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THE QUANTITATIVE STRUCTURE-ACTIVITY RELATIONSHIPS OF ANTIBACTERIAL ACTIVE 2-(p-SUBSTITUTED-PHENYL) BENZOXAZOLE DERIVATIVES AGAINST GRAM (—) BACTERIA USING THE COMBINATIONS OF SOME HYDROPHOBIC, ELECTRONIC AND STERIC PARAMETERS

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Key Word Index

2-(p-Substituted-phenyl) benzoxazoles, π, π^2, σ, F, R, MR, MW, P_r, QSAR, Best equation, E. coli, K. pneumonia, P. aeruginosa.

ABSTRACT

In this research, the quantitative structure-activity relationships of antibacterial active 2-(p-substituted-phenyl) benzoxazole derivatives against gram (—) bacteria were studied. Some hydrophobic (π, π^2), electronic (σ, F, R) and steric (MR, MW, P_r) constants were used as physicochemical parameters. The correlation equations of these relationships were given.

For the correlation of the antibacterial activity against gram (—) bacteria with the molecular criteria in the series of 2-phenylbenzoxazoles, the combinations of hydrophobic, electronic or steric parameters were found more significant as compared to hydrophobic, electronic or steric parameters used separately. The best equations obtained from QSAR studies were stated.

INTRODUCTION

Quantitative drug design can contribute both to the discovery of new therapeutic agents and to the progress of biomedical research in general. Developing techniques are becoming increasingly more capable of directing synthetic effort from compounds that have a low probability of success. For example, following the discovery of penicillin as an effective and useful antibiotic in the treatment of bacterial disease, many investigators set out to modify the structure of the molecule to improve its efficacy while reducing adverse side effects. Penicillin thus became a 'lead' structure-the point of departure for further synthesis and biological testing. For discovering a better drug, the lead structure can be modified by changing substituent groups. In the case of penicillin, for 20 substituents (including hydrogen) attached to 3 of the 5 available positions of the phenyl ring and the number of possible analogues is 36537[1]. Quantitative structure-activity relationships can reduce such synthetic effort from compounds that have a low probabilty of success and increase the chances of discovering successfull drugs.

Many benzoxazole derivatives were synthesized and their biological activities were studied, but not much work has been reported on the quantitative structure activity relationship studies (QSAR). Only Evans et al. carried out QSAR studies on some antiinflammatory active 2-substituted, 4 - and 7-benzoxazoleacetic and α-methylacetic acids[2] and Ayopova et al. investigated the quantitative relationships between 2-(alkylthio) benzoxazole derivatives and their herbicide activity using Hansch's equations[3].

It was stated by David et al. that five-membered heterocyles condensed with 2 benzene rings were chemotherapeutically active[4]. Antimicrobial active 2-phenylbenzoxazole derivatives having 2 benzene rings and a 5 membered heterocycle are in agreement with that postulate[5-13].

Benzoxazoles substituted at C-2 were prominently studied[10-20] trusting that this position is decisive for the biological activity. Evans et al. showed that para substituted 2-aryl-5-benzoxazolealkanic acid derivatives had the highest activity compared to its analogs[16,17]. Consequently, para substituted derivatives of 2-phenylbenzoxazoles were chosen for QSAR studies.

In our previous paper, the synthesis, structure elucidations and determination of antibacterial activity of 2-(p-substituted-phenyl)benzoxazoles against some gram (—) bacteria such as Escherichia coli, Klepsiella pneumonia and Pseudomonas aeruginosa were given[11]. In this research, we want to study these structurally similar compounds and their physicochemical parameters in order to design of more active compounds in these series. The antibacterial activity of these compounds are thought as the function of the physicochemical parameters on this lead optimization method.

We select some steric, electronic and hydrophobic parameters which are shown in Table - 1 for our quantitative structure activity relationship studies. The multiple regression analysis method is used which involves finding the best fit of a dependent variable (the microbiological activity) to a linear combination of the independent variables (descriptors) by the method of least squares. This is formally expressed as follows;

$$y = a_0 + a_1x_1 + a_2x_2 + \ldots\ldots\ldots + a_nx_n$$

where $x_1, x_2, \ldots\ldots\ldots x_n$ are the descriptor values (physicochemical substituent constants), y is related to the microbiological activity of benzoxazole derivatives, and $a_1, a_2, \ldots\ldots a_n$ are the coefficients determined by a least squares analysis. This equation is developed for each benzoxazole derivative in our analysis.

