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THE QUANTITATIVE STRUCTURE - ACTIVITY RELATIONSHIPS OF ANTIHISTAMINIC ACTIVE 5-SUBSTITUTED-2-(p-SUBSTITUTED-BENZYL)-BENZOXAZOLE DERIVATIVES

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Key Word Index

5-Substituted-2-(p-substituted-benzyl)benzoxalozes, log P, P_r, MR, *F*, *R*, Quantitative Structure Activity Relationships.

ABSTRACT

In this reserarch, quantitative structure-activity relationships of antihistaminic active 5-substituted-2-(p-substituted-benzyl)benzoxazoles were studied using various hydrophobic, steric and electronic parameters such as log P (experimental), parachor, molar refractivity, field effect and resonance effect. The linear correlation equations of these relationships were given.

For the correlation of the antihistaminic properties with the molecular criteria in the series of 2-benzylbenzoxazoles, log P was found as more merited parameter as compared to P_r, MR, *F* or *R*.

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INTRODUCTION

The importance of quantitative structure-activity relationships (QSAR) in medicinal and pharmaceutical chemistry has become clear in the last decade. In early years, it was reported that the biological activity of a compound is a function of its chemical structure [1]. This concept has been expanded to consider biological activity as a function of physicochemical (structural, physical and chemical) properties[2].

Benzoxazole derivatives have been known for long for their multiple biological activity, because they are izosters of naturally occuring cyclic nucleotides [3] and they may easily intereact with the biopolymers of the organism. Among these benzoxazole derivatives 2-benzylbenzoxazoles have the ability to consume suitable conformations and their property favors the possibility for binding to biopolymers easily. The different types of the substituents of this ring system are important for the selectiveness of the activity.

Benzoxazoles substituted at C-2 were prominently studied[4-12] trusting that this position is decisive for the biological activity whereas position 5[6,8,12,13] prevaling the intensity of the activity. Evans et al. showed that para substituted 2-aryl-5-benzoxazole-alkanoic acid derivatives had the highest activity compared to analogs[6,8]. Also Benoxaprofen[5,8] and Zoxazolamine[8] are the kind of benzoxazole derivatives which are substituted at both 2 and 5 positions.

Consequently, in this research 5-substituted-2-(p-substituted-benzyl) benzoxazoles have been selected as the target compounds for the quantitative structure-activity relationship studies. Totally, 15 compounds which were carrying H, Cl and NO_2 groups at the 5[th] position and H, OCH_3, Cl, Br, NO_2 groups at the para position were studied[14-16].

In our previous papers the synthesis, structure elucidations and determination of antihistaminic activities of these compounds were given[14-16].

Although many benzoxazole derivatives were synthesized and their biological activities were studied, not much work has

been reported on the quantitative structure-activity relationship studies. Only Evans et al. carried out QSAR studies on some antiinflammatory active 2-substituted, 4- and 7- benzoxazoleacetic and α-methylacetic acids[17] and Ayopova et al. investigated the quantitative relationships between 2-(alkyltio)benzoxazole derivatives and their herbicide activity using Hansch's equations[18].

It was reported that the activity of a compound is a function of three separable factors : electronic effects, steric effects and solvent-partitioning or hydrophobic effects, with provision for structural or therotical effects[19] as shown below;

f(biological activity) = f(electronic) + f(steric) + f(hydrophobic) + [f(structural) + f(theoretical)]

For that reasons the quantitative relationships between the structures and the activity of the compounds were studied by using various hydrophobic, steric and electronic parameters such as log P (experimental)[20,21], parachor (P_r)[22-24], molar refractivity (MR)[25], field effect (F)[25] and resonance effect (R)[25].

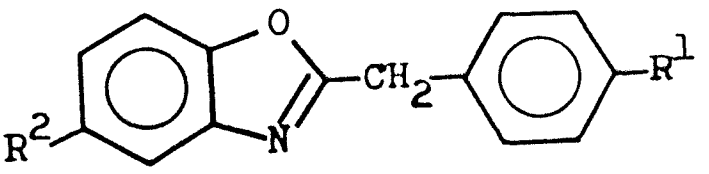
RESULTS AND DISCUSSION

In our previous studies, 5-substituted-2-(p-substituted-benzyl) benzoxazole derivatives were synthesized by heating an appropriate o-aminophenol derivative and phenylacetic acid derivative in the presence of polyphosphate ester or polyphosphoric acid[14-16].

Antihistaminic activity of the compounds were determined earlier using Magnus method[26] that works with guinea-pig ileum in isolated organ bath[14-16]. The compounds and their percent inhibitions against histamine-induced contractions were given in Table 1.

