc	3.92	4.07	–	–	4.23	4.11	3.92	3.81
IId	4.25	4.19	–	–	4.25	4.34	3.95	4.06
IIe	4.30	4.47	4.00	4.04	–	–	4.60	4.57
IIf	3.63	3.74	–	–	3.63	3.57	3.63	3.58

[a] Defined as log (1/*C*); [b] calculated using Eq. (*3*); [c] calculated using Eq. (*4*); [d] calculated using Eq. (*5*); [e] calculated using Eq. (*6*).

$$\text{PRESS} = \sum_i [(y_i - \bar{y}_i)^2/(1 - h_{ii})^2] \qquad (2)$$

here y_i and $\bar{y}_i$ are the response (activity) values of observation i (i = 1, 2, …, n), observed and calculated by the best equation, respectively. The diagonal elements of that matrix are denoted by h_{ii} in the equation, and calculated by the SPSS computer program.

Hydrophobic, electronic, steric and structural parameters used as descriptors are given in Table II. The structural variable I_Z expresses the replacement of –CH= by the group of –N= in the six membered ring of the fused ring system. I_Z is defined as 0 for type *I* and 1 for type *II* compounds. The other structural variable I_Y, which is used to represent the $(CH_2)_n$ group between the phenyl moiety and the fused ring system has a value of 1 for n = 1 and 0 for n = 0. The hydrogen donating/accepting capabilities (*HDONOR*/*HACCEPT*) of the substituents R^1, R^2, and R^3 are also used as the descriptors. The physicochemical parameters used in this work are π for the hydrophobic effects, *F* (field effect), *R* (resonance effect) as the electronic influences, *MR* (the molar refractivity) of the R^1, R^2, and R^3 substituents. *MR* values were scaled by 0.1 in the analysis. This makes *MR* and the other parameters approximately equiscalar. Values of all these physicochemical variables for R^1, R^2, and R^3 substituents were taken from the tables given by Hansch[25].

RESULTS AND DISCUSSION

The best fitted equations for the activities against *S. aureus*, *P. aeruginosa*, *E. coli*, and *B. subtilis* are given in Table III.

Activity Against S. aureus

Applied regression analysis of the activity against *S. aureus* and validation test results showed that Eq. (*3*) (Table III) is the best fitted equation for the predictions. In all the equations given, the values in parentheses are the standard errors of the regression coefficients, n is the number of compounds, R^2 is the square of multiple correlation coefficients, F is the significant test, and s is the standard error of estimate. The overall F test value is 19.89 at the significant level of $p < 0.0001$. The stepwise development of Eq. (*3*) reveals that the five physicochemical variables, F_{R^3}, π_{R^3}, R_{R^1}, R_{R^2}, and R_{R^3} all together significantly account for 85% of the variance in the activity against *S. aureus* at $p < 0.0001$ level. The resonance effects R_{R^2} (F = 14.50, p = 0.0013) and R_{R^3} (F = 5.15, p = 0.0357) cause a decrease while the resonance effect R_{R^1} (F = 11.56, p = 0.0032) produces an increase in activity against *S. aureus*. Equation (*3*) also shows that the electronic substituent effect F_{R^3} at R^3 (F = 22.00, p = 0.0002) is important and produces a negative effect on the potency. The positive coefficient of π_{R^3} indicates that more lipophilic substituents are generally favored at this position and cause an increase in the activity (F = 25.91, p = 0.0001). The negative coefficients of R_{R^2} and R_{R^3} indicate that the electron releasing substituents increase the potency while electron-withdrawing substituents decrease it. The negative coefficient of F_{R^3} suggests that electron-with-

drawing (through field-inductive effects) substituents at the R^3 position are not favored for increasing the potency. Correlation matrix of variables used in Eq. (*3*) is given in Table IV. It reveals that there is no colinearity between the independent variables.