The use of this method with physicochemical substituent constants and quantitative biological data forms the basis for the Hansch analysis. This metodology has also been called physicochemical structure-activity relationship (PSAR) approach and has been used primarily to analyse data on sets of congeners[21]. In general, this approach is to set up the equations involving different combinations of the substituent constants, then to allow the correlative method to aid in the selection of the best equation for our study.

EXPERIMENTAL

Material

Regression analysis equations of the QSAR studies were performed by using IBM-XT computer working with Microstat Statistic Package.

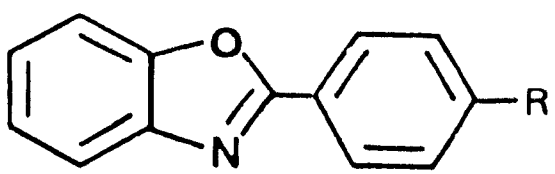
TABLE — 1 : Physicochemical parameters.

Physicochemical parameter	Symbol	Type of Effect
Pi substituent constant	π	Hydrophobic
Pi substituent constant	π^2	Hydrophobic
Sigma substituent constant	σ	Electronic
Field effect	$\mathcal{F}$	Electronic
Resonance effect	$\mathcal{R}$	Electronic
Molar refractivity	MR	Steric
Molecular weight	MW	Steric
Parachor	P_r	Steric

Determination of the parameters

Parachor (P_r) relates principally to molecular volume[22] and it is used in QSAR studies[23]. P_r values of each compound were calculated by the additive summation of the P_r values of all the atoms and the structural features using Quayle's Table[24]. π, π^2, σ, F, R, MR and MW values were taken from the table given by Hansch et al.[25]. These values were shown in Table - 2.

TABLE — 2 : The physicochemical parameters of 2-(p-substituted-phenyl)benzoxazole derivatives.



R	π	π^2	σ_p	$\mathcal{F}$	$\mathcal{R}$	MR	MW	P_r
H	0.00	0.0000	0.00	0.00	0.00	1.03	1.0	400.9
OCH_3	-0.02	0.0004	-0.27	0.26	-0.51	7.87	31.0	460.1
$C(CH_3)_3$	1.98	3.9204	-0.20	-0.07	-0.13	19.62	57.1	557.2
Cl	0.71	0.5041	0.23	0.41	-0.15	6.03	35.4	440.6
Br	0.86	0.7396	0.23	0.44	-0.17	8.88	79.9	453.4
NH_2	-1.23	1.5129	-0.66	0.02	-0.68	5.42	16.0	427.9
$NHCH_3$	-0.47	0.2209	-0.84	-0.11	-0.74	10.33	30.1	470.9

RESULTS

The quantitative structure-activity relationships of 2-(p-substitutedphenyl)benzoxazole derivatives were studied. Antibacterial activities of the compounds against gram (—) bacteria such as Escheria coli, Klepsiella pneumoniae and Pseudomonas aeroginosa were chosen as the biological activity. The merity of some hydrophobic (π, π^2), electronic (σ, F, R) and steric (MR, MW, P_r) parameters in correlating the biological activities of the compounds with the structural properties has been examined by multiple regression analysis. Log 1/C values were used in the regression equations, where C was the molar concentrations of the MIC values of the compounds[11]. The data on the parameters were stated in Table - 2. Observed and predicted values of log 1/C were given in Table - 10. The regression equations stated in Tables - 3, 5 and 7 and the parameters in the best equations were selected according to the correlation matrixes (Tables - 4, 6 and 8) and the squares of their partial regression coefficients. The best equations designed for E. coli, K. pneumoniae and P. aeruginosa were shown in Table - 9.

