ISSN 1015-3918

ANKARA ÜNİVERSİTESİ
ECZACILIK FAKÜLTESİ DERGİSİ

JOURNAL OF FACULTY OF PHARMACY OF ANKARA UNIVERSITY

Cilt/Vol : 27
Sayı/No : 1
Yıl /Year: 1998

ANKARA ÜNİVERSİTESİ
ECZACILIK FAKÜLTESİ DERGİSİ

JOUNAL OF FACULTY OF PHARMACY OF ANKARA UNIVERSITY

Cilt/Vol : 27
Sayı/No : 1
Yıl/Year: 1998

Ankara - 1998

ANKARA ÜNİVERSİTESİ ECZACILIK FAKÜLTESİ DERGİSİ

Sahibi: Prof.Dr. Seçkin ÖZDEN

Editör: Prof.Dr. Feyyaz ONUR

Ankara Üniversitesi Eczacılık Fakültesi dergisi yılda 2 sayı yayınlanır.

Yayımlanana yazıların sorumluluğu yazara aittir.

Bu dergi **Chemical Abstracts (CA), EMBASE / Excerpta Medica ve Medicinal Aromatic Plants Abstracts (MAPA)** da indekslenmektedir.

Yazışma adresi:
Ankara Üniversitesi,
Eczacılık Fakültesi,
06100 Tandoğan - Ankara

Tel: (0312) 222 04 71
Fax: (0312) 213 10 81
e-mail: ankfarmj@pharmacy.ankara.edu.tr.

Ankara Üniversitesi Basımevi,
1998

JOURNAL OF FACULTY OF PHARMACY OF
ANKARA UNIVERSITY

Published by : Prof .Dr. Seçkin ÖZDEN

Editor : Prof.Dr. Feyyaz ONUR

Journal of Faculty of Pharmacy of Ankara University is published in semi-annual volumes.

This journal is indexed in **Chemical Abstracts (CA), EMBASE / Excerpta Medica and Medicinal Aromatic Plants Abstracts (MAPA).**

Address:
Ankara University,
Faculty of Pharmacy,
06100 Tandoğan - ANKARA
TURKEY

Tel:+90 312 222 04 71
Fax:+90 312 213 10 81
e-mail: ankfarmj@pharmacy.ankara.edu.tr.

Ankara Üniversitesi Basımevi,
1998

İÇİNDEKİLER / CONTENTS

Ankara Ecz. Fak. Derg.
27 (1) 1-9, 1998

J.Fac.Pharm.Ankara
27 (1) 1-9,1998

QSAR OF SOME ANTIFUNGAL ACTIVE BENZOXAZOLES AND BENZIMIDAZOLES AGAINST *C. albicans*

BAZI ANTIFUNGAL ETKİLİ BENZOKSAZOL VE BENZİMİDAZOLLERİN *C. albicans'a.* KARŞI KANTİTATİF YAPI-ETKİ İLİŞKİLERİ

İlkay ÖREN*

* Ankara University, Faculty of Pharmacy, Pharmaceutical Chemistry Dept, Tandoğan 06100, Ankara, Turkey.

SUMMARY

In this study, QSAR analysis of some isosteric heterocyclic compounds including benzoxazole and benzimidazole derivatives were studied for the antifungal activity against Candida albicans. The Free-Wilson approach is a valuable alternative tool in QSAR analysis for evaluating the lead generation and / or optimization in drug design. Predictions for the lead optimization in this series of compounds have been described by the results obtained from Free-Wilson analysis with the determination of the activity contributions of the performed structural descriptors.

The results of Free-Wilson analysis suggest that having 2-cyclohexylethyl moiety at the 2nd position on the heterocyclic system is significant for the antifungal activity and 5-CI group is the most favorable substituent among the others.

Key words: Benzoxazole, Benzimidazole, Antifungal activity, QSAR, Free-Wilson analysis

ÖZET

Bu çalışmada, benzoksazol ve benzimidazol halkası içeren bazı izosterik heterosiklik bileşiklerin Kantitatif Yapı-Etki ilişkileri analizi Candida albicans'a karşı gösterdikleri antifungal aktiviteleri için araştırıldı, İlaç tasarımında kılavuz bileşik oluşumunun ve /veya optimizasyonunun sağlanmasında Free-Wilson metodu, Kantitatif Yapı-Etki İlişkileri analizinde yararlı alternatif bir yöntemdir. Bu seri bileşikler içinde kılavuz bileşiğin optimizasyonu, kullanılan yapısal parametrelerin Free-Wilson analizi sonucunda elde edilen aktiviteye katkıları ile belirlenmiştir.

