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The Antifungal Activity Of 2-(p-Substituted-Phenyl)Oxazolo (4,5-b)Pyridine derivatives Against Candida Albicans And The Quantitative Structure - Activity Relationships

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Summary : The antifungal activity of 2-(p-substituted-phenyl)oxazolo (4,5-b)pyridine derivatives was determined using The Dilution Technique. The compounds were found significantly active (MIC: 12.5-25 μg/ml).

The quantitative structure-activity relationships (QSAR) of the compounds were studied using some hydrophobic (π, π^2), electronic (δ, F, R) and steric (MR, MW, P_1-) physicochemical parameters. The correlation equations of these relationships which were designed according to the Hansch Analysis Method were given.

For the correlation of the antifungal activity against C. albicans with the molecular criteria in the series of 2-phenyloxazolo(4,5-b)pyridi-

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nes, the combinations of hydrophobic, electronic or steric parameters were found more significant as compared to hydrophobic, electronic or steric parameters used separately. The best equation obtained from QSAR studies were stated.

2-(p-SÜBSTİTÜE-FENİL)OKSAZOLO(4,5-b)PİRİDİN TÜREVLERİNİN CANDİDA ALBİCANSA KARŞI ANTİFUNGAL ETKİLERİ VE KANTİTATİF YAPI-ETKİ İLİŞKİLERİ

Özet : 2-(p-Sübstitüe-fenil)oxazolo(4,5-b)piridin türevlerinin C. albicansa karşı antifungal etkileri Tüpte Dilüsyon Yöntemi kullanılarak çalışılmıştır. Hansch'ın Analiz yöntemine göre bulunan korrelasyon denklemleri verilmiştir.

2-Feniloksazolo(4,5-b)piridin türevleri ile C. albicansa karşı antifungal etki arasındaki ilişki incelenildiğinde, hidrofobik, elektronik ve sterik parametrelerin ayrı ayrı kullanılmaları yerine, kombine halde kullanılmalarının anlamlı olduğu bulunmuştur. QSAR çalışmalarından elde edilen ideal denklem belirtilmiştir.

Keywords : 2-(p-Substituted-phenyl)oxazolo(4,5-b)pyridine, C. albicans, π, π^2, δ, F, R, MR, MW, Pr, Best equation.

INTRODUCTION

In our previous paper, the synthesis and structure elucidations of 2-(p-substituted-phenyl)oxazolo (4,5-b)pyridine derivatives were stated (1). In another report, we stated the quantitative structure-activity relationships (QSAR) of these compounds in gram (—) bacteria. In this research, we decided to study the antifungal activity of the compounds against C. albicans in order to design of more active compounds in these series. The antifungal activity of these compounds are thought as the function of the physicochemical parameters on lead optimization method.

We select some steric, electronic and hydrophobic parameters which are shown in Table 2 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;

$$y = a_o + a_1 x_1 + a_2 x_2 + \ldots\ldots\ldots\ldots + a_n x_n$$

where x_1, x_2, ... x_n are the descriptor values (physicochemical substituent constants), y is related to the microbiological activity of

oxazolopyridin derivatives, and a_o, a_1, ... a_n are the coefficients determined by a least squares analysis. This equation is developed fo reach oxazolopyridine derivative in our analysis.

MATERIAL AND METHOD

Antifungal Activity

For antifungal activity Candida albicans RSKK 628 were chosen. The antifungal activity were tested as described earlier (3,4).

The activity of the compounds against C. albicans were tested in Sabouraud's broth (Neopeptone: 10 g, Dextrose: 40 g, Distilled water: 1000 ml). 0.2 ml of fungal culture inoculated into broth and the respective inoculated broths were used for testing after incubation for 5 days at 25 C. The twofold serial dilution technique was applied. A set of tubes containing only inoculated broth was kept as controls. After incubation for 5 days, the last tupe with no growth of the microorganism was taken to represent the minimum inhibitory concentration (MIC, expressed in μg/ml).

The stock solution of the compounds were prepared in absolute alcohol (3-6). For that reason, the activity of ethyl alcohol against C. albicans were tested in the same dilutions and ethyl alcohol was found inactive. The antifungal activity of the compounds were given in Table 1.

