Ankara Ecz. Fak. Der.
16. 24 (1986)

J. Fak. Pharm. Ankara
16, 24 (1986)

The Quantitative Structure-Activity Relationships of Antifungal Active 2-(p-Substituted-Phenyl) Benzoxazole Derivatives Against Candida Albicans Using The Combinations of Some Hydrophobic, Electronic And Steric Parameters

Candida Albicans'a Karşı Antifungal Etkili 2-(p-Sübstitüe-Fenil) Benzoksazol Türevleri ile Bazı Hidrofobik, Elektronik, Sterik Parametreler Kombinasyonlarının Kantitatif Yapı-Etki ilişkileri

Esin ŞENER* **İsmail YALÇIN*** **Seçkin ÖZDEN***
Tuncel ÖZDEN*

SUMMARY

The antifungal active 2-(p-substitutcd-phenyl) benzoxazoles against C. albicans were studied in a QSAR (quantitative structure-activity relationships) work using the multiple regression method. Some of the hydrophobic (π, π^2), electronic ($\dot{\sigma}$, F, R) and steric (MR, MW, P_r) constants were used as physicochemical parameters. The correlation equations and the best equation obtained from regression analysis were given.

As a result of quantitative structure-activity relationships of 2-(p-substituted-phenyl) benzoxazoles for C. albicans, it was found that hydrophobic, electronic or steric parameters were more significant when they were used in combined forms than they were used separately.

ÖZET

Candida albicans'a karşı antifungal etkili 2-(p-sübstitüe-fenil)-benzoxazol türevlerinin, çoklu regresyon metodu kullanılarak, kantitatif yapı-etki ilişkileri (QSAR) çalışılmıştır. Fizikokimyasal para-

Redaksiyona verildiği tarih: 15.4.1986

* Department of Pharmaceutical Chemistry, Faculty of Pharmacy Ankara University,

metreler olarak bazı hidrofobik (π, π^2), elektronik ($\dot{\sigma}$, F, R) ve sterik (MR, MW, P_r) sabiteler kullanılmıştır. Regresyon analizleri sonucu ele geçen korelasyon denklemleri ve ideal denklem çalışmada verilmiştir.

2-(p-Sübstitüe-fenil) benzoksazol türevlerinin kantitatif yapı-etki ilişkileri incelendiğinde, C. albicans için hidrofobik, elektronik ve sterik parametrelerin tek tek kullanılmaları yerine, kombinasyonlarının oldukça dikkate değer sonuçlar verdiği saptanmıştır.

Key Word Index

2-(p-Substituted-phenyl) benzoxazoles, π, π^2, $\dot{\sigma}$, F, R, MR, MW, P_r, QSAR, Best equation, C. albicans.

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. Ayopova et al. investigated the quantitative relationships between 2-(alkylthio) benzoxazole derivatives and their herbicide activity using Hansch's equations (1) and Evans et al. carried out QSAR studies on some antiinflammatory active 2-substituted, 4- and 7-benzoxazoleacetic and -methylacetic acids (2). Recently, quantitative structure-activity relationships of antihistaminic active 5-substituted-2-(p-substituted-benzyl) benzoxazoles (3) and antimicrobial active 2-(p-substituted-phenyl) benzoxazoles (4,5) were studied using some hydrophobic, electronic and steric parameters.

Benzoxazoles substituted at G—2 were prominently studied (6-16) trusting that this position is decisive for the biological activity. Evans et al. showed that para substituted 2-aryl-5-benzoxazolealkanoic acid derivatives had the highest activity compared to its analogs (12, 13). For that reason, para substituted derivatives of 2-phenylbenzoxazoles were chosen for QSAR studies.

It was reported by David et al. that five-membered heterocycles condensed with 2 benzene rings were chemotherapeutically active (17). Antimicrobial active 2-phenyl benzoxazole derivatives having 2 benzene rings and a 5 membered heterocycle are in agreement with that postulate (6-9, 18-22).