TABLE II
Values of hydrophobic, electronic, steric and structural parameters for compounds *I* and *II*

Compound	π_R^2	π_R^3	F_R^3	R_R^1	R_R^2	R_R^3	MR_R^3	I_Z	I_Y	$HACCEPT_R^1$	$HACCEPT_R^3$
Ia	–0.02	–0.02	0.26	–0.13	–0.51	–0.51	7.87	0	0	0	1
Ib	0.56	0.56	–0.04	–0.15	–0.13	–0.13	5.65	0	0	0	0
Ic	0.56	0.00	0.00	0.16	–0.13	0.00	1.03	0	0	1	0
Id	0.00	0.56	–0.04	0.00	0.00	–0.13	5.65	0	0	0	0
Ie	–0.02	0.00	0.00	0.00	–0.51	0.00	1.03	0	0	0	0
If	–0.02	0.56	–0.04	–0.13	–0.51	–0.13	5.65	0	0	0	0
Ig	0.56	0.56	–0.04	0.16	–0.13	–0.13	5.65	0	0	1	0
Ih	0.00	–0.02	0.26	0.00	0.00	–0.51	7.87	0	0	0	1
Ii	0.00	0.00	0.00	–0.15	0.00	0.00	1.03	0	0	0	0
Ij	0.00	–0.02	0.26	–0.13	0.00	–0.51	7.87	0	0	0	1
Ik	0.00	–0.28	0.67	0.00	0.00	0.16	7.36	0	1	0	1
Il	0.00	0.71	0.41	0.00	0.00	–0.15	6.03	0	1	0	0
Im	0.00	0.86	0.44	–0.15	0.00	–0.17	8.88	0	1	0	0
In	0.00	0.56	–0.04	–0.15	0.00	–0.13	5.65	0	1	0	0
Io	0.00	–1.23	0.02	–0.15	0.00	–0.68	5.42	0	1	0	1
Ip	0.00	0.71	0.41	–0.15	0.00	–0.15	6.03	0	1	0	0
Iq	0.00	–0.02	0.26	0.16	0.00	–0.51	7.87	0	1	1	1
Ir	0.00	0.38	0.22	0.16	0.00	–0.44	12.47	0	1	1	1
Is	0.00	–0.28	0.67	0.16	0.00	0.16	7.36	0	1	1	1
It	0.00	0.56	–0.04	–0.13	0.00	–0.13	5.65	0	1	0	0
Iu	0.00	–0.02	0.26	–0.13	0.00	–0.51	7.87	0	1	0	1
Iv	0.00	0.38	0.22	–0.13	0.00	–0.44	12.47	0	1	0	1
IIa	0.00	0.00	0.00	0.00	0.00	0.00	1.03	1	0	0	0
IIb	0.00	0.71	0.41	0.00	0.00	–0.15	6.03	1	0	0	0
IIc	0.00	0.56	–0.04	0.00	0.00	–0.13	5.65	1	0	0	0
IId	0.00	1.02	–0.05	0.00	0.00	–0.10	10.30	1	0	0	0
IIe	0.00	1.98	–0.07	0.00	0.00	–0.13	19.62	1	0	0	0
IIf	0.00	0.14	0.43	0.00	0.00	–0.34	0.92	1	0	0	0

TABLE III
The best fitted equations for the predictions of the activities against *S. aureus*, *P. aeruginosa*, *E. coli* and *B. subtilis*

