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# QSAR of Some Antifungal-active Benzoxazoles Using the Quantum Chemical Parameters

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The quantitative structure activity relationships of 5-substituted-2-(p-substituted-phenyl)-benzoxazole derivatives were studied, using some physicochemical parameters, including quantum-chemical parameters, based on extrathermodynamic method. It was found, that the antifungal acitvity of these compounds against *Candida albicans* highly correlated with the decreasing order of $\varepsilon_{LUMO}$, mw (molecular weight), R (resonance effect) and $\varepsilon_{HOMO}$.

*QSAR antimykotisch wirkender Benzoxazole durch quantenchemische Parameter*

Die quantitativen Struktur-Wirkungsbeziehungen von 5-Substituierten-2-(p-substituierten-phenyl)-benzoxazole-Derivaten wurden mit Hilfe von einigen physikalisch-chemischen Parametern – inklusive quantenchemischen Parametern – nach der extrathermodynamischen Methode untersucht. Es wurde festgestellt, daß die antimykotische Aktivität verschiedener Substituenten gegen *Candida albicans* in besonderem Bezug zu $\varepsilon_{LUMO}$, ferner Molekulargewicht, R (Resonanzeffekt) und $\varepsilon_{HOMO}$ steht.

*(Keywords: Benzoxazoles, Candida albicans, QSAR, Quantum Chemical Parameters.)*

Biologically active benzoxazole derivatives have been known for long time, since they are the isosters of naturally occuring cyclic nucleotides and they may easily interact with the biopolymers of the organism. 2-Substituted benzoxazoles were prominently studied[1–9] and it was revealed, that the 2-position is critical for the biological activity, whereas position-5 determines the intensity of the activity[3, 5, 9, 10]. It was stated by Davis et al. that five-membered heterocycles, carrying two benzene rings were chemotherapeutically active[11]. Based on this phenomenon, the antifungal activity of 2-phenylbenzoazoles has been studied[12–15].

In this research, 5-substituted-2-(p-substituted-phenyl)-benzoxazoles with various electron donor and acceptor groups have been selected as the target compounds. The quantitative structure-activity relationships (QSAR) involving some physicochemical properties, including quantum-chemical parameters, have been investigated.

Biological systems are composed of a number of heterogeneous phases and the site drug administration is usually distant from the site of action. Thus, the drug must be transported through phase barriers and undergoes adsorption and desorption processes with proteins and membranes, as well as partitioning between different liquid phases, before it reaches the site of action. Moreover, the drug-receptor interaction at the site of action does not occur without perturbation by surrounding heterogeneous components such as water, serum protein, lipid particles, etc. Although, the transport processes and the drug-receptor interactions are essentially physicochemical, they are far more complex than the homogeneous equilibria. Therefore, it would rarely be possible to elucidate the mechanism of drug action without insisting upon only deterministic as well as microscopic models of individual stages of the transport and interaction processes[16].

The Hansch approach has been widely accepted and recognized as a versatile way to understand drug action by analyzing the structure-activity relationship in various biological systems[17, 18]. It was assumed, that the physicochemical factors governing the transport and drug-receptor intercation can be factored into electronic, hydrophobic and steric components. In general, it is assumed that the variations in biological response (BR) results from structural modifications in congeneric drugs, depending upon the concomitant changes in these physicochemical factors. The assumption is summarized in eq. 1.

$$f(BR) = f(E, H, S) + \text{Constant} \qquad (1)$$

In the present study, the observed biological responses of the effector series[19] shown in Table 1 were mainly found to be attributable to highest occupied (HOMO) and lowest unoccupied (LUMO) molecular orbital energies ($\varepsilon_{HOMO}$ and $\varepsilon_{LUMO}$), respectively. The entropic origin of hydrophobic interactions[20] occurring in the combination of a pharmacon with a receptor site were neglected.

The model is based on the *in vitro* activity of certain substituted benzoxazole derivatives (Table 1) against *Candida albicans*. The table tabulates log 1/C values, where C is the molar concentrations of the MIC value of the compounds.

