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QSARs OF SOME NOVEL BENZOXAZOLE, BENZIMIDAZOLE AND OXAZOLO(4,5-b)PYRIDINE DERIVATIVES AGAINST *C. albicans*

BAZI BENZOKSAZOL, BENZİMİDAZOL VE OKSAZOLO(4,5-b)PİRİDİN TÜREVLERİNİN *C. albicans'a* KARŞI KANTİTATİF YAPI-ETKİ İLİŞKİLERİ

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ABSTRACT

For QSAR analysis of a set of previously synthesized 2,5,6-trisubstituted benzoxazole, benz.imidazole and 2-substituted oxazolo(4,5-b)pyridine derivatives tested for growth inhibitory activity against Candida albicans, was peiformed by using the computer-assisted multiple regression procedure. The activity contributions for either heterocyclic ring systems or substituent effects of these compounds were determined from the correlation equation for predictions of the lead optimization. The resulting QSAR revealed that the oxazolo(4,5-b)pyridine ring system substituted with a benzyl moiety at position 2 was the most favourable structure among the analysed fused ring systems. Moreover, the 5 ' position in the heterocyclic nucleus was found more significant than the other positions for improving the activity.

Key Words: QSAR, benzoxazole, benzimidazole, oxazolo(4,5-b)pyridine

ÖZET

Önceden sentezlenmiş ve C. albicans'a karşı gelişimlerini inhibe eden aktiviteleri test edilmiş 2,5,6-trisilbstitüebenzoksazol, benziınidazol ve 2-sübstitüe oksazolo(4,5-b)piridin türevlerinin kantitatif yapı-etki ilişkileri analizleri bilgisayar kullanılarak basamaklı çoklu regresyon yöntemi uygulanarak gerçekleştirilmiştir. Bu bileşiklerin tümünde kullanılan heterosiklik sistemler için aktivite katkıları veya sübstitüent etkileri, öncü optimizasyon tahminleri için yararlanılan korelasyon eşitlikleri aracılığı ile belirlendi. Kantitatif yapı-etki ilişkileri analizleri sonuçları, 2. konumundan benzil grubu ile sübstitüe edilmiş, oksazolo(4,5-b)piridin halkasının analizleri yapılan halka sistemleri arasında en etkin yapı

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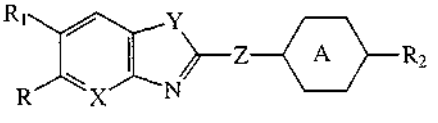
olduğunu ortaya çıkartmıştır. Ayrıca heterosiklik çekirdeğin 5. Konumu etki için diğer konumlardan daha önemli bulunmuştur.

Anahtar Kelimeler: Kantitatif yapı-etki ilişkileri analizleri, benzoksazol, benzimidazol, oksazolo (4,5-b)piridin

INTRODUCTION

Benzoxazoles, benzimidazoles and benzothiazoles were distinctively studied for their antitumoral, antiviral and antimicrobial activities as new non-nucleoside topoisomerase I poisons, HIV-1 reverse transcriptase inhibitors and/or potent DNA gyrase inhibitors respectively (1-18).

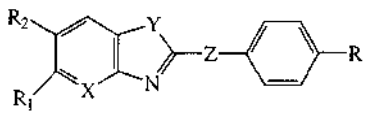
In the last few years, we reported the synthesis and the antimicrobial activity of some 2,5-disubstituted and 2,5,6-trisubstituted benzoxazoles, benzimidazoles, benzothiazoles and oxazolo(4,5-b)pyridines (Formula 1) against some Gram-positive, Gram-negative bacteria and the yeast *Candida albicans* (19-25) which provided a wide variety of *in vitro* antibacterial effects and significant antifungal activity against the yeast *C. albicans* (20).



X	=CH-, =N-
Y	-O-, -S-, -NH-
Z	—, $-CH_2-$, $-OCH_2-$, $-SCH_2-$, $-C_2H_4-$
A	Phenyl, cyclohexyl, 3-pyridyl
R	-H, -Cl, $-CH_3$, $-NO_2$, $-NH_2$
R_1;	-H, $-CH_3$, $-NO_2$
R_2(P);	-H, -Cl, -F, -Br, $-CH_3$, $-NO_2$, $-NH_2$, $-C_2H_5$, $-C(CH_3)_3$, $-OCH_3$, $-NHCH_3$, $-NHCOCH_3$, $-N(CH_3)_2$

Formula 1

In this study, QSAR analysis of some previously synthesized antifungal active benzoxazoles, benzimidazoles and oxazolo(4,5-b)pyridines **1-74** (19, 21, 23, 24) (Formula 2) was performed in order to determine the lead optimization by using the Hansch analysis method (26).



