12

FABAD Farm. Bil. Der.
12, 48 - 55, 1987

FABAD J. Pharm. Sci.
12, 48 - 55, 1987

THE QUANTITATIVE STRUCTURE — ACTIVITY RELATIONSHIPS OF ANTIBACTERIAL ACTIVE 2-(p-SUBSTITUTED-PHENYL) BENZOXAZOLE DERIVATIVES AGAINST GRAM (+) BACTERIA USING THE COMBINATIONS OF SOME HYDROPHOBIC, ELECTRONIC AND STERIC PARAMETERS

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

Summary : The antibacterial activity of 2-(p-substituted-phenyl) benzoxazole derivatives were thought as a function of their physicochemical parameters. From this phenomenon, we selected some hydrophobic (π, π^2), electronik (δ, F, R) and steric (MR, MW, P_i constants of 2-(p-substituted-phenyl)benzoxazoles as their physicochemical parameters and studied the quantitative structure-activity relationships of these compounds against the gram (+) bacteria such as S. faecalis and Staph. aureus. The correlation equations of these relationships which were designed from the Hansch analysis were given.

The correlation method of the antibacterial activity against gram (+) bacteria for 2-phenylbenzoxazoles, the combinations of hydrophobic, electronic and steric parameters were found more significant than hydrophobic, electronic or steric parameters used separately. The best equations obtained from QSAR studies were stated.

(*) A.Ü. Eczacılık Fakültesi, Farmasötik Kimya Anabilim Dalı, Tandoğan - Ankara

GRAM (+) BAKTERİLERE KARŞI ANTİBAKTERİYEL ETKİLİ 2-(p-SÜBSTİTÜE-FENİL) BENZOKSAZOL TÜREVLERİ İLE BAZI HİDROFOBİK, ELEKTRONİK VE STERİK PARAMETRELER KOMBİNASYONLARININ KANTİTATİF YAPI-ETKİ İLİŞKİLERİ

Özet : 2-(p-Sübstitüe-fenil)benzoksazol türevlerinin antibakteriyel etkilerinin, bileşiklerin fizikokimyasal özelliklerinden kaynaklandığı düşünülmüştür. Bu düşünceden hareketle, 2-(p-sübstitüe-feni)benzoksazol türevlerinin, S. faecalis ve Staph. aureus gibi gram (+) bakterilere karşı bulunan antibakteriyel etkileri arasındaki, kantitatif yapı-etki ilişkiler, bazı hidrofobik (π, π^2), elektronik (δ, F, R) ve sterik (MR, MW, P_r) parametreler kullanılarak incelenmiştir. Bu çalışmada, Hansch analizinden faydalanılarak bulunan korrelasyon denklemleri verilmiştir.

2-Fenilbenzoksazol türevleri için hidrofobik, elektronik ve sterik parametreler kombinasyonları kullanıldığında, gram (+) bakterilere karşı etki ile ilişki, bu parametreler tek başlarına kullanıldığı şekline göre daha dikkate değer bulunmuştur. QSAR çalışmaları sonucunda elde edilen ideal denklemler de bu çalışmada verilmiştir.

Keywords : 2-(p-Substituted-phenyl)benzoxazoles, π, π^2, δ, F, R, MR, MW, P_r QSAR, Best Equation, Streptococcus, faecalis, Staphylacoccus aureus.

INTRODUCTION

Five-membered heterocycles condensed with 2 benzene rings were postulated as chemotherapeutically active (1). Antimicrobial active 2-phenylbenzoxazole derivatives having 2 benzene rings and a 5 membered heterocycle are in agreement with that postulate (2-10).

In our previous paper, the synthesis, structure elucidations and determination of antibacterial activity of 2-(p-substituted-phenyl) benzoxazole derivatives were given (8), because of trusting benzoxazoles substituted at C-2 position is decisive for the biological activity (7, 11-17).

It was reported that the activity of a compound is a function of three separable factors : electronic effects, steric effects and hydrophobic effects with provision for structural or therotical effects (18) as shown below;

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

For that reason we select some steric, electronic and hydrophobic

parameters for our quantitative structure - activity relationship (QSAR) studies. The linear 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 follow;

$y = a_o + a_1 x_1 + a_2 x_2 + \ldots\ldots + a_n x_n$ where x_1, x_2, ... x_n are the descriptor values (physicochemical substituent constants), y is related to the microbiological activity of benzoxazole derivatives, and a_1, a_2, ... a_n are the coefficients determined by a least squares analysis. This equation ise developed for each benzoxazole derivative in our analysis.

