QSAR of Some Antifungal Benzoxazoles and Oxazolo(4,5-b)pyridines against C. *albicans*

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A congeneric set of 2,5-disubstituted benzoxazole (III) and 2-substituted oxazolo(4,5-b)pyridine (IV) derivatives 1 – 46, previously tested for their antifungal activity against C. albicans, were analyzed by quantitative structure-activity relationship (QSAR) techniques. The activity contributions for either ring system or substituent effects were determined from the correlation equations, and the predictions of the potent antifungally active derivatives were described by the results obtained from the computer-assisted stepwise regression procedure. The resulting QSAR revealed that oxazolo(4,5-b) pyridine ring system was more preferable than benzoxazole and the benzyl group at position 2 was more significant than the corresponding phenyl substituent. Although the para substitution of benzyl or phenyl moiety with electron donating/withdrawing groups was neglectable, the nature of the substituents at the 5th position (R_1) of the fused ring system was important for the potency. Substituting this position with electron withdrawing groups like nitro produces an increase in the antifungal activity.

Key words: Benzoxazoles, oxazolo(4,5-b)pyridines, antifungal activity

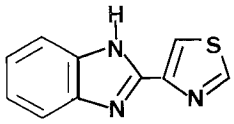
1 Introduction

Most fungi are completely resistant to the action of the antimicrobial drugs. Only a few substances have been discovered which exert an inhibitory effect on the fungi pathogenic for man, and most of these are relatively toxic [1]. The need for more and better antifungal agents is becoming more critical because of the increasing detection of systemic mycoses in patients suffering from debilitating diseases such as neoplasis and in persons on long-term total parenteral nutrition. For example, systemic mycoses have been found in 61% of patients dying with acute leukemia and in 45% of deaths in renal transplant recipients [2].

A variety of useful antifungal drugs have been developed in the last three decades. But, very few compounds have as yet been found which combine the properties required for the treatment of systemic yeast infections. Amphoteracin B and flucytosine are the only two agents that have been approved for such use [3].

The diversity of active structures and of their antifungal mechanisms of action sheds little light on the kind of molecules that should be tested in future screens. Moreover, no single type of structure thus far discovered possesses useful broad spectrum activity. Antifungal drugs with the remarkable selective toxicity of such antibacterial substances as the sulfonamides, or β-lactams are not yet available for systemic mycoses [4]. Consequently, the search for novel, effective and less toxic antifungal drugs will continue.

Recent studies led to the discovery of certain highly substituted imidazole derivatives such as miconazole and clotrimazole [5 – 7] which possess good clinical activity in dermatophytoses and nonsystemic candidiasis. Unfortunately, systemic use of miconazole has been accompanied by reversible thrombocytosis and anemia [8] and of clotrimazole by severe gastrointestinal disturbances [9]. Another imidazole derivative with good clinical efficacy in tropical therapy of dermatophytic infections is 2-(4-thiazolyl)benzimidazole (I) (thiabendazole) [10]. Since thiabendazole has been found effective in the treatment of several helmintic diseases [3], a variety of benzimidazole derivatives have been evaluated for their anti-infective effects. Of these compounds, 2-(α-hydroxybenzyl)benzimidazole (II) (HBB) which is a selective inhibitor of the RNA-containing Enteroviruses [4] has been most extensively studied.



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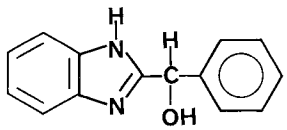

II

Mechanism of action studies indicate that HBB has no effect on virus adsorbtion, penetration and uncoating [11]. The primary site of action of this antiviral agent appears to be inhibition of viral RNA synthesis [11, 12], although the precise mechanism of this inhibition is still unclear. On the other hand, the in vivo antiviral efficiency of these compounds were accompanied by signs of toxicity [12].