The multiple regression analysis method, which involves finding the best fit of a dependent variable (the microbiological activity, biological response etc.) to a linear combination of independent variables (descriptors) by the method of least squares was used. This is formally expressed as follows;

$$y = B_0 + B_1X_1 + B_2X_2 + \ldots + B_nX_n + \varepsilon \qquad (2)$$

where y is related to the microbiological activity of 2-phenylbenzoxazole derivatives, $X_1$, $X_2, \ldots X_n$ are the descriptor values (physicochemical subs. constants), and $B_0, B_1, \ldots B_n$ are the coefficients determined by least square analysis, whereas $\varepsilon$ represents the residues. This equation is developed for each benzoxazole derivative in our analysis.

## Experimental

*Material*

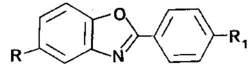
The regression analysis equations of the QSAR studies were performed by using IBM-XT computer working with Microstat Statistic Package.

*Determination of the parameters*

Parachor ($P_r$) relates principally to molecular volume[21] and it is used in QSAR studies[22]. $P_r$ 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[23]. $\pi$, $\pi^2$ (hydrophobic effects), F (field effect), R (resonance effect), MR (molecular refractivity) values were taken from the table given by Hansch et al.[24]. The values were shown in Table 1.

The HOMO and LUMO energy calculations are based on the Hückel molecular orbital (HMO) considerations[25, 26], within the zero differential overlap (ZDO) approximation[25]. The inductive model of hyperconjugation was adopted for alkyl substituents[26]. The heteroatom parameters ($h_\varrho$ and $K_{\mu\varrho}$) used in the calculations were excerpted from the literature[6]. The coplanar as well as non planar conformations of the compounds **1-21** were considered through our molecular orbital calculations.

Table 1: **The physicochemical and quantum chemical parameter values of 5-substituted-2-(p-substituted-phenyl)benzoxazole derivatives.**




| Com. | R | $R_1$ | log1/C[a] | $\Sigma\pi$ | $\Sigma\pi^2$ | $\Sigma F$ | $\Sigma R$ | $\Sigma MR$ | $\Sigma MW$ | $P_r$ | $\varepsilon^b_{HOMO}$ | $\varepsilon^b_{LUMO}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **1** | H | $C(CH_3)_3$ | 4.0023 | 1.9800 | 3.9204 | –.7000 | –.1300 | 19.6200 | 57.1000 | 557.2000 | .5542 | –.5982 |
| **2** | H | $NHCH_3$ | 3.9528 | –.4700 | .2209 | –.1100 | –.7400 | 10.3300 | 30.1000 | 470.9000 | .5300 | –.5786 |
| **3** | $NO_2$ | H | 4.2837 | –.2800 | .0784 | .6700 | .1600 | 8.3900 | 47.0000 | 442.5000 | .6044 | –.0197 |
| **4** | $NO_2$ | $CH_3$ | 4.3083 | .2800 | .0784 | .6300 | .0300 | 13.0100 | 61.0000 | 478.8000 | .5594 | –.0203 |
| **5** | $NO_2$ | $C(CH_3)_3$ | 4.3748 | 1.7000 | 2.8900 | 1.6000 | 1.0300 | 26.9800 | 103.1000 | 598.8000 | .5594 | –.0203 |
| **6** | $NO_2$ | $NH_2$ | 4.3100 | –1.5100 | 2.2801 | 1.6900 | –.5200 | 12.7800 | 62.0000 | 469.5000 | .5425 | –.0202 |
| **7** | $NO_2$ | Cl | 4.3418 | .4300 | .1849 | 1.0800 | .0100 | 13.3900 | 81.4000 | 482.2000 | .5950 | –.0198 |
| **8** | $NO_2$ | Br | 4.4070 | .5800 | .3364 | 1.1100 | –.0100 | 16.2400 | 125.9000 | 495.0000 | .5962 | –.0197 |
| **9** | Cl | $C_2H_5$ | 4.0132 | 1.7300 | 2.9929 | .3600 | –.2500 | 16.3300 | 64.5000 | 516.9000 | .5628 | –.5875 |
| **10** | Cl | $NHCOCH_3$ | 4.0595 | –.2600 | .0676 | .6900 | –.4100 | 20.9600 | 93.5000 | 539.4000 | .5363 | –.5770 |
| **11** | Cl | $NHCH_3$ | 4.0148 | .2400 | .0576 | .3000 | –.8900 | 16.3600 | 65.5000 | 510.6000 | .5290 | –.5787 |
| **12** | Cl | Cl | 4.0238 | 1.4200 | 2.0164 | .8200 | –.3000 | 12.0600 | 70.8000 | 480.3000 | .5890 | –.5470 |
| **13** | $NH_2$ | $C_2H_5$ | 4.0005 | –.2100 | .0441 | –.0300 | –.7800 | 15.7200 | 45.1000 | 504.2000 | .5513 | –.5874 |
| **14** | $NH_2$ | Br | 4.1141 | –.3700 | .1369 | .4600 | –.8500 | 14.3000 | 95.9000 | 480.4000 | .5767 | –.5450 |
| **15** | $NH_2$ | $N(CH_3)_2$ | 4.0258 | –1.0500 | 1.1025 | .1200 | –1.6000 | 20.9700 | 60.1000 | 540.9000 | .5120 | –.5811 |
| **16** | $CH_3$ | $CH_3$ | 3.9509 | 1.1200 | 1.2544 | –.0800 | –.2600 | 11.3000 | 30.0000 | 473.5000 | .5466 | –.5991 |
| **17** | $CH_3$ | $C_2H_5$ | 3.9773 | 1.5800 | 2.4964 | –.0900 | –.2300 | 15.9500 | 44.1000 | 513.5000 | .3686 | –.4852 |
| **18** | $CH_3$ | $OCH_3$ | 3.9809 | .5400 | .2916 | .2200 | –.6400 | 13.5200 | 46.0000 | 504.4000 | .5627 | –.5659 |
| **19** | $CH_3$ | $NHCH_3$ | 3.9791 | .0900 | .0081 | –.1500 | –.8700 | 15.9800 | 45.1000 | 507.2000 | .4997 | –.5258 |
| **20** | $CH_3$ | $N(CH_3)_2$ | 4.0040 | .7400 | .5476 | .0600 | –1.0500 | 21.2000 | 59.1000 | 550.2000 | .5149 | –.5814 |
| **21** | $CH_3$ | $NHCOCH_3$ | 3.9863 | –.4100 | .1681 | .2400 | –.3900 | 20.5800 | 73.1000 | 536.0000 | .5430 | –.5491 |