No.	Equation	*n*	R^2	*s*	*F*
(*3*)[a]	$\log 1/C = -0.601(\pm0.128)F_R^3 + 0.267(\pm0.052)\pi_R^3 - 0.725(\pm0.190)R_R^2 + 0.851(\pm0.250)R_R^1 - 0.298(\pm0.131)R_R^3 + 3.862$	24	0.85	0.13	19.89
(*4*)[b]	$\log 1/C = -0.631(\pm0.075)F_R^3 + 0.196(\pm0.037)HACCEPT_R^3 + 0.236(\pm0.042)HACCEPT_R^1 - 0.211(\pm0.089)\pi_R^2 + 3.993$	20	0.87	0.06	25.78
(*5*)[c]	$\log 1/C = -0.569(\pm0.053)F_R^3 + 0.452(\pm0.042)MR_R^3 + 0.165(\pm0.028)I_Z + 0.300(\pm0.054)R_R^3 + 3.709$	22	0.93	0.05	52.98
(*6*)[d]	$\log 1/C = 0.537(\pm0.041)\pi_R^3 - 0.538(\pm0.056)I_Z - 0.114(0.042)I_Y + 4.047$	20	0.92	0.08	61.20

[a] Equation (*3*) for the activity against *S. aureus*; [b] Eq. (*4*) for the activity against *P. aeruginosa*; [c] Eq. (*5*) for the activity against *E. coli*; [d] Eq. (*6*) for the activity against *B. subtilis*.

TABLE IV
Correlation matrix of variables used in Eq. (*3*)

	$\log 1/C$	F_R^3	π_R^3	R_R^2	R_R^1	R_R^3
$\log 1/C$	1.00					
F_R^3	–0.69	1.00				
π_R^3	0.63	–0.36	1.00			
R_R^2	–0.38	0.17	0.01	1.00		
R_R^1	0.12	0.16	–0.01	0.20	1.00	
R_R^3	0.01	0.03	0.33	0.04	0.29	1.00

TABLE V
Correlation matrix of variables used in Eq. (*4*)

	$\log 1/C$	F_R^3	$HACCEPT_R^3$	$HACCEPT_R^1$	π_R^2
$\log 1/C$	1.00				
F_R^3	–0.46	1.00			
$HACCEPT_R^3$	0.21	0.60	1.00		
$HACCEPT_R^1$	0.50	0.09	0.16	1.00	
π_R^2	0.19	–0.35	–0.31	0.49	1.00

Activity Against P. aeruginosa

The stepwise development of Eq. (*4*) (Table III) begins by the selection of MR_{R^1} as the first variable in the equation correlated with the activity. Then F_{R^3} with the highest partial correlation coefficient enters into the equation. $HACCEPTR_{R^3}$ enters at the third step and $HACCEPTR_{R^1}$ enters at the fourth step. Then MR_{R^1} is removed by the program from the model at the fifth step because this variable provides a non-significant contributions at 0.05 significant level ($F = 0.18$, $p = 0.6781$). The variable π_{R^2} enters into the equation at the sixth stage. In the QSAR analysis, Eq. (*4*) indicates that the overall F test value is 25.78 that is statistically significant at the $p < 0.0001$ level.

The four predictors F_{R^3}, $HACCEPT_{R^3}$, $HACCEPT_{R^1}$, and π_{R^2} altogether significantly correlate with the activity and account for 87% of the variance in the activity. The electronic influences of negative field effects F_{R^3} enhance the potency ($F = 71.30$, $p < 0.0001$). The hydrogen accepting capabilities of the substituents $HACCEPT_{R^3}$ and $HACCEPT_{R^1}$ produce additive contributions to the activity in the positive direction with ($F = 28.29$, $p = 0.0001$) and ($F = 31.03$, $p = 0.0001$), respectively. On the other hand, lipophilic effect π_{R^2} induces negative contribution to the potency ($F = 5.56$, $p = 0.0324$). Negative dependence on π indicates that the biological activity is expected to be larger when the character of the substituents at R^2 is less lipophilic. The negative influence of lipophilicity was already noted and interpreted as a reflection of hydrophobic binding between the binding sites[31,32]. Correlation matrix of variables in Eq. (*4*) is given in Table V. It shows that there is no high intercorrelation in a set of predictor variables.

Activity Against E. coli

QSAR analysis reveals that for the biological activity against *E. coli*, Eq. (*5*) (Table III) is the best fitted equation. The stepwise development of this equation shows that overall F test value is 52.98 which is statistically significant at the $p < 0.0001$ level.