In our previous papers, the synthesis, structure elucidations and determination of antifungal activity of 2-(p-substituted-phenyl)

benzoxazole derivatives were given (7). It was stated that the activity of a compound is a function of t?three separable factor-: electronic effects, steric effects and hydrophobic effects with provision for structural or therotical effects (23) as shown below;

f (biological activity) — f (electronic) + f (steric) + f (hydrophobic) + [f (structural) + f (therotical)]

Consequently, we chose some steric, electronic and hydrophobic parameters for our quantitative structure-activity relationship (QSAR) studies (Table 1). 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;

Table 1. Physicochcmical parameters.

Physicochemical parameter	Symbol	Type of Effect
Pi substituent constant		Hydrophobic
Pi substituent constant	π^2	Hydrophobic
Sigma substituent constant		Electronic
Field effect	σ_F	Electronic
Resonance effect	R	Electronic
Molar refractivity	MR	Steric
Molecular weight	MW	Steric
Parachor	Pr	Steric

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

where xi, x_2,..... x_n are the descriptor values (pyhsicochemical substituent constants), y is related to the microbiological activity of benzoxazole derivatives, and the coefficients determined by a least squares analysis. This equation is developed for each benzoxazole derivative in our analysis.

In our previous papers, QSAR studies of 2-phenylbenzoxazoles in some gram (—) (4) and gram (+) bacteria (5) were reported. In this research, the activity of the same compounds against C. albicans is analized using physicochemical parameters, in order to design of more active derivatives. On this lead optimization method, the antifungal activity against G. albicans is thought as the function of the physicochemical parameters for these compounds.

EXPERIMENTAL

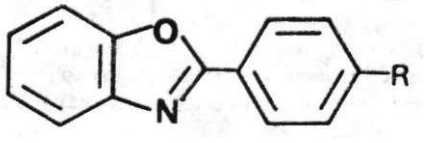
Material

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

Determination of the parameters

π, π^2, $\dot{\sigma}$, F, R, MR and MW values were taken from the table given by Hansch et al. (24). Parachor (P_r) relates principally to molecular volume (25) and it is used in QSAR studies (26). 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 (27). These values were shown in Table 2.

Table 2. The physicochemical parameters of 2-(p-substituted-phenyl) benzoxazole derivatives.



R	π	π^2	σp	F	R	MR	MW	Pr
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	468.1
$C(CH_3)_3$	1.98	3 9204	-0.20	-0.07	-0.13	19.62	57.1	557.2
C1	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
NFL	-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 AND DISCUSSION

Some hydrophobic (π, π^2), electronic ($\dot{\sigma}$, F, R) and steric (MR, MW, P_r) parameters were used as physicochemical constant for the quantitative structure-activity relationships of 2-(p-substituted-phenyl) benzoxazole derivatives. The best equation was obtained by multiple regression analysis using the Microstat computer program. Log 1/C values were used in the regression equations, where C was molar concentrations of the MIC values of the compounds against

C. albicans (7). The regression equations were stated in Table 3. The parameters in the best equation were selected using correlation matrix (Table 4). The best equation designed for C. albincans was shown in Table 5. According to the best equation observed values of log 1/C together with the calculated values were given in Table 6.

Table 3. Regression equations generated for 2-(p-substituted-phenyl) benzoxazole derivatives in C. albicans.