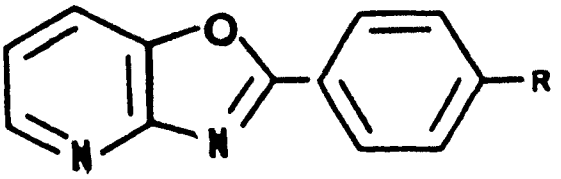
Determination of the parameters

Regression analysis equations of the QSAR studies were performed by using IBM-XT computer working with Microstat Statistic Package. Parachor (P_r) values of each compound were calculated by the additive summation of the P values of all the atoms and the structural features using Qayle's Table (7). π, π^2, δ, F, RMR and MW values were taken from the table given by Hansch et al. (8). These values were shown in Table 2.

RESULTS

For QSAR studies, to design the best equations of 2-(p-substituted)-phenyl) oxazolo (4,5-b) pyridine derivatives, the antifungal activity against C. albicans was chosen as the biological activity Some hydrophobic (π, π^2), electronic (δ, F, R) and steric (MR, MW, P_r) parameters used as physicochemical constants for the quantitative structure-activity relationships of these compounds. The lead optimization method has been examined by multiple regression analysis using the Microstat computer program. Log 1/C values were used in the regression equations, where C was the molar concentrations of the MIC values of the compounds The data on the paramaters were stated in Table 2. The regression equations stated in Tables 4 and the parameters in the best equation

Table 1 : Antifungal activity of 2-p-substituted-phenyl) oxazolo (4,5-b) pyridine derivatives against C. albicans (MIC in μg/ml)



Comp. no	R	C. albicans
1	CH_3	12.5
2	C_2H_5	12.5
3	$C(CH_3)_3$	25
4	OCH_3	12.5
5	OC_2H_5	12.5
6	NH_2	12.5
7	NO_2	12.5
8	Cl	25
9	Br	25

(Table 3) were selected according to the correlation matrix (Table 5) and the squares of their partial regression coefficients. Observed and calculated values of log 1/C were given in Table 6.

Table 2 : The physicochemical parameters of 2-(p-substituted-phenyl) oxazolo (4,5-b) pyridine derivatives

Comp. no	π	π^2	σ	$\mathcal{F}$	$\mathcal{R}$	MR	MW	P_r
1	0.56	0.3136	-0.17	-0.04	-0.13	5.65	15.0	412.5
2	1.02	1.0404	-0.15	-0.05	-0.10	10.30	29.1	452.5
3	1.98	3.9204	-0.28	-0.07	-0.13	19.62	57.1	532.5
4	-0.02	0.0004	-0.27	0.28	-0.51	7.87	31.4	443.4
5	0.38	0.1444	-0.24	0.22	-0.44	12.47	45.1	483.4
6	-1.23	1.5129	-0.68	0.02	-0.68	5.42	16.0	403.2
7	-0.28	0.0784	0.78	0.67	0.16	7.38	46.0	417.8
8	0.71	0.5041	0.23	0.41	-0.15	8.03	35.4	415.9
9	0.86	0.7396	0.23	0.44	-0.17	8.88	73.9	429.7

Table 3 : Best equations generated for 2-(p-substituted-phenyl) oxazolo (4,5-b) pyridine derivatives in C. albicans

Best Equation
$\log 1/C = -0.1971(\pm 0.0313)\pi - 0.1238(\pm 0.0207)\pi^2 + 0.3210(\pm 0.0862)\sigma$ $- 0.7239(\pm 0.1425)\mathcal{F} + 0.0345(\pm 0.0065)MR + 4.2172$
n: 9 ; R^2: 0.9605 ; s: 0.04 ; F: 14.59 (P<0.05)

C is the molar concentrations of the MIC values of the compounds, 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 coefficient, s is standart deviation of the regression and F is the F test for the significance of the regression, P is the probability of F test.