Free-Wilson analizi sonucunda, antifungal aktivite için heterosiklik sistemin 2. konumda 2-siklohekziletil yapısını içermesi ve 5-Cl grubunun diğerlerine göre daha önemli olduğu saptanmıştır.

Anahtar Kelimeler: Benzoksazol, Benzimidazol, Antifungal aktivite, Kantitatif yapı-etki ilişkileri. Free-Wilson analizi

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 (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 (3).

Recent studies led to the discovery of certain highly substituted imidazole derivatives such as miconazole and clotrimazole (4, 5) which possess good clinical activity in dermatophytoses and nonsystemic candidiasis. Unfortunately, systemic use of miconazole has been accompained by reversible thrombocytosis and anemia and of clotrimazole by severe gastrointestinal disturbances (2).

Recently, we reported the synthesis and their *in vitro* antifungal activities of different derivatives of 5-substituted-2-cyclohexyl, 2-cyclohexylmethyl, 2-(2-cyclohexylethyl), 2-cyclopentyl, 2-cyclopentylmethyl, 2-(2-cyclopentylethyl) benzoxazoles and benzimidazoles against the fungus *Candida albicans* (6,7).

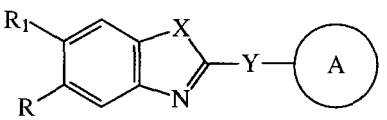
The Free-Wilson approach is a satisfactory method applied for quantitative structure-activity relationships (8-10). The basic assumption of this procedure is that within a homologues series of drugs individual segments of molecules make additive and constant contributions to biological activity. If such contributions are known, biological activity can be estimated by simple addition for all the compounds obtainable by any new combination of the segments involved.

Free-Wilson analysis can be applied to homologues series where only substituents are varied in a constant parent molecule. The selection of these substituents, however, must not meet all of the requirements of the extrathermodynamic approach. In particular, series where only a few substituents are varied in many positions can be analysed by the Free-Wilson method.

One possible way to deal with such situations is to use parameters derived directly from two-dimensional chemical structures as molecular descriptors; such descriptors will be called "structural parameters". The structures to be considered are broken down into fragments and the structural parameters then indicate the occurrence of these fragments in these structures. Fragmentation and description of molecules in structural terms can be performed in many different ways, and different approaches can be used to related structural parameters to biological activity. In the most simple case it

is assumed that substituents at certain positions (fragments) make additive and constitutive contributions to biological activity which can be expressed in terms of a linear model called the Free-Wilson model.

In this present study, QSAR analysis of some antifungal active fused heterocycles **1-20** having cyclohexyl, cyclohexylmethyl, 2-cyclohexylethyl, cyclopentyl, cyclopentylmethyl or 2-cyclopentylethyl moieties at the position 2 and bearing H, CI, NO_2 groups at the position 5 or/and 6 given in Figure 1 against C. *albicans* were determined using the Free-Wilson method.



X = O, NH R = H, CI, $N0_2$
Y= —, CH_2, C_2H_4 R_1 = H, $N0_2$
A = cyclohexyl, cyclopentyl

Figure 1

7

EXPERIMENTAL SECTION

The basic assumption of the Free-Wilson method is that within a set of congeners of compounds, individual segments of molecules called as molecular descriptors make additive and constant contributions to biological activity (9).

This expression is formulated as,

$$\text{Log } 1/C = \Sigma a_i x_i + \mu \qquad \text{Eq 1}$$

Where a_i is the contribution of the ith substituent, and if the substituent is present in the molecule, x_i has a value of 1, otherwise a value of 0. The overall average activity calculated for the unsubstituted (constant) molecule is indicated as μ.

At the first step, the structure matrix given in Table 1 has been drawn up by listing the structural parameters x_i and used in Eq 1 that yielded the linear equation set of the compounds **1-20.**

At the next step, additional restrictive equations, so called symmetry conditions, have been formulated that the sum of the varying groups equaled to 0.

Symmetry equations for the sample are;

For position R,

$9a_{11}+8a_{12}+3a_{13}= 0$ Eq2

For position R_1,

$16a_{21} + 4a_{22} = 0$ Eq 3

For position X,

$9a_{31}+11a_{32} = 0$ Eq4

For position Y,

$7a_{41}+7a_{42}+6a_{43} = 0$ Eq 5

For position A,

$14a_{51}+6a_{52} = 0$ Eq 6

a_{11}, a_{21}, a_{31}, a_{41} and a_{51} have been selected as a dependent variable at each position from Eqs 2-6.