X; =CH-, =N-

Y; -O-, -NH-

Z; —, $-CH_2-$, $-C_2H_4-$, $-CH_2O-$, $-CH_2S-$

R; -H, -CI, -Br, -F, $-N0_2$, $-NH_2$, $-CH_3$, $-C(CH_3)_3$, $-C_2H_5$, $-OCH_3$, $-NHCH_3$, - NHCOCH3,

R,; -H, -CI, $-N0_2$, $-NH_2$, $-COOCH_3$

R_2; -H, $-N0_2$

Formula 2

EXPERIMENTAL SECTION

Material and Methods

Data Processing

Hansch analysis method which is an extra-thermodynamic approach in QSAR analysis was applied in order to determine the lead optimization due to various physicochemical (electronic, steric and hydrophobic) parameters and structural indicator parameters (27, 28).

For the procedure of descriptor selection related to the activity among the candidate set of variables, forward step-wise multiple regression of elimination technique was applied to the data set. During the development of the best fit model of the correlation equation, the minimum F value for entering and removing the variables in the step-wise multiple regression was taken as 4.0 which is statistically significant at the 1 % level of probability.

On the other hand, in order to judge the predictive power as Q^2 and / or S_{PRESS} values of the performed QSAR model was also calculated by Cross-validation technique which is a method to check validity of regression models by eliminating each object leave-one-out technique (29).

Regression analysis and calculations were run on a PC using the BILIN statistical program package (26). In equations, the figures in parentheses are the standard errors of the regression coefficients. For a given equation, n is the number of compounds, R_2 denotes the square of the multiple correlation coefficients, F is the significance test and s represents the residual standard deviation.

Determination of parameters

In this study, the model is based on the *in vitro* activity of certain 2,5,6-trisubstituted benzoxazole, benzimidazole and 2-substituted oxazolo(4,5-b)pyridine derivatives **1-74** against *C. albicans,* where C is the MIC value expressed in molar concentration units (Table 1).

The variables used as descriptors in the analysis are electronic, steric and structural parameters. The structural indicator variable Ix expresses the replacement of -CH= by the isosteric group -N= in the six membered ring of the fused ring system. Ix defined as 1 for -N= and 0 for -CH= in the compounds. The other indicator variable Iz has a value of 1 for the presence of a methylene group and 0 for its absence between the p-substituted phenyl moiety and the fused ring system in position 2. The indicator variable Iy has a value of 1 for NH and 0 for its absence in the five membered ring of the fused ring system (See Table 2).

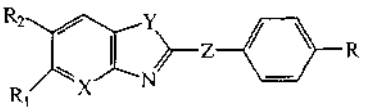
The screened physicochemical parameters in this QSAR study are π for the hydrophobic effects, σ, *F* (field effect), R (resonance effect) as electronic influences and Verloop's STERIMOL parameters *(L and* B_1 B_4*)* for the steric interactions of the substituents R and R_1 .Values for all candidate physicochemical variables used in this QSAR study were taken from the table of Hansch and Leo (30). The values of the descriptors used in the best equation (eqn 5) are shown in Table 1.

In vitro antifungal activity

The antifungal activities against the strain *C. albicans* were determined as the minimum inhibitory concentration (MIC) values in vitro by a two-fold serial dilution technique (31-32). The test was performed using the compounds which were dissolved in absolute ethanol (0.4 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 µg/ml concentrations. In order to ensure that the solvent per se had no effect on bacterial growth, a control test was also performed containing inoculated broth supplemented with only ethanol at the same dilutions used in our experiments and found inactive in culture medium.

For the antifungal assay, the yeast C. *albicans* was maintained in Sabouraud dextrose broth at pH 7.4 and the two-fold serial dilution technique was applied. The final inoculum size was 10^4 CFU/ml. A set of tubes containing only inoculated broth was kept as controls. After incubation for 48 h at 25 ± 1°C, the last tube with no growth of yeast 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. MIC and the observed log 1/C values of the compounds are listed in Table 1.