a: C is the molar concentrations of the MIC values of the compounds against *C. albicans*.
b: Energies of the coplanar systems are tabulated only.
Σ: Summations are over the substituents R and $R_1$.

## Results and Discussion

In order to design new active structures, in the present QSAR study, various physicochemical parameters, such as hydrophobic, electronic (field and resonance effects) and steric such as molecular refractivity, molecular weight (MW), parachor as well as molecular orbital descriptors, HOMO and LUMO energies were correlated with the observed biological response values (log of inverse minimal inhibitory concentration) of benzoxazole derivatives against *Candida albicans* within the extrathermodynamic approach[27].

In Table 1 various physicochemical parameters and frontier molecular orbital energy levels[26] are tabulated for compounds **1–21.** Of these various potential biological activity variables HOMO-LUMO energies are not only affected by the character of the substituents present (R and $R_1$) but also they are the function of stereochemistry of the molecules, namely the twist angles, developed between the planar parts of the molecules vary the magnitudes of molecular orbital energies.

On the other hand, it is generally accepted, that electron donating substituents raise up both of the frontier molecular orbitals, thus easing electrophilic attack on the substrate and making nucleophilic attack less probable. The effects of electron attracting substituents operate in the opposite direction.

In Table 1, the various substituents of position 5 in the benzoxazole ring and of the paraposition in the 2-phenyl ring are listed, and designated as R and $R_1$, respectively. The physicochemical parameters as aromatic substituent constants are also listed in Table 1 as the summations of the substituents R and $R_1$. The parachor (Pr) – as a steric parameter – is a molecular constant.

The antifungal activities of the benzoxazole derivatives, studied against *Candida albicans,* are represented with the log 1/C values. C is the molar concentration of the observed minimum inhibitory concentration (MIC). An increase in log 1/C value indicates the enhancement of the antifungal activity.