In order to alter the toxic effects and reach to the desired selective activity, one of the methods is to apply structural modifications and obtain new derivatives or analogues of the initial compound [13]. Based on this concept, some of benzoxazole and oxazolo(4,5-b)pyridine derivatives which are the analogues of benzimidazole were synthesized and studied for their antifungal activity against Candida albicans in our previous papers [14 – 20].

In this paper, QSAR analysis of some antifungal active 2,5-disubstituted benzoxazole (III) and 2-substituted oxazolo (4,5-b)pyridine (IV) derivatives is reported.

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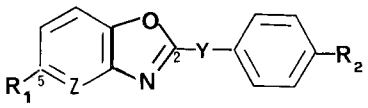
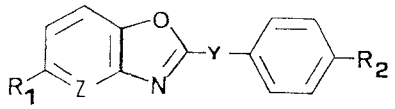


III, Z: CH Y: CH_2 or –
IV, Z: N Y: –

The substituents at R_1 and R_2 in the compounds which are given in Table 1, are electron donating and withdrawing groups. The activity contributions for either ring systems or substituent effects on position 2 and 5 have been determined from the correlation equations, and the prediction of the potent antifungal derivative (lead compound) has been described by the results obtained from the QSAR analysis.

Table 1. Compounds and parameters used to develop the Eq. 5 and 12.