The merity of the parameters, log P (experimental) as well as P_r, MR, F, R in correlating the biological activity of the compounds with structural properties has been examined by regression analysis. The data on the parameters were stated in Tables 2 and 3.

Table 1 : 2-Benzylbenzoxazole derivatives and their ($1.24 x10^{-8}$ mol/ml) % inhibition values against histamine-induced contractions.



Comp. No	*R^1*	*R^2*	*% Inh.*
1	H	H	22.05
2	OCH_3	H	29.56
3	Cl	H	47.56
4	Br	H	58.11
5	NO_2	H	18.62
6	H	Cl	49.59
7	OCH_3	Cl	63.77
8	Cl	Cl	69.45
9	Br	Cl	75.43
10	NO_2	Cl	35.27
11	H	NO_2	28.16
12	OCH_3	NO_2	31.43
13	Cl	NO_2	52.72
14	Br	NO_2	65.79
15	NO_2	NO_2	11.04

Table 2: Log P values of 2-benzylbenzoxazole derivatives.

Comp. No	*The amount of the compound in l-octanol*	*The amount of the compound in H_2O (Buffer)*	*Log P*
1	10.4719	0.5281	1.2973
2	12.7683	0.6317	1.3056
3	10.8735	0.4264	1.4065
4	12.6645	0.3355	1.5769
5	10.2340	0.5660	1.2572
6	11.7154	0.3845	1.4838
7	11.4081	0.2419	1.6736
8	11.9712	0.2295	1.7174
9	11.3000	0.2000	1.7520
10	10.1680	0.4320	1.3718
11	9.5238	0.4762	1.3010
12	11.0643	0.5357	1.3150
13	11.5570	0.3430	1.5275
14	11.0756	0.2245	1.6932
15	11.8814	0.7186	1.2184

Table 3: P_r, MR, F and R values of 2-benzylbenzoxazole derivatives.

Comp. No	P_r	MR	F	R
1	445.1	1.03	0.00	0.00
2	504.9	7.87	0.26	−0.51
3	488.6	6.03	0.41	−0.15
4	501.4	8.88	0.44	−0.17
5	486.7	7.36	0.67	0.16
6	484.4	6.03	0.41	−0.15
7	543.7	13.90	0.67	−0.66
8	528.3	12.06	0.82	−0.30
9	541.1	14.91	0.85	−0.32
10	526.4	13.36	1.08	0.01
11	486.6	7.36	0.67	0.16
12	545.6	15.23	0.93	−0.35
13	530.2	13.39	1.08	0.01
14	541.1	14.91	0.85	−0.32
15	528.3	14.72	1.34	0.32

The regression analysis equations were given below:

1) $\%\ \text{Inh.} = -112.88\ (\mp 8.83) + 107.40\ (\mp 6.00)\ \log P$

$n: 15;\ R^2: 0.961;\ s: 4.14;\ F: 319.98$

2) $\%\ \text{Inh.} = -105.08\ (\mp 19.98) + 108.97\ (\mp 7.15)\ \log P - 0.02\ (\mp 0.04)\ P_r$

$n: 15;\ R^2: 0.962;\ s: 4.28;\ F: 149.65$

3) % Inh. = −113.77(∓9.09) + 109.39(∓6.73) log P — 0.19(∓0.27) MR

n: 15; R^2: 0.963; s: 4.23; F: 153.98

4) % Inh. = −111.46(∓8.96) + 107.91(∓6.03) log P — 3.10(∓3.16) *F*

n: 15; R^2: 0.964; s: 4.16; F: 159.54

5) % Inh. = −107.37(∓10.51) + 103.10(∓7.46) log P — 5.02(∓5.16) *R*

n: 15; R^2: 0.964; s: 4.16; F: 159.53

6) % Inh. = −245.11(∓95.57) + 104.00(∓7.58) log P + 0.31(∓0.22) P_r −2.07(∓1.38) MR

n: 15; R^2: 0.968; s: 4.08; F: 111.33

7) % Inh. = −129.06(∓30.46) + 104.59(∓8.27) log P — 0.05(∓0.07) P_r −5.96(∓5.73) *F*

n: 15; R^2: 0.965; s: 4.27; F: 101.22

8) % Inh. = −95.83 (∓21.82) + 104.83(∓8.17) log P — 0.03(∓0.04) P_r −5.57(∓5.38) *R*

n: 15; R^2: 0.965; s: 4.27; F: 101.22

9) % Inh. = −294.5(∓158.60) + 104.95(∓8.23) log P + 0.417(∓0.35) P_r −3.07(∓2.89) MR + 4.57(∓11.43) *F*