TABLE — 3 : Regression equations generated for 2-(p-substituted-phenyl)benzoxazole derivatives in E. coli

Equ. No	Equations
1	log 1/C = -0.29(±0.07)π + 3.61 n: 7 ; R^2: 0.7845 ; s: 0.17 ; F: 18.20
2	log 1/C = -0.30(±0.10)π + 0.03(±0.24)σ + 3.61 n: 7 ; R^2: 0.7852 ; s: 0.19 ; F: 7.31
3	log 1/C = -0.37(±0.07)π + 0.53(±0.25)σ - 0.33(±0.36)F + 3.87 n: 7 ; R^2: 0.9327 ; s: 0.12 ; F: 13.85
4	log 1/C = -0.09(±0.45)π - 0.12(±1.06)σ - 0.57(±0.70)F -0.09(±0.06) MR + 3.33 n: 7 ; R^2: 0.9440 ; s: 0.14 ; F: 8.42
5	log 1/C = -0.44(±0.05)π + 0.61(±0.12)σ - 0.82(±0.06)F -0.09(±0.01)MR + 0.01(±0.01)P_r -0.77 n: 7 ; R^2: 0.9987 ; s: 0.01 ; F: 682.72 ($P < 0.05$)

C is the molar concentrations of the MIC values of the compounds[11], the numbers in paranthesis in the regression equations represent the standart errors of the regression coefficients, n is the number of the compounds, R^2 is the square of the multiple correlation coeffi-

cient, s is standart deviation of the regression and F ise the F test for the significance of the regression, P is the probability of F test.

TABLE — 4 : Correlation matrix between regression parameters for 2-(p-substituted-phenyl)benzoxazole derivatives in E. coli.

	Log 1/C	π	σ	$\mathcal{F}$	MR	P_r
Log 1/C	1.00					
π	-0.89	1.00				
σ	-0.52	0.61	1.00			
$\mathcal{F}$	-0.40	0.21	0.74	1.00		
MR	-0.71	0.66	-0.14	-0.25	1.00	
P_r	-0.68	0.68	-0.13	-0.25	0.99	1.00

TABLE — 5 : Regression equations generated for 2-(p-substituted-phenyl)benzoxazole derivatives in K. pneumoniae.

Eq. no	Equations
1	log 1/C = 0.15(±0.13) π^1 + 3.73 n: 7 ; R^2: 0.1947 ; s: 0.45 ; F: 1.21
2	log 1/C = 0.13(±0.11) π^2 - 0.66(±0.37) σ + 3.60 n: 7 ; R^2: 0.5434 s: 0.38 F: 2.44
3	log 1/C = 0.03(±0.06) π^1 + 0.15(±0.29) σ - 2.03(±0.55) $\mathcal{F}$ + 4.15 n: 7 ; R^2: 0.9183 s: 0.19 F: 11.24
4	log 1/C = 0.12(±0.10) π^1 + 0.05(±0.30) σ - 1.06(±0.56) $\mathcal{F}$ -0.02(±0.02) MR + 4.23 n: 7 ; R^2: 0.9483 s: 0.13 F: 9.18
5	log 1/C = -0.05(±0.01) π^1 - 0.17(±0.01) σ - 1.44(±0.02) $\mathcal{F}$ +0.14(±0.00) MR_4 - 0.02(±0.00) P_r + 12.91 n: 7 ; R^2: 0.9999 ; s: 0.01 ; F: 3175.75 (P<0.02)

TABLE — 6 : Correlation matrix between regression parameters for 2-(p-substituted-phenyl)benzoxazole derivatives in K. pneumoniae.

	log 1/C	π^2	σ	$\mathcal{F}$	MR	P_r
log 1/C	1.00					
π^2	0.44	1.00				
σ	-0.62	-0.05	1.00			
$\mathcal{F}$	-0.95	-0.35	0.74	1.00		
MR	0.21	0.80	-0.15	-0.25	1.00	
P_r	0.18	0.78	-0.13	-0.25	0.99	1.00

TABLE — 7 : Regression equations generated for 2-(p-substituted-phenyl)benzoxazole derivatives in P. aeruginosa.