compound	R_1	R_2	Z	Y	HAC-CEPT$_{R1}$	HDO-NOR$_{R1}$	F_{R1}	I_Z	I_Y	π_{R1}	R_{R1}	Sb_{R1}	MIC (μg/ml)	obsd.[a]	calcd.[b]	resi-dual	calcd.[c]	resi-dual
1	H	H	CH	–	0	0	0.00	0	0	0.00	0.00	0.00	25	3.89	3.97	−0.08	3.94	−0.06
2	H	$C(CH_3)_3$	CH	–	0	0	0.00	0	0	0.00	0.00	0.00	25	4.00	3.97	0.03	3.94	0.06
3	H	NH_2	CH	–	0	0	0.00	0	0	0.00	0.00	0.00	25	3.93	3.97	−0.04	3.94	−0.01
4	H	$NHCH_3$	CH	–	0	0	0.00	0	0	0.00	0.00	0.00	25	3.95	3.97	−0.02	3.94	0.01
5	Cl	C_2H_5	CH	–	0	0	0.41	0	0	0.71	−0.15	1.20	25	4.01	4.03	−0.02	4.01	0.00
6	Cl	$NHCOCH_3$	CH	–	0	0	0.41	0	0	0.71	−0.15	1.20	25	4.06	4.03	0.03	4.01	0.05
7	Cl	$NHCH_3$	CH	–	0	0	0.41	0	0	0.71	−0.15	1.20	25	4.02	4.03	−0.01	4.01	0.01
8	Cl	Cl	CH	–	0	0	0.41	0	0	0.71	−0.15	1.20	25	4.02	4.03	−0.01	4.01	0.01
9	Cl	NO_2	CH	–	0	0	0.41	0	0	0.71	−0.15	1.20	25	4.06	4.03	0.03	4.01	0.05
10	NO_2	H	CH	–	1	0	0.67	0	0	−0.28	0.16	3.00	12.5	4.28	4.34	−0.06	4.33	−0.05
11	NO_2	CH_3	CH	–	1	0	0.67	0	0	−0.28	0.16	3.00	12.5	4.31	4.34	−0.03	4.33	−0.02
12	NO_2	$C(CH_3)_3$	CH	–	1	0	0.67	0	0	−0.28	0.16	3.00	12.5	4.37	3.34	0.03	4.33	0.04
13	NO_2	NH_2	CH	–	1	0	0.67	0	0	−0.28	0.16	3.00	12.5	4.31	4.34	−0.03	4.33	−0.02
14	NO_2	Cl	CH	–	1	0	0.67	0	0	−0.28	0.16	3.00	12.5	4.34	4.34	0.00	4.33	0.01
15	NO_2	Br	CH	–	1	0	0.67	0	0	−0.28	0.16	3.00	12.5	4.41	4.34	0.07	4.33	0.07
16	NH_2	C_2H_5	CH	–	1	1	0.02	0	0	−1.23	−0.68	1.00	25	4.00	4.04	−0.04	4.04	−0.04
17	NH_2	Br	CH	–	1	1	0.02	0	0	−1.23	−0.68	1.00	25	4.11	4.04	0.07	4.04	0.07
18	NH_2	F	CH	–	1	1	0.02	0	0	−1.23	−0.68	1.00	25	4.02	4.04	−0.02	4.04	−0.02
19	NH_2	$N(CH_3)_2$	CH	–	1	1	0.02	0	0	−1.23	−0.68	1.00	25	4.03	4.04	−0.01	4.04	−0.01
20	CH_3	CH_3	CH	–	0	0	−0.04	0	0	0.56	−0.13	1.00	25	3.95	3.96	−0.01	4.00	−0.05
21	CH_3	C_2H_5	CH	–	0	0	−0.04	0	0	0.56	−0.13	1.00	25	3.98	3.96	0.02	4.00	−0.02
22	CH_3	OCH_3	CH	–	0	0	−0.04	0	0	0.56	−0.13	1.00	25	3.98	3.96	0.02	4.00	−0.02
23	CH_3	F	CH	–	0	0	−0.04	0	0	0.56	−0.13	1.00	25	3.96	3.96	0.00	4.00	−0.04
24	CH_3	$NHCOCH_3$	CH	–	0	0	−0.04	0	0	0.56	−0.13	1.00	25	3.99	3.96	0.03	4.00	−0.01
25	CH_3	$NHCH_3$	CH	–	0	0	−0.04	0	0	0.56	−0.13	1.00	25	3.98	3.96	0.02	4.00	−0.02
26	CH_3	$N(CH_3)_2$	CH	–	0	0	−0.04	0	0	0.56	−0.13	1.00	25	4.00	3.96	0.04	4.00	0.00
27	H	CH_3	N	–	0	0	0.00	1	0	0.00	0.00	0.00	12.5	4.23	4.26	−0.03	4.26	−0.03
28	H	C_2H_5	N	–	0	0	0.00	1	0	0.00	0.00	0.00	12.5	4.25	4.26	−0.01	4.26	−0.01
29	H	OCH_3	N	–	0	0	0.00	1	0	0.00	0.00	0.00	12.5	4.26	4.26	0.00	4.26	0.00
30	H	OC_2H_5	N	–	0	0	0.00	1	0	0.00	0.00	0.00	12.5	4.28	4.26	0.02	4.26	0.02
31	H	NH_2	N	–	0	0	0.00	1	0	0.00	0.00	0.00	12.5	4.23	4.26	−0.03	4.26	−0.03
32	H	NO_2	N	–	0	0	0.00	1	0	0.00	0.00	0.00	12.5	4.29	4,26	0.03	4.26	0.03
33	H	H	CH	CH_2	0	0	0.00	0	1	0.00	0.00	0.00	12.5	4.22	4.29	−0.07	4.29	−0.07
34	H	OCH_3	CH	CH_2	0	0	0.00	0	1	0.00	0.00	0.00	12.5	4.28	4.29	−0.01	4.29	−0.01
35	H	Br	CH	CH_2	0	0	0.00	0	1	0.00	0.00	0.00	12.5	4.36	4.29	0.07	4.29	0.07
36	H	Cl	CH	CH_2	0	0	0.00	0	1	0.00	0.00	0.00	12.5	4.29	4.29	0.00	4.29	0.00
37	H	NO_2	CH	CH_2	0	0	0.00	0	1	0.00	0.00	0.00	12.5	4.31	4.29	0.02	4.29	0.02
38	Cl	H	CH	CH_2	0	0	0.41	0	1	0.71	−0.15	1.20	12.5	4.29	4.36	−0.07	4.35	−0.06
39	Cl	OCH_3	CH	CH_2	0	0	0.41	0	1	0.71	−0.15	1.20	12.5	4.34	4.36	−0.02	4.35	−0.01
40	Cl	Br	CH	CH_2	0	0	0.41	0	1	0.71	−0.15	1.20	12.5	4.41	4.36	0.05	4.35	0.06
41	Cl	NO_2	CH	CH_2	0	0	0.41	0	1	0.71	−0.15	1.20	12.5	4.36	4.36	0.00	4.35	0.01
42	NO_2	H	CH	CH_2	1	0	0.67	0	1	−0.28	0.16	3.00	6.25	4.61	4.67	−0.06	4.68	−0.07
43	NO_2	OCH_3	CH	CH_2	1	0	0.67	0	1	−0.28	0.16	3.00	6.25	4.66	4.67	−0.01	4.68	−0.02
44	NO_2	Br	CH	CH_2	1	0	0.67	0	1	−0.28	0.16	3.00	6.25	4.73	4.67	0.06	4.68	0.05
45	NO_2	Cl	CH	CH_2	1	0	0.67	0	1	−0.28	0.16	3.00	6.25	4.67	4.67	0.00	4.68	−0.01
46	NO_2	NO_2	CH	CH_2	1	0	0.67	0	1	−0.28	0.16	3.00	6.25	4.68	4.67	0.01	4.68	0.00