Table 1: The structure and *in vitro* antifungal activity of the analyzed compounds **1-74** and standard drugs against *C. albicans* and parameters used in the best fitted equation



Com. No.	X	Y	Z	R	R_1	R_2	1x	Iy	Iz	O_{RI}	MIC mg/ml	Log l/C observed	Log l/C calculated	Residuals
1	CH	0		**H**	**H**	H	**0**	**0**	0	0	25	3.89	4016	-0.126
2	CH	**0**		**$C(CH_3)_3$**	H	H	**0**	**0**	0	(1	25	4.00	4.016	-0,016
3	CH	0		**NH2**	**H**	H	**0**	**o**	0	0	**25**	3.93	4.016	-0.086
4	**CH**	**0**		**$NHCH_2$**	H	**H**	**0**	0	0	0	**25**	3.95	4.016	-0.066
5	CH	**0**		**C_2H_5**	CI	H	0	0	0	(1.37	**25**	4.01	4.163	-0.153
6	CH	0		**$NHCOCH_3$**	**CI**	H	0	**0**	0	0.37	25	4.06	4,163	-0.103
7	**CH**	**0**		**$NHCH_3$**	CI	**H**	0	0	0	**0.37**	**25**	4.02	4,163	-0.143
8	CH	**0**		**CI**	CI	**H**	0	**0**	0	0.37	**25**	4.02	4.163	-0.163
9	CH	**0**		**NO_2**	CI	H	**0**	**0**	0	0.37	25	**4.06**	4.163	-0.103
10	CH	0		**H**	NO_2	H	0	0	0	**0.71**	12.5	4.28	4.298	-0.018
11	CH	0		**CH_3**	NO_2	H	0	**0**	0	0.71	12.5	4.31	4.298	11.012
12	CH	**0**		**$C(CH_3)_3$**	NO_2	H	**0**	**0**	0	0.71	12.5	**4.37**	4.298	0.072
13	CH	**0**		**NH2**	NO_2	**H**	0	**0**	0	0.71	12.5	4.31	4.298	0.012
14	CH	0		**CJ**	NO_2	**H**	**0**	0	0	**0.71**	12.5	4.34	4,298	0.042
15	CH	0		**Br**	**NO_2**	H	0	0	**0**	0.71	**12.5**	**4.41**	4.298	0.112
16	CH	**0**		**C_2H_5**	NH_2	**H**	**0**	0	0	-0.16	**25**	4,00	**3.953**	**0.047**
17	CH	0		**Br**	NH_2	H	0	0	0	-0.16	25	4.11	**3.953**	**0.157**
18	CH	**0**		**F**	NH_2	H	0	0	0	-0.16	25	**4.02**	3.953	**0.067**
19	**CH**	**0**		**N(CH_3)2**	NH_2	H	0	0	0	-0.16	**25**	4.03	3.953	0.077
20	CH	**0**		**CH3**	CH_3	H	0	0	0	-0.07	**25**	3.95	3.989	-0.039
21	CH	O		C_2H5	CH_3	H	0	0	0	-0.07	**25**	3.98	3.989	-0.009
22	CH	0		**OCH_3**	CH_3	H	0	0	0	**-0.07**	**25**	3.98	3.989	-0.009
23	CH	**0**		**F**	CH_3	H	0	0	0	-0.07	**25**	3.96	3.989	-0.029
24	CH	**0**		**$NHCOCH_3$**	CH_3	H	**0**	0	0	-0.07	**25**	**3.99**	.3989	0.001
25	CH	**0**		**$NHCH_3$**	CH_3	H	**0**	0	0	-0.07	25	3.98	3.989	-0.009
26	CH	0		$N(CH_3)_2$	H	H	0	0	0	-0.07	**25**	4.00	**3.989**	0.011
27	**N**	0		CH_3	H	**H**	1	0	0	0	**12.5**	**4.23**	**4.257**	-0.027
28	**N**	**0**		**C_2H_5**	H	H	1	0	0	0	**12.5**	**4.25**	4.257	-0.007
29	**N**	**0**		**OCH_3**	**H**	H	**1**	0	0	0	12.5	**4.26**	4.257	0.003
30	**N**	**0**		**OC_2H_5**	H	H	1	0	0	0	12.5	4.28	4.257	0.023
31	N	**0**		NH_2	H	H	**1**	0	0	0	12.5	4.23	4.257	-0.027
32	**N**	0		NO_2	H	H	**1**	0	0	0	12.5	4.29	4.257	0.03.3
33	CH	O	**CH_2**	H	**H**	H	**0**	0	1	0	12.5	4.22	4.301	-0,081
34	CH	**0**	**CH_2**	OCH_3	H	H	**0**	0	1	0	12.5	**4.28**	4.301	-0.021
35	**CH**	**0**	**CH_2**	Br	H	H	0	0	1	0	12.5	4.36	4.301	0.059
36	CH	**0**	**CH_2**	Cl	H	H	**0**	0	1	0	12.5	4.29	4.301	-0.011
37	CH	**0**	**CH_2**	NO,	H	H	0	0	1	0	12.5	**4.31**	4.301	0.009
38	CH	**0**	**CH_2**	**H**	CI	H	**0**	0	**1**	**0.37**	12.5	4.29	4.448	-0.158
39	**CH**	0	**CH_2**	**OCH_3**	CI	**H**	0	0	**1**	**0.37**	**12.5**	4.34	4.448	-0.108
40	**CH**	0	**CH_2**	Br	**CI**	H	0	0	**1**	**0.37**	12.5	4.41	4.448	-0.0.38