The use of this method with physicochemical substituent constants and quantitative biological data forms the basis for the Hansch analysis. This metodology has also been called physicochemical structure-activity relationship (PSAR). PSAR has been used primarily to analyse data on sets of congeners (18). In general, this approach is to set up the equations involving different combinations of the substituent constants, then to allow the correlative method to aid in the selection of the best equation for our study.

In our previous paper, QSAR studies of 2-phenylbenzoxazoles in gram (—) bacteria were reported (19). In this research, the activity of the same compounds against gram (+) bacteria such as S. faecalis and Staph. aureus are analized for the first time using physicochemical parameters, in order to design of more active derivatives. The antimicrobial activity against gram (+) bacteria for these compounds are thought as the function of the physicochemical parameters on this lead optimization method.

MATERIAL AND METHOD

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

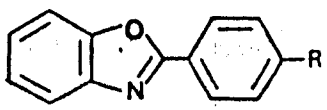
P_r (Parachor) relates principally to molecular volume (20) and it is used in QSAR studies (21). P_r values of each compound were calculated by the additive summation the P_r values of all the atoms and the structural features using Qayle's Table (22). π (p i substituent constant), π^2 (the square of p i substituent constant), δ (sigma substituent constant), F (field effect), R (resonace effect), MR (molar refractivity) and MW (molar value) were taken from the table given by Hansch et al. (23). These values were shown in Table 1.

RESULTS

To design the best equations of 2-(p-substituted-phenylbenzoxa-

zoles, the antibacterial activity against gram (+) bacteria such as S. faecalis and Staph. aureus were chosen as the biological activity. Some hydrophobic (π, π^2), electronic (δ, F R) and steric (MR, MW, P_r) parameters used as pyhsicochemical constants for the

Table 1 : The physicochemical parameters of 2-(p-substituted-phenyl)benzoxazole derivatives.



R	π	π^2	σ_p	$\mathcal{F}$	$\mathcal{R}$	MR	MW	P_r
H	0.00	0.0000	0.00	0.00	0.00	1.03	1.0	400.3
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
Cl	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
NH_2	-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

Table 2 : Regression equations generated for 2-(p-substituted-phenyl)benzoxazole derivatives in S. faecalis.

Equ. No	Equations
1	log 1/C = -0.14(±0.11)π + 3.44 n: 7 ; R^2: 0.2515 ; s: 0.27 ; F: 1.68
2	log 1/C = -0.12(±0.11)π - 0.37(±0.51)$\mathcal{F}$ + 3.48 n: 7 ; R^2: 0.3400 ; s: 0.28 ; F: 1.03
3	log 1/C = -0.27(±0.13)π - 0.55(±0.44)$\mathcal{F}$ + 0.77(±0.48)$\mathcal{R}$ + 3.81 n: 7 ; R^2: 0.6462 ; s: 0.24 ; F: 1.83
4	log 1/C = 0.97(±0.22)π - 1.6(±0.23)$\mathcal{F}$ - 2.09(±0.52)$\mathcal{R}$ -0.17(±0.03) MR + 4.05 n: 7 ; R^2: 0.9795 ; s: 0.07 ; F: 23.85
5	log 1/C = 1.09(±0.03)π + 1.99(±0.05)$\mathcal{F}$ - 2.37(±0.07)$\mathcal{R}$ -0.19(±0.00)MR + 0.004(±0.00) MW + 4.09 n: 7 ; R^2: 0.9998 ; s: 0.01 ; F: 1181.20 (P < 0.02)

C is the molar concentrations of the MIC values of the compounds (6), 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 probabilty of F test.

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 con-

Table 3 : Correlation matrix between regression parameters for 2-(p-substituted-phenyl)benzoxazole derivatives in S. feacalis.

	Log 1/C	π	$\mathcal{F}$	$\mathcal{R}$	MR	MW
Log 1/C	1.00					
π	-0.50	1.00				
$\mathcal{F}$	-0.40	0.21	1.00			
$\mathcal{R}$	-0.03	0.71	0.32	1.00		
MR	-0.65	0.66	-0.25	-0.02	1.00	
MW	-0.79	0.66	0.46	0.21	0.63	1.00

Table 4 : Regression equations generated for 2-(p-substituted-phenyl)benzoxazole derivatives in Staph, aureus