$a_{11} = -8/9a_{12} - 3/9a_{13}$ Eq 7

$a_{21} = -4/16a_{22}$ Eq8

$a_{31} = -11/9a_{32}$ Eq9

$a_{41} = -7/7a_{42}-6/7a_{43}$ Eq 10

$a_{51} = -6/14a_{52}$ Eq 11

Expression obtained from Eqs 7-11 are combined as substitutes of a_{11}, a_{21}, a_{31} ,a_{41} and a_{51} in the equation set of the linear system and a correlation matrix derived. The correlation matrix given in Table 2.

Molecular descriptor values used in the Multiple Regression analysis were obtained from the correlation matrix and the observed log 1/C values have been used as dependent variable.

Besides the group contributions, the ranges of the activity contribution values of the substition position sides were also calculated by the equations given below;

$R = a_{12} - a_{13}$ Eq 12

$R_1 = a_{22} - a_{21}$ Eq 13

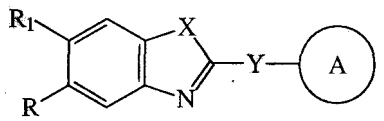
$X = a_{32} - a_{31}$ Eq 14

$Y = a_{43} - a_{41}$ Eq 15

$A = a_{51} - a_{52}$ Eq 16

Correlation and regression analysis of this QSAR study performed by using IBM-computer working with Statgraff 2.6 Statistic Program package.

Table 1: Structure matrix of the compounds 1-20 for the Free-Wilson analysis



Comp No:	R	R_1	X	Y	A	R			R_1		X		Y			A		MIC	log 1/C
						a_{11} -H	a_{12} -CI	a_{13} -NO2	a_{21} -H	a_{22} -NO2	a_{31} -0-	a_{32} -NH-	a_{41} —	a_{42} -CH2-	a_{43} -C2H4-	ası cyclohexyl	a_{52} cyclopentyl	mg/ml	
1	CI	H	0	—	cyclohexyl		1		1		1					1		50	3.6730
2	H	NO2	O	—	cyclohexyl					1	1					1		50	3.6702
3	CI	NO_2	O	—	cyclohexyl		1			1	1					1		50	3.7299
4	H	H	NH	—	cyclohexyl							1				1		25	3.9031
5	NO_2	H	NH	—	cyclohexyl			1				1				1		50	3.6902
6	H	H	NH	—	cyclopentyl							1					1	50	3.5416
7	CI	H	NH	—	cyclopentyl		1					1					1	50	3.6201
8	NO_2	H	O	CH_2	cyclohexyl			1			1					1		50	3.7160
9	H	NO2	O	CH_2	cyclohexyl					1	1					1		25	3.9965
10	CI	NO_2	0	CH_2	cyclohexyl		1			1	1					1		25	4.0531
11	H	H	NH	CH_2	cyclohexyl							1				1		25	3.9325
12	CI	H	NH	CH_2	cyclohexyl		1					1				1		25	3.9974
13	NO_2	H	NH	CH_2	cyclohexyl			1				1				1		50	3.7143
14	H	H	NH	CH_2	cyclopentyl							1					1	50	3.5752
15	H	H	O	C2H4	cyclohexyl						1					1		12.5	4.2629
16	CI	H	0	C2H4	cyclohexyl		1				1					1		12.5	4.3239
17	H	H	NH	C2H4	cyclohexyl							1				1		12.5	4.2610
18	CI	H	0	C2H4	cyclopentyl		1				1						1	25	3.9777
19	H	H	NH	C2H4	cyclopentyl							1					1	25	3.9074
20	CI	H	NH	C2H4	cyclopentyl		1					1					1	25	3.9759
Sum.						9	8	3	16	4	9	11	7	7	6	14	6		

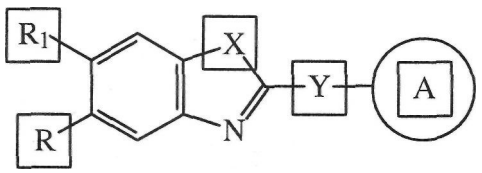
Table 2: Correlation matrix derived from symmetry equations