The four predictors, F_{R^3}, MR_{R^3}, I_Z, and R_{R^3} together significantly correlate with the activity and account for 93% of the variance. The fitted model indicates that electronic influences of negative field effects F_{R^3} highly enhance the potency ($F = 117.18$, $p < 0.0001$). The molar refractivity MR_{R^3} is also highly significant for the activity ($F = 116.39$, $p < 0.0001$) in the positive direction. The positive coefficient on MR_{R^3} term indicates that the bulkier group R^3 facilitates the activity of the benzimidazole and imidazopyridine derivatives against *E. coli*. The resonance effect R_{R^3} produces a positive effect on the potency ($F = 30.54$, $p < 0.0001$). Besides these features, Eq. (*5*) shows that the structural parameter I_Z is also significant ($F = 35.44$, $p < 0.0001$). This result reveals that the six-membered ring of the fused system is favorable against *E. coli*. The search of the simple correlation coefficients of predictors given in Table VI indicates no high relationships between independent variables.

Activity Against B. subtilis

Equation (*6*) (Table III), the best fitted equation for the activity against *B. subtilis*, shows that the overall F test value is 61.20, which is statistically significant at the $p < 0.0001$ level. The predictor variables π_{R^3}, I_Z, and I_Y altogether significantly account for 92% of the variance in the activity. The fitted model showes that π_{R^3} causes a highly significant positive effect on the potency ($F = 172.32$, $p < 0.0001$). The structural parameters I_Z and I_Y also induce some influences on the activity. In the fused ring system I_Z has some

TABLE VI
Correlation matrix of variables used in Eq. (*5*)

	log 1/*C*	F_{R^3}	MR_{R^3}	I_Z	R_{R^3}
log 1/*C*	1.00				
F_{R^3}	–0.54	1.00			
MR_{R^3}	0.37	0.30	1.00		
I_Z	0.40	–0.13	–0.19	1.00	
R_{R^3}	0.10	0.09	–0.35	0.14	1.00

TABLE VII
Correlation matrix of variables used in Eq. (*6*)

	log 1/*C*	π_{R^3}	I_Z	I_Y
log 1/*C*	1.00			
π_{R^3}	0.66	1.00		
I_Z	–0.20	0.55	1.00	
I_Y	–0.002	–0.23	–0.52	1.00

TABLE VIII
The calculated overall PRESS and SSY (sum of the squares of the response values of the total observations) values

	PRESS	SSY	PRESS/SSY
S. aureus	0.5278	1.6447	0.3209
P. aeruginosa	0.1249	0.3755	0.3326
E. coli	0.0951	0.5963	0.1595
B. subtilis	0.1332	1.1571	0.1151

importance in the negative direction (F = 92.44, p < 0.0001). The contribution of the structural parameter I_Y also shows that the compounds having methylene group moiety in the structure causes a decrease in the activity (F = 7.44, p = 0.0149). Correlation matrix of variables used in Eq. (*6*) (Table VII) reveals that a low intercorrelation in a set of descriptors is produced. For this reason, the regression analysis was performed effectively.

To show the validity of Eqs (*3*), (*4*), (*5*), and (*6*) (Table III), the cross-validation is applied to the original data set and the resulting PRESS is calculated. The calculated overall PRESS and SSY (sum of the squares of the response values of the total observations) values for each biological activity are given in Table VIII.

The calculated overall PRESS values for each biological activities are smaller than the values of SSY of the given sets. This proves that the best fitted equations predict better than chance and can be considered statistically significant[29,30]. The ratios PRESS/SSY for each set, which are the approximate confidence interval of prediction of new compounds, are smaller than 0.4. This result shows that our QSAR model is highly predictive and reasonable[30], and these investigations can be helpful for a further investigation on the antibacterial benzimidazoles and imidazopyridine derivatives.

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