Eq. no	Equations
1	log 1/C = -0.42(±0.12)π + 3.86 n: 7 ; R^2: 0.7166 ; s: 0.21 ; F: 12.77
2	log 1/C = -0.41(±0.17)π - 0.43(±0.58)$\mathcal{F}$ + 3.31 n: 7 ; R^2: 0.7503 ; s: 0.22 ; F: 8.06
3	log 1/C = -0.29(±0.21)π - 0.73(±0.73)$\mathcal{F}$ - 0.03(±0.04) MR + 4.17 n: 7 ; R^2: 0.7933 ; s: 0.24 ; F: 3.85
4	log 1/C = -0.39(±0.08)π - 0.63(±0.29)$\mathcal{F}$ - 0.28(±0.06) MR +0.03(±0.00) P_f - 7.73 n: 7 ; R^2: 0.9788 ; s: 0.13 ; F: 23.08 (P<0.05)

TABLE — 8 : Correlation matrix between regression parameters for 2-(p-substituted-phenyl)benzoxazole derivatives in P. aeruginosa.

	log 1/C	π	$\mathcal{F}$	MR	P_f
log 1/C	1.00				
π	-0.85	1.00			
$\mathcal{F}$	-0.36	0.21	1.00		
MR	-0.62	0.66	-0.25	1.00	
P_f	-0.56	0.68	-0.25	0.99	1.00

TABLE — 9 : Best equations generated for 2-(p-substituted-phenyl) benzoxazole derivatives in gram (—) bacteria.

System	Equation
E.coli	log 1/C = -0.44(±0.05)π + 0.61(±0.12)σ - 0.93(±0.08)$\mathcal{F}$ -0.09(±0.00) MR + 0.01(±0.01) P_f - 0.77 n: 7 ; R^2: 0.9997 ; s: 0.01 ; F: 602.72 (P<0.05)
K.pneumoniae	log 1/C = -0.05(±0.01)π^2 - 0.17(±0.01)σ - 1.44(±0.02)$\mathcal{F}$ +0.14(±0.00) MR - 0.02(±0.00) P_f + 12.91 n: 7 ; R^2: 0.9999 ; s: 0.00 ; F: 3178.75 (P<0.02)
P. aeruginosa	log 1/C = -0.39(±0.08)π - 0.63(±0.29)$\mathcal{F}$ - 0.28(±0.06) MR + 0.03(±0.00) P_f - 7.73 n: 7 ; R^2: 0.9788 ; s: 0.13 ; F: 23.08 (P<0.05)

TABLE — 10 : Antibacterial activity of 2-(p-substituted-phenyl)benzoxazole derivatives (log 1/C).

Com. No	E. coli			K. pneumoniae			P. aeruginosa		
	Obsd	Calcd	Residual	Obsd	Calcd	Residual	Obsd	Calcd	Residual
1	2.89	3.62	0.27	4.19	4.19	0.00	4.19	3.86	0.33
2	3.65	3.61	0.04	3.35	3.35	0.00	4.26	3.87	0.39
3	3.10	3.02	0.08	3.30	3.30	0.00	3.01	3.00	0.01
4	3.36	3.41	-0.05	3.36	3.37	-0.01	3.36	3.55	-0.19
5	3.14	3.37	-0.23	3.44	3.43	0.01	3.14	3.49	-0.35
6	3.82	3.86	-0.04	4.23	4.23	0.00	4.23	4.39	-0.16
7	3.65	3.73	-0.08	4.26	4.26	0.00	3.95	4.06	-0.11

DISCUSSION

The QSAR study reveals that there is relationship between the antibacterial activity of the compounds against gram (—) bacteria and the combination of hydrophobic, electronic and steric parameters. It is an interesting discovery that the parameters used alone do not show good correlations with the activity. However, when the parameters are used in combinations significant relationships can be seen with the biological activities. The P values of the F-tests for best equations are found less than 0.05. This situation shows that the descriptors are related to the dependent variables[26].

As a result of regression analysis, the activity against E. coli is fundementally a function of the combination of some hydrophobic (π), electronic (σ, F) and steric (MR, P_r) parameters. When π and σ have been tested in the absence of steric parameters R^2 values are predicted as 0.7845 and 0.7852 (Table : 3). With the participation of F and MR the R^2 values are increased (R^2=0.9327, 0.9440). The best equations involve π (hydrophobic), σ, F (electronic), MR, P_r (steric) together (R^2=0.9997).

It is found similar with the activity against K. pneumoniae and P. aeruginosa. The combinations of some hydrophobic, electronic and steric parameters create the best equations (Table - 9).

With the help of QSAR studies the most active compounds among antibacterial active 2-(p-substituted-phenyl)benzoxazoles against gram (—) bacteria can be found by using these best equations without synthesizing them. Thus, synthetic effort from compounds that have a low probability of success among these derivatives can be reduced.

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