Comp. No:	R	R_1	X	Y	A	R		R_1	X	Y		A	MIC mg/ml	log 1/C
						a_{12} -CI	-NO_2	a_{22} -NO_2	a_{32} -NH-	a_{42} -CH_2-	a_{43} -C_2H_4-	a_{52} cyclopentyl		
1	CI	H	0	—	cyclohexyl	1	0	-0.25	-1.22	-1	-0.857	-0.43	50	3.6730
2	H	NO_2	0	—	cyclohexyl	-0.89	-0.33	1	-1.22	-1	-0.857	-0.43	50	3.6702
3	CI	NO_2	0	—	cyclohexyl	1	0	1	-1.22	-1	-0.857	-0.43	50	3.7299
4	H	H	NH	—	cyclohexyl	-0.89	-0.33	-0.25	1	-1	-0.857	-0.43	25	3.9031
5	NO_2	H	NH	—	cyclohexyl	0	1	-0.25	1	-1	-0.857	-0.43	50	3.6902
6	H	H	NH	—	cyclopentyl	-0.89	-0.33	-0.25	1	-1	-0.857	1	50	3.5416
7	CI	H	NH	—	cyclopentyl	1	0	-0.25	1	-1	-0.857	1	50	3.6201
8	NO_2	H	0	CH_2	cyclohexyl	0	1	-0.25	-1.22		0	-0.43	50	3.7160
9	H	NO_2	0	CH_2	cyclohexyl	-0.89	-0.33	1	-1.22		0	-0.43	25	3.9965
10	CI	NO_2	0	CH_2	cyclohexyl	1	0	1	-1.22		0	-0.43	25	4.0531
11	H	H	NH	CH_2	cyclohexyl	-0.89	-0.33	-0.25	1		0	-0.43	25	3.9325
12	CI	H	NH	CH_2	cyclohexyl	1	0	-0.25	1		0	-0.43	25	3.9974
13	NO_2	H	NH	CH_2	cyclohexyl	0	1	-0.25	1		0	-0.43	50	3.7143
14	H	H	NH	CH_2	cyclopentyl	-0.89	-0.33	-0.25	1		0	1	50	3.5752
15	H	H	0	C_2H_4	cyclohexyl	-0.89	-0.33	-0.25	-1.22	0		-0.43	12.5	4.2629
16	CI	H	0	C_2H_4	cyclohexyl	1	0	-0.25	-1.22	0		-0.43	12.5	4.3239
17	H	H	NH	C_2H_4	cyclohexyl	-0.89	-0.33	-0.25	1	0		-0.43	12.5	4.2610
18	CI	H	0	C_2H_4	cyclopentyl	1	0	-0.25	-1.22	0		1	25	3.9777
19	H	H	NH	C_2H_4	cyclopentyl	-0.89	-0.33	-0.25	1	0		1	25	3.9074
20	CI	H	NH	C_2H_4	cyclopentyl	1	0	-0.25	1	0		1	25	3.9759
Sum.						0	0	0	0	0	0	0		

RESULTS AND CONCLUSION

QSAR analysis for the lead optimization predictions obtained from Free-Wilsonapproach in these set of compounds **1-20** indicating group activity contributions, the ranges of position side values was summarized in Table 3. Observed, calculated and residual log 1/C values of the compounds **1-20** were also given in Table 4.

Table 3: Group activity contributions, ranges of position side values and the statistical data obtained from Free-Wilson analysis against *C. albicans*



Position	Group	Activity	contributions
		Position	Group
R		**0.231**	
	-H		0.008
	-CI		0.056
	$-NO_2$		-0.175
R1		**0.016**	
	-H		-0.003
	-NO2		0.013
X		**0.064**	
	-O-		-0.035
	-NH-		0.029
Y		**0.476**	
	—		-0.196
	-CH2-		-0.044
	-C2H4-		0.280
A		**0.320**	
	cyclohexyl		0.096
	cyclopentyl		-0.224
Constant contribution (μ)		3.8761	
Number of compounds (n)		20	
Square of correlation coefficient (R^2)		0.9164	
Standart deviation (s)		0.0852	
F value (F)		18.80	
F table value (F) (%99)		4.64	

Table 4: Observed, calculated and residual log 1/C values of the compounds **1-20** obtained from Free-Wilson analysis