Table 4 : Regression equations generated for 2-(p-substituted-phenyl) (4,5-b) pyridine derivatives in C. albicans

Equ. No	Equations
1	log 1/C = -0.08(±0.04)π + 4.21 n: 9 ; R^2: 0.3320 ; s: 0.11 ; F: 3.48
2	log 1/C = -0.06(±0.05)π - 0.03(±0.04)π^2 + 4.23 n: 9 ; R^2: 0.3939 ; s: 0.12 ; F: 1.95
3	log 1/C = -0.05(±0.06)π - 0.04(±0.05)π^2 - 0.07(±0.12)σ + 4.23 n: 9 ; R^2: 0.4355 ; s: 0.12 ; F: 1.29
4	log 1/C = -0.09(±0.07)π - 0.06(±0.05)π^2 + 0.17(±0.23)σ -0.46(±0.37)$\mathcal{F}$ + 4.36 n: 9 ; R^2: 0.5892 ; s: 0.12 ; F: 1.43
5	log 1/C = -0.20(±0.03)π - 0.12(±0.02)π^2 + 0.32(±0.09)σ -0.72(±0.14)$\mathcal{F}$ + 0.04(+0.01) MR + 4.22 n: 9 ; R^2: 0.9605 ; s: 0.04 ; F: 14.59
6	log 1/C = 0.01(+0.02) MR - 0.19(±0.37)$\mathcal{F}$ -0.06(±0.24)σ -0.10(±0.07)π^2 + 4.22 n: 9 ; R^2: 0.4395 ; s: 0.14 ; F: 0.78
7	log 1/C = -0.01(±0.01) MR + 0.01(±0.39)$\mathcal{F}$ - 0.06(±0.24)σ + 4.25 n: 9 ; R^2: 0.1151 ; s:0.15 ; F: 0.25
8	log 1/C = -0.01(±0.01) MR - 0.08(±0.20)$\mathcal{F}$ + 4.28 n: 9 ; R^2: 0.1026 ; s: 0.14 F: 0.34
9	log 1/C = -0.01(±0.01) MR + 4.25 n: 9 ; R^2: 0.0805 ; s: 0.13 ; F: 0.61

Table 5 : Correlation matrix between regression parameters for 2-(p-substituted-phenyl) oxazolo (4,5-b) pyridinederivatives.

	log 1/C	π	π^2	σ	$\mathcal{F}$	$\mathcal{R}$	MR	MW	P_c
log 1/C	1.00								
π	-0.58	1.00							
π^2	-0.51	0.51	1.00						
σ	-0.15	0.14	-0.31	1.00					
$\mathcal{F}$	-0.05	-0.26	-0.54	0.82	1.00				
$\mathcal{R}$	-0.20	0.49	0.01	0.83	0.36	1.00			
MR	-0.28	0.72	0.74	-0.12	-0.34	0.13	1.00		
MW	-0.48	0.49	0.22	0.48	0.45	0.34	0.49	1.00	
P_c	-0.21	0.70	0.66	-0.20	-0.37	0.04	0.98	0.48	1.00

Table 6 : Antifungal activity of 2-(p-substituted-phenyl) oxazolo (4,5-b) pyridine derivatives (log 1/C).

Comp. No	Observed	Calculated	Residual
1	4.23	4.24	-0.01
2	4.25	4.23	0.02
3	4.00	4.01	-0.01
4	4.26	4.22	0.04
5	4.28	4.32	-0.04
6	4.23	4.23	-0.00
7	4.29	4.28	0.01
8	3.97	4.00	-0.03
9	4.04	4.02	0.02

DISCUSSION

The antifungal activity of 2 (p substituted-phenyl) oxazolo-(4,5-b) pyridin derivatives against C. albicans were tested and the compounds were found significantly active (MIC : 12,5-25μg/ml).

The multiple regression analysis results show that the activity against C. albicans is fundamentally a function of the combinations of some hydrophobic, electronic and steric parameters. It is found that the parameters used alone do not show good correlations with the activity in the QSAR studies. The P value of the F-test for the best equation is found less than 0.05 which shows us that the physicochemical parameters used as independent variables are related to the dependent variable (log 1/C) in the multiple regression analysis. In addition, the standart deviation(s) is minimized and forward elimination procedures, are stated in our study (Table 4). These situations are statistically justified the best equations given in Table 3 (9).

The best equations which are obtained from the regression analysis, involve π, π^2 values as hydrophobic, δ and F as electronic and MR as steric parameters. The δ

(sigma) and MR (Molar Refractivity) constants are found having additive effect on biological activity.

The square of multiple regression coefficient (R^2) were obtained for C. albicans as 0.9605. This means that the best equation which we have established can be used to predict the antifungal activity for untested 2-(p-substituted-phenyl) oxazolo (4,5-b) pyridines against C albicans. Of course, this observation supplies a lot of advantages in designing the most active compound.

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