Equ. No	Equations
1	log 1/C = -0.40(±0.14)π + 3.80 n: 7 ; R^2: 0.6266 ; s: 0.35 ; F: 8.38
2	log 1/C = -0.51(±0.20)π + 0.56(±0.70)$\mathcal{R}$ + 4.03 n: 7 ; R^2: 0.6776 ; s: 0.36 ; F: 4.20
3	log 1/C = -0.66(±0.73)π + 1.00(±2.05)$\mathcal{R}$ + 0.02(±0.10)MR + 4.03 n: 7 ; R^2: 0.6933 ; s: 0.41 ; F: 2.16
4	log 1/C = -0.17(±0.91)π - 0.08(±2.26)$\mathcal{R}$ - 0.01(±0.10) MR -0.01(±0.01) MW + 4.18 n: 7 ; R^2: 0.7950 ; s: 0.40 ; F: 1.95
5	log 1/C = -1.43(±0.03)π + 2.50(±0.21)$\mathcal{R}$ - 0.33(±0.02) MR -0.01(±0.00) MW + 0.05(±0.00) P_r - 15.64 n: 7 ; R^2: 0.9994 ; s: 0.03 ; F: 360.25 (P<0.05)

Table 5 : Correlation matrix between regression parameters for 2-(p-substituted-phenyl)benzoxazole derivatives in Staph. aureus.

	Log 1/C	π	$\mathcal{R}$	MR	MW	P_r
Log 1/C	1.00					
π	-0.79	1.00				
$\mathcal{R}$	-0.40	0.71	1.00			
MR	-0.66	0.66	-0.02	1.00		
MW	-0.33	0.66	0.21	0.63	1.00	
P_r	-0.59	0.63	0.01	0.39	0.57	1.00

centrations of the MIC values of the compounds (8). The data on the parameters were stated in Table 1. Observed and calculated values of log 1/C were given in Table 6. The regression equations stated in Tables 2 and 4 and the parameters in the best equations were selected according to the correlation matrixes (Table 3 and 5) and the squares of their partial regression coefficients.

Table 6 : Observed and calculated log 1/C values of 2-(p-substitutedphenyl)-benzoxazole derivatives according to the best equations given in Tables 2 and 4.

Com. No	S. faecalis			Staph. aureus		
	Obsd	Calcd	Residual	Obsd	Calcd	Residual
1	2.93	3.68	0.00	4.18	4.18	0.01
2	3.35	3.35	0.00	4.26	4.26	0.00
3	3.01	3.01	0.00	3.10	3.10	0.00
4	3.36	3.37	-0.01	3.36	3.38	-0.02
5	3.14	3.14	0.00	3.14	3.13	0.01
6	3.32	3.32	0.00	4.23	4.24	-0.01
7	3.65	3.65	0.00	3.65	3.64	0.01

DISCUSSION

The multiple regression analysis results show that the activity against S. faecalis and Staph. aureus are fundamentally a function of the combinations of some hydrophobic, electronic and steric parametrs. It is interesting that the parameters used alone do not show good correlations with the activity in the QSAR studies. But, if they are used in combinations significant relationships can be seen with the antibacterial activity.

The P values of the F-tests for the best equations (Table 2, equ. no : 5 and Table 4, equ. no: 5) are 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 procedure, one of stepwise regression method, is stated in our study (Tab.

le 2 and 4). These situations are statistichally justified the best equations.

The best equations which are obtained from the regression analysis, involve π value instead of π^2 as hydrophobic parameter which cause a linear relationship, F and/or R are more available than the δ, as the electronic parameters and the values of the MW and MR as steric parameters fit both of the best equations. P_r, a steric parameter, is only adapted for Staph. aureus.

The square of multiple regression coefficient (R^2) were obtained for Staph. aureus as 0.9994 and for S. faecalis as 0.9998. This means that the best equation which we have established can be used to predict the antibacterial activity for untested 2-(p-substituted-phenylbenzoxazoles against S. faecalis and Staph. aureus. Of. course, this observation supplies a lot of advantages in designing the most active compound.