Equ. No	Equations
1	log 1/C = -0.09 (±0.18) π ± 3.64 n:7; R^2: 0.0498; s: 0.45; F: 0.26
2	log 1/C = -0.27 (±0.18) π + 0.24 (±0.13)π^2 ± 3.46 n: 7; R^2: 0.4734; s: 0.37; F: 1.80
3	log 1/C = -0.03 (±0.28) π + 0.12 (±0.17) π^2 0.64 (+ 0.57) F + 3.37 n: 7; R^3: 0.6274; s: 0.36; F: 1.68
4	log 1/C = —0.11(±0.05) π + 0.06 (±0.03) π^2 1.78 (±0.15) F ±2.01 (±0.2) R ± 3.88 n: 7; R^2: 0.9928; s: 0.06 ; F: 70.14
5	log 1/C = —0.63 (±0.11) π — 0.02 (±0.02) π^2 1.45 (±0.08) F ±2.98 (±0.21) R ± 0.08 (±0.02) MR ± 3.81 n: 7; R^2: 0.9997; s: 0.02; F: 648.56 (P < 0.03)

C is the molar concentrations of the MIC values of the compounds (7), the numbers in paranthesis in the regression equations represent the standart errors of the regriession 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 probabilty of F test.

Table 4. Correlation matrix between refgression parameters for 2-(p-substituted-phenyl) benzoxazole derivatives in C. albicans.

	Log 1/C	π	π^2	F	R	MR
Log 1/C	1.00					
π	-0.22	1.00				
π^2	0.40	0.58	1.00			
F	-0.70	0.61	-0.06	1.00		
R	-0.28	0.71	0.18	0.87	1.00	
MR	0.23	0.66	0.80	-0.15	-0.02	1.00

Table 5. Best equations generated for 2-(p-substituted-phenyl) benzoxazole derivatives in C. albicans.

System	Equation
C. albicans	log 1/C = - 0.6281 (±0.11) π - 0.0204 (±0.02)π^2 - 1.4500 (±0.08) F + 2.9790 (±0.21) R + 0.0823 (± 0.02) MR + 3.8058 n:7; R^2: 0.9997; s: 0.02; F: 648.56 (P<0.03)

Table 6. Antifungal activity of 2-(-psubstituted-phenyl) benzoxazole derivatives against C. albicans, (log 1/C).

Com. No	C. albicans		
	Obsd	Calcd	Residual
1	3.893	3.891	0.002
2	3.353	3.338	0.015
3	4.002	4.000	0.002
4	3.060	3.066	-0.006
5	3.137	3.142	-0.005
6	3.925	3.925	0.000
7	3.953	3.960	-0.007

The multiple regression analysis results show that the antifungal activity of 2-(p-substituted-phenyl) benzoxazoles against C. albicans are fundementally a function of the combinations of some hydrophobic, electronic and steric parameters. The parameters used alone do not show good correlations with the activity.

The P value of the F-test in the best equation is found less than 0.05. This shows us that the physicochemical parameters used as independent variables are related to the dependent variable (log 1 /C) in the multiple regression analysis (28). In addition, the standart deviation (s) is minimized and forward elimination procedure which is one of the stepwise regression method is stated (Table 3). At last, the multiple regression coefficient squared (R^2) which is proportional to the amount of variance explained by the equation is maximized (Table 5).

As a result of examination of the best equation which is parabolic and established for 2-phenylbenzoxazoles against C. albicans, it is found that the hydrophobic parameters π and π^2 are necessary for the activity. F and R constants are also adapted as the electronic parameters in the equation, only MR is available as a steric parameter among the others. R^2 is established in the best equation as 0.9997 which denotes that the best equation can be used to predict the antifungal activity for untested 2-(p-substituted-phenyl) benzoxazole derivatives against C. albicans.

.

REFERENCES

1- **Ayopova, A.T., Molchanov, L.V., Kadyrov, Ch. Sh., Aliev ,N.A., Giyasov, K., Loi, N.P., Tsoi, Z.I., Umarov, A.A.:** *Agrokhimiya,* **10,** 107, (1977). Ref.: Chem. Abstr., 92, 53261 s., (1980).

2- **Evans, D., Smith, C.E., Williamson, W.R.N.:** J. *Med. Chem.,* **20** (1), 169, (1977).