n: 15; R^2: 0.969; s: 4.25; F: 77.04

10) % Inh. = −456.9(∓279.80) + 105.61(∓7.95) log P + 0.78(∓0.62) P_r −4.92(∓3.80) MR + 11.39(∓14.11) *R*

n: 15; R^2: 0.970; s: 4.15; F: 80.75

11) % Inh. = −108.87(∓11.43) + 105.48(∓8.58) log P — 0.69(∓1.57) MR + 6.53(∓20.29) *F* — 9.24(∓14.28) *R*

n: 15; R^2: 0.966; s 4.43; F: 70.34

12) % Inh. = $-694.20(\mp413.10) + 104.63(\mp8.20)$ log P + $1.31(\mp0.92)$ P_r $-6.48(\mp4.34)$ MR — $22.25(\mp28.03)$ F + $37.09(\mp35.43)$ R

n : 15 ; R^2 : 0.972 ; s : 4.22 ; F : 62.55

% Inh. is the percent inhibitions of equal mol-grams (1.24×10^{-8} mol/ml) of the compounds against the contractive activity of histamine, the numbers in paranthesis in the regression coefficients, n is the number of the compounds, R^2 is the square of the multiple correlation coefficient, s is the standart deviation of the regression and F is the F test for the significance of the regression.

The outcome of regression analysis shows that antihistaminic activity of compounds is fundamentally a function of their relative lipophilicity as defined by the logs of octanol-water partition coefficients.

5-Chloro substituted derivatives have the highest activity and the highest liposolubility. Two compounds (No : 8 and 9) exhibit an activity against the contractive effect of histamine which is superior to the others. For the rest of the compounds, substitution of benzyl group at the para position with OCH_3, Cl, Br increase the activity together with log P, whereas substitution with nitro groups generally results in decrease due to deactivating effects. On the countrary, when the compounds are substituted with nitro groups at position 5, except 5-nitro-2-(p-nitrobenzyl)benzoxazole (No : 15), they become more active, because of their better liposolubility, than those that are not substituted at position 5. The decrease of the activity of the compound 15 is due to the fact that the nitro group being at the para position has unfavorable inductive and mesomeric effects. These effects are superior to liposolubility of nitro group at position 5.

From the results it could be concluded that, for the correlation of the antihistaminic properties with the molecular criteria in the series of 2-benzylbenzoxazoles, log P is more merited parameter as compared to P_r, MR, F and R. The introduction of P_r, MR, F and R to the regression analysis cause small increases

in the correlation coefficient, because these parameters play role in binding of the molecules to the receptors.

EXPERIMENTAL

Material

UV maxima for log P determination were measured on a Pye Unicam SP 1700 spectrometer. The solutions were prepared 1.69×10^{-5} M in l-octanol. Regression analysis equations of the QSAR studies were performed by using IBM-Corona, Data System PPC 400 computer working with Minitab Statistics Package.

Preparation of Phosphate Buffer

Each 53.72 g disodium hydrogen phosphate (12 H_2O) and 20.4 g potassium dihydrogen phosphate were made up the volume to 1000 ml with distilled water separately. 45 ml of these 0.15 M solutions were mixed. The pH of this final solution was found as 7.8.

Determination of log P Values

The log P values were determined in the system l-octanol/ aqueous phosphate buffer (pH : 7.8)[20,21]. The aqueous phase was saturated with l-octanol and vice versa prior to each experiment. Stirring for 1 hour at 37°C was sufficient to ensure an equilibrium distribution of each compound between the two phases. After separating the phases, the absorbance values at maximums were measured by UV spectrometer between 230 and 291 nm. The concentrations of compounds in each phase were calculated mathematically using the UV measurements of known concentrations (standarts) according to the formulas below :

$$C_1 = \frac{C_2 \cdot A_1}{A_2} \qquad C_B = C_2 - C_1$$

C_1 is the concentration of the sample solution, C_2 ise the concentration of the standart solution, A_1 is the absorbance value of the sample solution, A_2 is the absorbance value of the

standart solution, C_B is the concentration of the compound in the buffer solution (H_2O) at the end of the reaction.

$$\text{Log } P = \text{Log} \left(\frac{\text{The amount of the compound in 1-octanol}}{\text{The amount of the compound in } H_2O \text{ (Buffer solution)}} \right)$$

The amount of the compounds in 1-octanol and H_2O phases together with their log P values were given in Table 2.

Determination of P_r, MR, *F* and *R*.

Parachor (P_r) relates principally to molecular volume[22] and it is used in QSAR studies[23]. P_r values of the compounds were calculated using Quayle's table[24]. MR, *F* and *R* values were taken from the table given by Hansch et al.[25]. These values were shown in Table 3.

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