Comp No:	R	R_1	X	Y	A	MIC µg/ml	Observed log 1/C	Calculated log 1/C	Residual
1	CI	H	O	—	cyclohexyl	50	3.6730	3.7942	-0.1212
2	H	NO_2	0	—	cyclohexyl	50	3.6702	3.7618	-0.0916
3	CI	NO_2	0	—	cyclohexyl	50	3.7299	3.8104	-0.0805
4	H	H	NH	—	cyclohexyl	25	3.9031	3.8090	0.0940
5	NO_2	H	NH	—	cyclohexyl	50	3.6902	3.6262	0.0639
6	H	H	NH	—	cyclopentyl	50	3.5416	3.4888	0.0527
7	CI	H	NH	—	cyclopentyl	50	3.6201	3.5374	0.0826
8	NO_2	H	O	CH_2	cyclohexyl	50	3.7160	3.7154	0.0005
9	H	NO_2	O	CH_2	cyclohexyl	25	3.9965	3.9144	0.0820
10	CI	NO_2	O	CH_2	cyclohexyl	25	4.0531	3.9630	0.0900
11	H	H	NH	CH_2	cyclohexyl	25	3.9325	3.9616	-0.0291
12	CI	H	NH	CH_2	cyclohexyl	25	3.9974	4.0102	-0.0128
13	NO_2	H	NH	CH_2	cyclohexyl	50	3.7143	3.7788	-0.0645
14	H	H	NH	CH_2	cyclopentyl	50	3.5752	3.6414	-0.0662
15	H	H	O	C2H4	cyclohexyl	12.5	4.2629	4.2222	0.0406
16	CI	H	0	C2H4	cyclohexyl	12.5	4.3239	4.2708	0.0530
17	H	H	NH	C2H4	cyclohexyl	12.5	4.2610	4.2855	-0.0245
18	CI	H	O	C2H4	cyclopentyl	25	3.9777	3.9506	0.0270
19	H	H	NH	C2H4	cyclopentyl	25	3.9074	3.9654	-0.0580
20	CI	H	NH	C2H4	cyclopentyl	25	3.9759	4.0140	-0.0381

Table 3 reveals that the lead optimization predictions obtained from Free-Wilson approach in these set of compounds 1-20 can be summarized as follows;

The constant contribution descriptor µ is decisive for the antifungal activity as a leading segment at the molecule.

Additive contribution range of the position side values of the groups are found significant as the following order of;

$$Y > A > R > X > R_1$$

Nonpolar group like C1 at position R is causing an increase in the activity.

It is shown that the position 2 is important for the antifungal activity against *C. albicans* and substituting this position with 2-cyclohexylethyl, enhances the potency.

REFERENCES

1) **Meyers, F.H., Jawetz, E. and Goldfien,** A., Review of Medical Pharmacology, Lange Medical Publication, California, p. 567 (1976).

2) **Weinberg, E.D.,** " Antifungal agents" in *Burger's Medicinal Chemistry II,* Wolff, M.E.(Eds.), John Wiley and Sons, New York , 531 (1979)

3) **Martin, A.R.,** " Anti-infective agents" in *Wilson and Gisvold's Textbook of Organic Medicinal and. Pharmaceutical Chemistry,* Doerge, R.F. (Eds.), J.B. Lippincott, Philadelphia, 151 (1982)

4) **Rippon, J.W.,** Medical Mycology, WB Saunders Company, Philadelphia, p. 531 (1974)

5) **Weinberg, E.D.,** " Antifungal agents" *Principles of Medicinal Chemistry,* Foye, W.O. (Eds.), Leo and Febiger, Philadelphia, 809 (1981)

6) **Şener, E., Yalçın, I., Temiz, Ö., Ören, I., Akın, A. and Uçartürk, N.** "Synthesis and structure-activity relationships of some 2,5-disubstituted benzoxazoles and benzimidazoles as antimicrobial agents" *Il Farmaco* 52, 99-103 (1997)

7) **Ören, I., Temiz, Ö., Yalçın, I., Şener, E. and Altanlar, N.** " Synthesis and antimicrobial activity of some novel 2,5- and/or 6-trisubstituted benzoxazole and benzimidazole derivatives" (send).

8) **Free, S.M. and Wilson, J.M.** " A mathematical contribution to structure-activity studies" J. *Med. Chem., 7,* 395-399 (1964).

9) **Chu,** K.C., " The quantitative analysis of structure activity relationships" in *Burger's Medicinal Chemistry,* Wolff, M.E. (Eds.), John Wiley and Sons, New York, 407 (1980)

10) **Franke, R.,** Theoretical Drug Design Methods, Elseiver, Amsterdam, p. 256 (1984)

Başvuru tarihi : 17.12.1997

Kabul tarihi : 05.03.1998