Firstly, the multivariable regression analysis[28, 29] of the BR values of compounds **1–21** were carried out using $\pi$, F, R, MR, Pr, $\varepsilon_{HOMO}$, $\varepsilon_{LUMO}$ as independent variables. Some regression statistics of the analysis have been outlined in Table 2. Although the coefficient of determination, $R^2$, values for the coplanar, non-planar and nearly perpendicular forms of the molecules are 0.98, 0.99 and 0.99 respectively, the simple correlation[29] coefficients between the BR values and the variables, $\pi$ and MR are low. In

Table 2: **Some regression characteristics of nine-variable* linear model (I) as the function of twist angle Q**

| | Q = 0 | Q = 45 | Q = 80 |
|---|---|---|---|
| $r_{yx1}$ | $3.34\ 10^{-3}$ | $3.34\ 10^{-3}$ | $3.34\ 10^{-3}$ |
| $r_{yx2}$ | 0.82 | 0.82 | 0.82 |
| $r_{yx3}$ | 0.60 | 0.60 | 0.60 |
| $r_{yx4}$ | $-5.13\ 10^{-3}$ | $-5.13\ 10^{-3}$ | $-5.10\ 10^{-3}$ |
| $r_{yx5}$ | 0.61 | 0.61 | 0.61 |
| $r_{yx6}$ | –0.13 | –0.13 | –0.13 |
| $r_{yx7}$ | 0.46 | 0.44 | 0.34 |
| $r_{yx8}$ | 0.96 | 0.95 | 0.95 |
| $R^2$ | 0.98 | 0.99 | 0.99 |

* Variables $X_1$–$X_8$ are $\pi$, F, R, MR, MW, $P_r$, $\varepsilon_{HOMO}$ and $\varepsilon_{LUMO}$ respectively.

addition to that, the standard error of the partial regression coefficients[29] for the above mentioned descriptors exceed the simple correlation coefficients.

Secondly, F, R, Mw, $P_r$, $\varepsilon_{HOMO}$ and $\varepsilon_{LUMO}$ values of the molecules **1–21** in various conformations were chosen as the independent variables $X_1$ through $X_6$ in the regression analysis. Table 3 tabulates some of the regression characteristics of seven-variable regression model. This time, F and $P_r$ values were found to be discardable.

Table 3: **Some regression characteristics of seven-variable* linear model (III) as the function of twist angle Q**

| | Q = 0 | Q = 45 | Q = 80 |
|---|---|---|---|
| $r_{yx1}$ | 0.82 | 0.82 | 0.82 |
| $r_{yx2}$ | 0.60 | 0.60 | 0.60 |
| $r_{yx3}$ | 0.61 | 0.61 | 0.61 |
| $r_{yx4}$ | −0.13 | −0.13 | −0.13 |
| $r_{yx5}$ | 0.46 | 0.44 | 0.34 |
| $r_{yx6}$ | 0.96 | 0.95 | 0.95 |
| $R^2$ | 0.98 | 0.98 | 0.98 |
| $B_1$ | $-1.423\ 10^{-3}\pm0.014$ | $-6.103\ 10^{-5}\pm0.013$ | $1.237\ 10^{-3}\pm0.013$ |
| $B_2$ | $-0.018\pm0.011$ | $-0.018\pm0.010$ | $-0.015\pm0.010$ |
| $B_3$ | $1.546\ 10^{-3}\pm2.90\ 10^{-4}$ | $1.592\ 10^{-3}\pm2.691\ 10^{-4}$ | $1.845\ 10^{-3}\pm2.620\ 10^{-4}$ |
| $B_4$ | $1.329\ 10^{-4}\pm1.650\ 10^{-4}$ | $9.004\ 10^{-5}\pm1.510\ 10^{-4}$ | $-7.129\ 10^{-5}\pm1.437\ 10^{-4}$ |
| $B_5$ | $0.290\pm0.113$ | $0.252\pm0.091$ | $0.154\pm0.070$ |
| $B_6$ | $0.551\pm0.034$ | $0.487\pm0.028$ | $0.406\pm0.023$ |

* Variables $x_1$–$x_6$ are F, R, MW, Pr, $\varepsilon_{HOMO}$, $\varepsilon_{LUMO}$ respectively.