[a]Defined as the log 1/C. [b]Using Eq. 5. [c]Using Eq. 12.

2 Methods

2.1 Data Processing

Correlation and regression analyses of the QSAR study were run on an EPSON PC AX2 computer using the MICROSTAT program package. In the equations, the figures in parantheses 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 significance test and s is the standard error of estimate.

Multiple regression analysis which involves finding the best fit of dependent variable (antifungal activity) to a linear combination of independent variables (descriptors) are used by the least squares method. The correlation equations were performed by the stepwise regression procedure where the enter and remove of the F level for each variable in the regression was 8.0. The tabulated F(5,40,0.99) is 3.51 whereas the overall F test values for Eqs. 5 and 12 were 288 and 274 which are statistically significant at the 1% level of probability [21]. The complete analysis of variance tables of Eqs. 5 and 12 are given in Tables 3 and 6 for further informations. The correlation coefficients which are given in Tables 4 and 7 reveal that there is no collinearity [22] between the independent variables.

In order to prove the predictive powers of Eqs. 5 and 12, a diagnostic checking test of residuals was established. As a result of this test general assumptions (i.e. normality, constant variance, independence) for error term is satisfactory and 100% of residuals are within the 2σ limits for both model [23]. Values of the sample statistics are given in Table 8.

2.2 Determination of Parameters and QSAR Study

A congeneric set of 2,5-disubstituted benzoxazole and 2-substituted oxazole(4,5-b)pyridine derivatives 1 – 46 were considered for this study. Their antifungal activity against C.

Table 2. Stepwise development of Equation 5.

Eq No	Equation	n	R^2	s	F
1	log 1/C = 0.335(±0.053)I_Y + 4.11	46	0.48	0.16	40
2	log 1/C = 0.268(±0.041)I_Y + 0.388(±0.064)F_{R1} + 4.039	46	0.72	0.12	54
3	log 1/C = 0.307(±0.027)I_Y + 0.476(±(0.044)F_{R1} + 0.287(±0.037)I_Z + 3.966	46	0.88	0.08	105
4	log 1/C = 0.332(±0.019)I_Y + 0.314(±0.037=F_{R1} + 0.312(±0.025)I_Z + 0.159(±0.022)HACCEPT$_{R1}$ + 3.944	46	0.95	0.05	189
5	log 1/C = 0.326(±0.014)I_Y + 0.149(±0.039)F_{R1} + 0.287(±0.019)I_Z + 0.273(±0.025)HACCEPT$_{R1}$ − 0.203(±0.034)HDONOR$_{R1}$ + 3.969	46	0.97	0.04	288

Table 3. Complete Analysis of Variance Table of Eq. 5.