REFERENCES

1. Davis, D., Lo, C., «Chemotherapeutic Activity of Unsubstituted Heterocyclic Compounds», Phytopathology, 44, 680, 1954.
2. Cossey, H.D., Sharpe, C.J., Stephens, F.F., «Some Antimicrobial Compounds in the Heterocyclic Series», J. Chem. Soc., 4322, 1963.
3. Haskell, T.H., Peterson, F.E., Watson, D., Plessas, N.R., Culbertson, T., «Neuraminidase Inhibition and Viral Chemotheraphy», J. Med. Chem., 13(4), 897, 1970.
4. Elnima, E.I., Zubair, M.V., Al. Badr, A.A., «Antibacterial and Antifungal Activities of Benzimidazole and Benzoxazole Derivatives», Antimicrob. Agents Chemother., 19(1), 29, 1981. Ref.: Chem. Abstr., 94, 133032z, 1981.
5. Tabata, T., Kondo, T., «Protection of Shiitake Fungus from Myocoparasites by Fungicial Agents», Mokuzai Gakkaish, 23 (10, 504, 1977. Ref. : Chem. Abstr., 88, 33004z, 1978.
6. Croker, H.P., Raper, W.G.C., «2-Substituted Benzoxazoles», U.S. 3,452,036, 24 Jun 1969.
7. Cossey, H.D., Gartside, R.N. Stephens, F.F., «The Antimicrobial Activity of Benzothiazole Basic Ethers and Related Compounds», Arzneim. Forsch./Drug Res., 16(1), 33, 1966.
8. Şener, E., Özden, S., Yalçın İ., Akın, A., Yıldız, S., «2-(p-Sübstitüefenil)benzoksazol Türevlerinin Sentez, Yapı Aydınlatması ve Mikrobiyolojik Etkisi, FABAD J. Pharm. Sci., 11(3), 190, 1986.
9. Yalçın, İ., Şener, E. Özden, S., Özden, T., Akın, A., Yıldız, S., «5-Kloro-2- (p-sübstitüefenil benzoksal Türevlerinin Sentez, Yapı Aydınlatması ve Mikrobiyolojik Etkisi», FABAD J. Pharm. Sci., 11(4), 157, 1986.
10. Özden, S., Özden, T., Şener, E., Yalçın, İ., Akın, A., Yıldız, S., «5-Nitro-2-(psübstitüefenil)

benzoksazol Türevlerinin Sentez, Yapı Aydınlatması ve Mikrobiyolojik Etkisi», FABAD J. Pram. Sci., 1986 (in Press).

11. Bywater, W.G., Coleman, W.R., Kamm, O., Merrit, H.H., «Synthetic Anticonvulsants», J. Amer. Chem. Soc., 67, 905, 1945.
12. Cashin, C.H., Dawon, W., W., Kitchen, E.A., «The Pharmacology of Benoxaprofen (2-(4-Chlorophenyl)- -methyl-5-benzoxazoleacetic Acid), LRCL 3794, a New Compound with Antiinflamatory Activity Apprantely Unrelated to Inhibition of Prostaglandin Synthesis», J. Pharm. Pharmac., 29, 350, 1977.
13. Cashin, C.H., Dunwell, D.W., Evans, D., Hicks, T.A., Kitchen, E.A., «2-Aryl-5-benzoxazolealkanoic Acid Derivatives with Notable Antiinflammatory Activity», J. Med. Chem., 18(1), 53, 1975.
14. Evans, D., Dunwell, D.W., Hicks, T.A., «Synthesis and Antinflammatory Activity of Some 2-Heteroaryl- α-Methyl-5-Benzoxazoleacetic Acids», J. Med. Chem., 18(11), 1158, 1975.
15. Haugwitz, R.D., Angel, R.G., Jacops, G.A., Maurer, B.V., Narayanan, V.L., Cruthers, L.R., Szanto, J., «Antiparasitic Agents», J. Med. Chem., 25(8), 969, 1982.
16. Rips, R., Lachaize, M., Albert, O., Dupont, M., «Antiinflammatory 2-Arylbenzoxazoles», Chim. Ther., 6(2), 126, 1971.
17. Schulze, W., Gutsche, W., Jungstand, W., «Schiff Bases and Phenylnitrones of Some N-Heteroycylic Compounds», Arzneim. -Forsch./Drug Res., 15(10, 1235, 1965.
18. Chu, K.C., «The Quantitative Analysis of Structure-Activity Relationships, Wollf, M.E. (ed), Burger's Medicinal Chemistry, New York, John Wiley and Sons Ltd., Vol. I, 393, 1980.
19. Şener, E., Yalçın, İ., Özden, S., Özden, T., «The Quantitative Structure-Activity Relationships of Antibacterial Active 2-(p-Substitued-phenyl)benzoxazole Derivatives against Gram (—) Bacteria using the Combinations of Some Hydrophobic, Electronic and Steric Parameters» J. Fac. Pharm. Gazi, 1986 (in press).
20. Hansch, C., Leo, A., Church, C., «Comparasition of Parameters Currently used in the Study of Structure-Activity Relationships», J. Med. Chem., 12(5), 766, 1969.
21. Ahmad, P., Fyfe, C.A., Mellors, A., «Parachors in Drug Design», Biochem. Pharmacol., 24, 1103, 1975.
22. Quayle, O.R., «The Parachors in Drug Design, Chem. Rev., 53, 439, 1953.
23. Hansch, C., Leo, A., Unger, S.H., Kim, K.H., Nikaitani, D., Lier, E.J. «Aromatic Substituent Constants for Structure-Activity Correlations», J. Med. Chem., 16(11), 1207, 1973.