3- **Noyanalpan, N., Şener, E.:** *J. Fac. Pharm. Gazi,* **3** (1), 1, (1986).

4- **Şener, E., Yalçın, İ., Özden, S., Özden, T.:** *Ibid.,* (1986) (in Press).

5- **Yalçın, İ., Şener, E., Özden, T., Özden, S.** *Fabad J. Pharm.* Sei., (1986) (in Press).

6- **Cossey, H.D., Gartsıde, R.N., Stephens, F.F.:** *Arzneim. Forsch. Drug Res.,* **16** (1), 33, (1966).

7- **Şener, E., Özden, S., Yalçın, İ., Akm.A,. Yıldız, S.:** *Fabad J. Pharm. Sci.,* **11,** 190, (1986).

9- **Özden, S., Özden, T., Şener, E., Yalçın, İ., Akın, A., Yıldız,** S.: ***Ibid.,*** (1986) (in Press). *

10- **Bywater, W.G., Coleman, W.R., Kamm, O., Merrit, H.H.:** *J. Amer. Chem. Soc.,* **67,** 905, (1945).

11- **Cashın, C.H., Danwell. D.W., Evans, D., Hicks, T.A., Kitchen, E.A.:** *J. Pharm. Pharmac,* **29,** 330, (1977).

12- **Cashin, C.H., Dunwell, D.W., Evans, D., Hicks, T.A., Kitchen, E. A.:** *J. Med. Chem.,* **18** (1), 53, (1975).

13- **Evans, D., Dunwell, D.W., Hicks, T.A.:** *Ibid.,* **18** (1), 1158, (1975).

14- **Haugwitz, R.D., Angel, R.G., Jacops, G.A., Maurer, B.V., Narayanan, V.L., Cruthers, L.R., Szanto, J.:** *Ibid.,* **25,** 969, (1982).

15- **Rips, R., Lachaize, M., Albert, O., Dupont, M.:** *Chim. Ther.,* **6** (2), 126, (1971).

16- **Schulze, W., Gutsche, W., Jungstand, W.:** *Arzneim.-Forsch./ Drug Res.,* **15** (10), 1235, (1965).

17- **Davis, D., Lo, C:** *Phytopathology,* **44,** 680, (1954).

18- **Cossey, H.D., Sharpe, C.J., Stephens, F.F.:** *J. Chem. Soc,* 4322, (1963).

19- **Haskell, T.H., Peterson, F.E., Watson, D., Plessas, N.R., Culbertson, T.:** J. *Med. Chem.,* **13** (4), 697, (1970).

20- **Elnima, E. I., Zubair, M.V., Al-Badr, A.A.:** *Antimicrob. Agents Chemother.,* **19** (1), 29, (1981). Ref.: Chem. **Abstr., 94,** 133032z, (1981).

21- **Tabata, T., Kondo, T.:** *Mokuzai Gakkaish,* 1977, **23** (10), 504. Ref.: Chem. Abstr., 88, 33004z, (1978).

22- **Crocker, H.P., Raper, W.G.C.:** U.S. 3.452.036, 24Jun 1969.

23- **Wollf, M.E.:** Burger's Medicinal Chemistry, Vol. I, John Wiley and Sons Ltd., New York, 397, (1980).

24- **Hansen, C, Leo, A., Unger, S.H., Kim, K.H., Nikaitani, D., Lien, E. J.:** J. *Med. Chem.,* **16** (11), 1207, (1973).

25- **Hansch, C, Leo, A., Church, C:** *Ibid.,* **12,** 766, (1969).

26- **Ahmad, P., Fyfe, C.A., Mellors. A.:** *Biochem. Pharmacol., **24,*** 1103, (1975).

27- **Quayle, O.R.:** *Chem. Rev.,* **53,** 439, (1953).

28- **Wollf, M.E.**: Burger s Medicinal Chemistry, *Vol. I.* John Wiley and Sons Ltd., New York, 406, (1980).