Source of Variation	Degrees of Freedom	Sum of Squares	Mean Square	partial	
				F	r^2
Total (corrected)	45	2.2790			
Regression	5	2.2174	0.4435		
I_Y	1	1.0946	1.0946	574	0.94
F_{R1}/I_Y	1	0.5429	0.5429	15	0.27
I_Z/I_Y, F_{R1}	1	0.3744	0.3744	228	0.85
HACCEPT$_{R1}$/I_Y, F_{R1}, I_Z	1	0.1500	0.1500	121	0.75
HDONOR$_{R1}$/I_Y, F_{R1}, I_Z, HACCEPT$_{R1}$	1	0.0555	0.0555	36	0.47
Residual	40	0.0615	0.0015		

Table 4. Correlation Matrix of Variables Used in Eq. 5.

	log 1/C	I_Y	I_Z	HACCEPT$_{R1}$	HDONOR$_{R1}$	F_{R1}
log 1/C	1.00					
I_Y	0.69	1.00				
I_Z	0.08	−0.26	1.00			
HACCEPT$_{R1}$	0.49	0.04	−0.27	1.00		
HDONOR$_{R1}$	−0.24	−0.20	−0.12	0.44	1.00	
F_{R1}	0.66	0.27	−0.31	0.62	−0.23	1.00

Table 5. Stepwise Development of Eq. 12.

Eq no	Equation	n	R^2	s	F
8	$\log 1/C = 0.335(\pm0.053)I_Y + 4.110$	46	0.48	0.16	40
9	$\log 1/C = 0.305(\pm0.040)I_Y + 0.095(\pm0.017)Sb_{R1} + 4.005$	46	0.71	0.13	51
10	$\log 1/C = 0.360(\pm0.018)I_Y + 0.138(\pm0.008)Sb_{R1} + 0.365(\pm0.027)I_Z + 3.891$	46	0.94	0.05	246
11	$\log 1/C = 0.363(\pm0.016)I_Y + 0.132(\pm0.007)Sb_{R1} + 0.356(\pm0.024)I_Z - 0.046(\pm0.014)\pi_{R1} + 3.900$	46	0.96	0.05	234
12	$\log 1/C = 0.344(\pm0.014)I_Y + 0.115(\pm0.007)Sb_{R1} + 0.312(\pm0.022)I_Z - 0.071(\pm0.013)\pi_{R1} + 0.154(\pm0.035)R_{R1} + 3.944$	46	0.97	0.04	274

Table 6. Complete Analysis of Variance Table of Eq. 12.

Source of Variation	Degrees of Freedom	Sum of Squares	Mean Square	partial	
				F	r^2
Total (corrected)	45	2.2790			
Regression	5	2.2144	0.4429		
I_Y	1	1.0946	1.0946	594	0.94
Sb_{R1}/I_Y	1	0.5138	0.5138	260	0.87
I_Z/I_Y, Sb_{R1}	1	0.5479	0.5479	194	0.83
π_{R1}/I_Y, Sb_{R1}, I_Z	1	0.0274	0.0274	32	0.44
R_{R1}/I_Y, F_{R1}, I_Z, π_{R1}	1	0.0307	0.0307	19	0.32
Residual	40	0.0646	0.0016		

Table 7. Correlation matrix of variables used in Eq. 12.

	log 1/C	R_{R1}	π_{R1}	I_Z	Sb_{R1}	I_Y
log 1/C	1.00					
R_{R1}	0.54	1.00				
π_{R1}	−0.21	0.28	1.00			
I_Z	0.08	0.12	−0.04	1.00		
Sb_{R1}	0.56	0.34	−0.19	−0.41	1.00	
I_Y	0.69	0.25	0.06	−0.26	0.13	1.00

Table 8. Values of the sample statistics obtained from the residuals[a].

	n	Mean	Median	STDEV
$Residual_1$[b]	46	−0.0009	0.0000	0.0372
$Residual_2$[c]	46	−0.0011	−0.0100	0.0377

[a]Given in Table 1. [b]Differences between observed and calculated log 1/C values using Eq. 5. [c]Differences between observed and calculated log 1/C values using Eq. 12.