Continue Table 1:

Com. No.	X	Y	Z	R	R1	R;	Ix	y	Iz	ORI	MIC m,g/ml	Log 1/C observed	Log 1/C calculated	Residuals
41	CH	0	CH_2	NO2	CI	H	0	0	1	0.37	12.5	4.36	4.448	-0.088
42	**CH**	O	CH_2	H	NO_2	H	0	0	1	**0.71**	6.25	4.61	4.583	0.027
43	**CH**	0	CH_2	OCH3	NO2	H	0	0	1	**0.71**	6.25	**4.66**	4.583	0.077
44	CH	0	CH_2	Br	NO2	H	0	0	1	0.71	6.25	4.73	4.583	0.147
45	CH	0	CH_2	Cl	NO_2	H	0	0	1	0.71	6.25	4.67	4.583	0.087
46	CH	0	CH_2	NO,	NO_2	H	0	0	1	0.71	6.25	4.68	4.583	0.097
47	CH	0	CH_20	II	CI	H	0	0	0	0.37	12.5	4.317	4.163	0.154
48	CH	0	CH_2O	H	CH_3	H	0	0	0	-0.07	25	3.981	3.989	-0.008
49	CH	0	CH_20	CI	H	H	0	0	0	0	25	4.016	4.016	0.000
50	CH	0	CH_20	CI	H	NO_2	0	0	0	0	25	4.086	4.016	0.069
51	CH	0	CH_20	II	NO_2	H	0	00		**0.71**	12.5	4.360	4.298	0.061
52	CH	O	CH_2O	H	CI	H	0	00		0.37	12.5	4.343	4.163	0.180
53	**CH**	0	CH_20	H	CH_3	H	0	0	0	-0.07	25	4.010	3.989	0.020
54	N	0	CH,0	II	H	H	1	0	0	0	12.5	4.260	4,257	0.003
55	CH	NH	CH_20	H	H	H	0		0	0	12.5	4.252	**4.180**	0.072
56	CH	NH	CH,0	II	CI	H	0		0	0.37	12.5	4.316	4.327	-0 011
57	CH	Nil	CH20	H	NO;	H	0		0	**0.71**	12.5	4.283	4.462	-0.179
58	CH	NH	CH20	H	CH_3	H	0		0	-0.07	12.5	4.176	4.152	0.124
59	CH	NH	CH,0	CI	H	H	0		0	0	25	4.015	4.180	-0.İ65
60	CH	NH	CH_20	CI	CI	H	0		0	0.37	12.5	4.370	4.327	0.043
61	**CH**	NH	CH_20	CI	CH_3	H	0		0	-0.07	25	4.037	4.152	-0.115
62	CH	NH	CH_2S	H	H	H	0		0	0	12.5	4.283	4.180	0.103
63	CH	NH	CH_2S	H	**NO_2**	H	0		0	**0.71**	12.5	4.357	4.462	-0.105
64	CH	NH	CH_2S	H	**CH3**	H	0		0	-0.07	25	4.009	4.152	-0.143
65	CH	NH	CH,NH	H	H	H	0		0	0	12.5	4.252	4.180	0.072
66	CH	NH	CH.NH	H	CH_3	H	0		0	-0.07	12,5	4.278	4.152	0.126
67	CH	NH	CH_2CH_2	H	CH3	H	0		0	-0.07	12.5	4.276	4.152	0.124
68	CH	NH	$CH2CH_2$	H	Cl	H	0		0	0.37	12.5	4.310	4.327	-0.017
69	CH	0	CH2O	H	$COOCH_3$	H	0	0	0	0.37	25	4.054	4.163	-0.110
70	CH	O	CH,S	H	$COOCH_3$	H	0	0	0	0.37	25	4.078	4.163	-0.085
71	CH	0	CH_2CH_2	H	CI	H	0	0	0	0,37	12.5	4.314	4.163	0.151
72	CH	**O**	CH_2CH_2	H	NO_2	H	0	0	0	0.71	12.5	4.331	4.298	0.033
73	N	0	CH2CH2	H	H	H	1	0	0	0	12.5	4.253	4.257	-0.003
74	CH	NH	CH2CH2	H	H	H	0		0	0	12.5	4.249	4.180	0.070
Clotrimazole											6.25			
Oxicona/olc											6.25			
Halopr ogin											3.12			