albicans were determined as minimum inhibitory concentration (MIC) [17–20]. For the test the compounds were dissolved in absolute ethanol (0.8 mg/ml) and further control dilutions in the test medium were furnished at the required quantities of 400, 200, 100, 50, 25, 12.5, 6.25, 3.12, 1.56, 0.78 and 0.39 μg/ml concentrations. For the antifungal assay, the fungus was maintained in Sabouraud Dextrose broth (Difco). Testing was done in Sabouraud Dextrose broth and the twofold serial dilution technique was applied. After incubation, the last tube with no growth of the fungus was recorded to represent MIC expressed in 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.

The variables used as descriptors in the analysis are hydrophobic, electronic, steric and structural parameters. The indicator variable I_Z expresses the replacement of $-CH=$ by the isosteric group of $-N=$ in the six membered ring of the fused ring system. I_Z is defined as 0 for type III compounds and 1 for type IV compounds. The other indicator variable I_Y has a value of 1 for the presence of a methylene group and 0 for the absence of it between the p-substituted phenyl moiety and the fused ring system in position 2. The hydrogen donating/accepting capabilities (HDONOR/HACCEPT) of the substituents at R_1 and R_2 are the other indicator variables.

Physicochemical parameters taken into consideration in QSAR study are π, f (Rekker's fragmental constant) for the hydrophobic effects, σ, F (field effect), R (resonance effect) as the electronic influences and Es, MW, MR (molar refractivity), Verloop's STERIMOL parameters (L,B_1,B_4) and Sb (steric branching) [24] for the steric interactions of the substituents R_1 and R_2. Values for these parameters were taken from the table given by Hansch et. al [25]. Among these descriptors, parachor (Pr) and bridge effect (Yb) were also studied as independent variables. Pr relates principally to the molecular volume of the compounds and the values for each compound was calculated by the summation of the Pr values of all atoms and structural features using Quayle's table [26]. Bridge effect (Yb) indicates the ability to transmit the polar effects between two aromatic ring systems where the π electron system of the phenyl group is separated by a CH_2 group at position 2. It was calculated by the Hammett constant using an attenuation factor for the bridge element [13]. The values of the variables used in the correlation equations are shown in Table 1.

3 Results and Conclusion

Biologically active benzoxazole derivatives have been known since long time and 2-substituted ones were prominently studied [27 – 33]. It was seen that position 2 is decisive for the biological activity, whereas position 5 determines the intensity of the activity [28, 30, 34].

In a previous QSAR study of benzoxazole derivatives [35], it was found that overall charge transfer interactions between the compounds and site of action, as the energy of the lowest unoccupied molecular orbital values (E_{LUMO}) of the benzoxazoles, showed additive contributions for the antifungal activity against C. albicans. From the study it was concluded that the benzoxazole ring moiety was the most important part in the molecule for the interaction and when the electron accepting property of this moiety increased, the antifungal activity increased too. In addition it was denoted that powerful electron withdrawing substituents at position 5 increased the electron accepting ability of the benzoxazole ring moiety and improved the potency.

When the QSAR analysis obtained from Eq. 5 is compared to the previous results given above [28, 30, 34, 35], similar conclusions are also obtained.

The stepwise development of Eq. 5 which is shown in Table 2 reveals that the indicator variables I_Y, I_Z, $HACCEPT_{R1}$ and $HDONOR_{R1}$ together with the physicochemical parameter F_{R1} correlate with the activity. Eq. 5 exhibites that variables I_Y, I_Z and $HACCEPT_{R1}$ have additive contributions showing highly significant partial r^2 values (see Table 3). Additive contributions of I_Y and I_Z indicate that type IV compounds having a methylene group on position 2 are favourable for the activity. Additionally, the hydrogen accepting/donating capability of the substituents at R_1($HACCEPT_{R1}$/$HDONOR_{R1}$) also induces some influences on the potency. While hydrogen accepting property of a substituent at this position produces an increase, the hydrogen donating ability causes a decrease in the activity. Eq. 5 also shows that the electronic substituent effect F_{R1}, consisting of inductive interactions on position 5, is important and performs a positive effect on the potency. Moreover, the QSAR analysis reveals that R_1 is more important than R_2, because there is no statistically significant relationship found between the activity and any parameter combinations that included variables related to R_2.