Table 2

Stepwise development of Eqn 5

Eqn no.	Equation	*n*	R^2	*s*	*F*	Q^2	S_{FRESS}
2	Log 1/C = + 0.286 (±0.094) Iz + +4.157 (±0.041)	74	0.58	0.159	36.671	0.295	0.164
3	Log 1/C = +0.223 (±0.076) Iz + + 0.336 (±0.097) σ_{R1} + + 4.100 (±0.036)	74	0.777	0.124	54.133	0.578	0.128
4	Log 1/C = +0.241 (±0.068)Iz + + 0.376 (±0.088) σRI + + 0.189 (±0.085) *Ix* + + 4.068 (±0.035)	74	0.831	0.110	51.951	0.667	0.115
5	Log 1/C = +0.284 (±0.058) Iz + + 0.397 (±0.073) σ_{R1}+ + 0.240 (±0.073) *Ix* + + 0.163 (±0.056) *Iy* + + 4.016 (±0.034)	74	0.890	0.091	65.882p <0.05	0.764	0.097

RESULTS AND DISCUSSION

In the present paper, a set of previously synthesized 2,5,6-trisubstituted benzoxazole, benzimidazole and 2-substitutedoxazolo(4,5-b)pyridine derivatives **1-74** were tested for their *in vitro* growth inhibitory activity against *C. albicans* and indicated MIC (Minimum Inhibitory Concentration) values between 6.25-25 μg/ml. The activity of the compounds were compared to clotimazole, oxiconazole and haloprogin as standard drags (19,20) (Table 1).

After applying multiple regression technique, the equation 5 was obtained, shown in Table 2, representing the best fit for the predictions according to the examined validation test results.

As can be deduced from Fig. 1, the goodness of fit of eqn. 5 is significant, possessing a high R^2 (89 %) and a small s (0.091) with an overall *F* test value of 65.882 at the significant level of $p < 0.05$.

In order to avoid the risk of chance correlation, with $R^2 \geq 0.9$ at the level or less which was pointed out by Topliss (33) have been taken into consideration that 74 observations (compounds) were used to screen the 15 variables.

To prove the predictive power of Eqn 5, cross-validation is applied to the original data set and the squared error of predictions PRESS is used to calculate Q^2 and S_{PRESS} values (29). The calculated overall S_{PRESS} is 0.097 and the calculated Q^2 is 0.764.

QSAR analysis, reveals that position R_1 of the fused ring system is important for the antifungal activity against *C. albicans*. The electronic positive sigma effect of a substituent at this position (σRI) produces an additive contribution to the activity indicating the significance of the electron withdrawing groups for the activity.

In addition to this feature, Eqn 5 also reveals that the structural parameters, *Ix, Iy* and Iz are important for the activity. Compounds possessing a methylene group between the p-substitutedphenyl moiety and the fused ring system at position 2 (Iz) provides an improvement in the activity. Additionally, activity contributions of the other structural parameters *Ix* and *ly* indicates that the oxazolo(4,5-b)pyridine ring system is the preferred structure over the other heterocyclic nuclei for the antifungal activity.

On the other hand, it was observed that there was no statistical significant relationships between the activity and any parameters related to the positions R and R_2.

According to the predictions obtained from QSAR analysis, the lead optimization in this set of compounds can be defined as the lead compound should have a heterocyclic structure of an oxazolo(4,5-b)pyridine ring system with a substitution of benzyl moiety at position 2. Moreover, a substituent which possesses electron withdrawing effect at position R, improves the activity against *C. albicans*.

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