In order to interpret the nature and the effects of the substituent by physicochemical variables, subsequent analyses were performed. By testing only continuous R_1 variables which were applied either individual or combinations, statistically insignificant correlation equations were observed. This observation is not a surprise, because the substituent in position 5 plays a part in improving the intensity instead of being responsible for the activity [35].

However, an alternative to analyze the related physicochemical interactions of the substituent R_1 with the activity is to describe the indicator variables $HACCEPT_{R1}$ and $HDONOR_{R1}$ by their physicochemical features. In Eqs. 6 and 7 the alternative explanations of the $HACCEPT_{R1}$ and $HDONOR_{R1}$ are given.

$$HACCEPT_{R1} = -0.536(\pm 0.006)\pi_{R1} + 0.282(\pm 0.003)Sb_{R1} + 0.017 \quad (6)$$

$n = 46 \quad R^2 = 0.998 \quad s = 0.02 \quad F = 11488.1$

$$HDONOR_{R1} = -0.275(\pm 0.008)\pi_{R1} - 0.905(\pm 0.020)R_{R1} + 0.037 \quad (7)$$

$n = 46 \quad R^2 = 0.990 \quad s = 0.03 \quad F = 2167.5$

As a result of the replacement of these indicator parameters by the variables obtained from Eqs. 6 and 7, a new correlation, Equation 12 was created which is given in Table 5 as an alternative to Eq. 5. Eq. 12 reveals that the electronic and the steric effects of R_1 are important to improve the potency. QSAR results obtained from Eqs. 5 and 12 show that the electronic influences which are the polar interactions including inductive (F_{R1}) and resonance (R_{R1}) effects, produce additive contributions. These positive contributions indicate that R_1 must be substituted by an electron withdrawing group for increasing the potency (see compounds 10 – 15 in the Table 1).

From the derived QSAR we conclude that a more potent compound must possess an oxazolo(4,5-b)pyridine ring system substituted with an electron withdrawing group at position 5 and benzyl moiety at position 2. The necessity of a bridge element like a methylene group at position 2 can be explained by

conformational influences. This group provides flexibility to the molecule in order to enhance the activity (compare compounds, 1, 33, 9, 41, 10, 42, 14, 45 respectively in Table 1). Even, the nitro or other isosteric groups possessing similar physicochemical properties could be the candidates of R_1 at position 5 to improve the potency.

References

[1] Meyers, F.H., Jawetz, E. and Goldfien, A., *Review of Medical Pharmacology,* Lange Medical Publication, California 1976.

[2] Bennett, J.E., *Prevent. Med. 3,* 515 (1974).

[3] R.F. Doerge (Ed.), *Wilson and Gisvold's Textbook of Organic Medicinal and Pharmacological Chemistry,* J.B. Lippincott, Philadelphia 1982.

[4] M.E. Wolff (Ed.), *Burger's Medicinal Chemistry,* John Wiley & Sons, New York 1980.

[5] Rippon, J.W., *Medical Mycology,* Saunders, Philadelphia 1974.

[6] Smith, E.B., *Cutis. 17,* 54 (1976).

[7] Brincker, H., *Scand. J. Infect. Dis. 8,* 117 (1976).

[8] Marmion, L.C., Desser, K.B., Lilliy, R.B. and Stevens, D.A., *Antimicrob. Agents Chemother. 10,* 447 (1976).

[9] Beggs, W.H., Sarosi, G.A. and Steele, N.M., *Antimicrob. Agents Chemother. 9,* 863 (1976).

[10] Bottistini, F., Zaias, N., Sierra, R. and Rebell, G., *Arch. Dermatol. 109,* 695 (1974).

[11] W.A. Carter (Ed.), *Selective Inhibitors of Viral Functions, CRC Press,* Cleveland 1973.

[12] D.J. Bauer (Ed.), *International Encyclopedia of Pharmacology and Therapeutics,* Pergamon Press, Oxford 1972.

[13] W.Th. Nauta & R-F. Rekker (Eds.), *Theoretical Drug Design Methods,* Akademia-Verlag, Berlin 1984.

[14] Sener, E., Özden, S., Yalçin, İ., Özden, T., Akin, A. and Yildiz, S., *FABAD J. Pharm. Sci. 11,* 190 (1986).

[15] Yalçin, İ., Şener, E., Özden, T., Özden, S., Akin, A. and Yildiz, S., *FABAD J. Pharm. Sci. 11,* 257 (1986).

[16] Özden, S., Özden, T., Şener, E., Yalçin, İ., Akin, A. and Yildiz, S., *FABAD J. Pharm. Sci. 12,* 39 (1987).

[17] Şener, E., Yalçin, İ., Özden, S., Özden, T., Akin, A. and Yildiz, S., *DOGA TU J. Med. & Pharm. 11,* 391 (1987).

[18] Şener, E., Yalçin, İ., Özden, S., Özden, T., Akin, A. and Yildiz, S., *FABAD J. Pharm. Sci. 12,* 281 (1987).

[19] Şener, E., Yalçin, İ., Akin, A. and Noyanalpan, N., *J. Pharm. Gazi 4,* 1 (1987).

[20] Yalçin, I., Şener, E., Özden. T., Özden, S. and Akin, A., *Eur. J. Med. Chem. 25,* 705 (1990).

[21] Draper, N. and Smith, H., *Applied Regression Analysis,* John Wiley & Sons, New York 1966.

[22] Salvatore, D., *Statistics and Econometrics,* McGraw-Hill, New York 1982.

[23] Anderson, T.W. and Sclove, S.L., *An Introduction to The Statistical Analysis of Data,* Houghton Mifflin Company, Boston 1978.

[24] Ijzerman, A.P., Aué, G.H.J., Bultsma, T., Linschoten, M.R. and Timmermann, H., *J. Med. Chem. 28,* 1328 (1985).

[25] Hansch, C. and Leo, A., *Substituent Constants for Correlation Analysis in Chemistry and Biology,* John Wiley & Sons, New York 1979.

[26] Quayle, O.R., *Chem. Rew. 53,* 439 (1953).

[27] Cashin, C.H., Dunwell, D.W., Evans, D., Hicks, T.A. and Kitchen, E.A., *J. Pharm. Pharmac. 29,* 330 (1977).

[28] Cashin, C.H., Dunwell, D.W., Evans, D., Hicks, T.A. and Kitchen, E.A., *J. Med. Chem. 18,* 53 (1975).

[29] Cossey, H.D., Gartside, R.N. and Stephens, F.F., *Arzneim. Forsch./Drug Res. 16,* 33 (1966).

[30] Evans, D., Dunwell, D.W. and Hicks, T.A., *J. Med. Chem. 18,* 1158 (1975).

[31] Haugwitz, R.D., Angel, R.G., Jacops, G.A., Maurer, B.V., Narayanan, V.L., Cruthers, L.R. and Szanto, J., *J. Med. Chem. 25,* 969 (1982).

[32] Rips, R., Lachaize, M., Albert, O. and Dupont, M., *Chim. Ther. 6,* 126 (1971).

[33] Shulze, W., Gutsche, W. and Jungstand, W., *Arzneim. Forsch./Drug. Res. 15,* 1235 (1965).

[34] Holder, G.M., Little, P.J., Ryan, A.J. and Watson, T.R., *Biochem. Pharmacol. 25,* 2747 (1976).

[35] Turker, L., Şener, E., Yalçin, İ., Akbulut, U. and Kayalidere, I., *Sci. Pharm. 58,* 107 (1990).

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