Finally, the multivariable linear regression analysis based on independent variables, R, Mw, $\varepsilon_{HOMO}$ and $\varepsilon_{LUMO}$ were used. Table 4 displays the rigorous regression statistics of the analysis for coplanar as well as non planar conformations of compounds **1–21.** As it is seen from the table, BR values highly of $\varepsilon_{LUMO}$, Mw, R, and $\varepsilon_{HOMO}$. It has been shown, that F-test values for the regressions, based on coplanar, non-planar and nearly perpendicular forms of the molecules **1–21** vary from 330 to 384. Whereas the tabulated $F_{4\cdot17}$ ($F_{n-1.k-n}$ where n and k are the independent variables and the number of samples[28, 29]) at the 1 % level of probability is 4.67. Hence, the regression analyses are statistically significant. The search of simple correlation coefficients also reveals that there exists no colinearity[29] between the independent variables in any case.

The preliminary equations obtained from the linear free energy relationships indicate, that hydrophobic effects have no influence on the drug-receptor interactions for the antifungal activity of benzoxazole derivatives. This result can occur, because of the minimum inhibitory concentration values of benzoxazoles against *Candida albicans* were obtained *in vitro* conditions.

The correlation results, shown in Table 4 exhibit, that the quantum chemical parameters are much more important for the antifungal activity against *Candida albicans* than the physicochemical ones. Overall charge transfer interactions between benzoxazole compounds and receptor site indicate, that $\varepsilon_{LUMO}$ (energy of the lowest unoccupied molecular orbital) value of the derivatives are playing an additive role for the antifungal activity against *Candida albicans*. This situation reveales, that benzoxazole ring moiety is the most important part in the molecule for the interaction with the receptor site.

Table 4: **Some regression characteristics of five-variable* linear model (III) as the function of twist angle Q**

| | Q = 0 | Q = 45 | Q = 80 |
|---|---|---|---|
| $B_0$ | 4.071320 | 4.068790 | 4.086890 |
| $B_1$ | −0.0150667 | −0.0162009 | −0.0173623 |
| $B_2$ | 1.646040 $10^{-3}$ | 1.665820 $10^{-3}$ | 1.806090 $10^{-3}$ |
| $B_3$ | 0.250910 | 0.231906 | 0.161748 |
| $B_4$ | 0.538350 | 0.480384 | 0.412868 |
| $R^2$ | 0.988054 | 0.989711 | 0.989448 |
| $F_{4,17}$ | 330.838 | 384.748 | 375.088 |
| $r_{yx1}$ | 0.608540 | 0.60854 | 0.60854 |
| $r_{x1x2}$ | 0.349386 | 0.349386 | 0.349386 |
| $r_{x1x3}$ | 0.286757 | 0.267615 | 0.196656 |
| $r_{x1x4}$ | 0.637887 | 0.639396 | 0.641593 |
| $r_{yx2}$ | 0.617242 | 0.617242 | 0.617242 |
| $r_{x2x3}$ | 0.383846 | 0.37392 | 0.290413 |
| $r_{x2x4}$ | 0.410173 | 0.406235 | 0.393085 |
| $r_{yx3}$ | 0.469294 | 0.442903 | 0.343598 |
| $r_{x3x4}$ | 0.359176 | 0.325557 | 0.237927 |
| $r_{yx4}$ | 0.960150 | 0.959651 | 0.956319 |
| $Sb_{x1}$ | 0.010483 | 9.749090 $10^{-3}$ | 9.90251 $10^{-3}$ |
| $Sb_{x2}$ | 2.049940 $10^{-4}$ | 1.900340 $10^{-4}$ | 1.88663 $10^{-4}$ |
| $Sb_{x3}$ | 0.0983266 | 0.080350 | 0.0643985 |
| $Sb_{x4}$ | 0.0232977 | 0.019123 | 0.0164333 |

* Variables $X_1$–$X_4$ are R, MW, $\varepsilon_{HOMO}$, $\varepsilon_{LUMO}$ respectively.

As the electron accepting property in the benzoxazole moeity decreases, the antifungal activity increases as seen in Table 1 (compounds **3–8**). The nitro group as the most powerful electron withdrawing substituent in the compounds studied, increases the electron accepting ability of the benzoxazole moeity. Indeed, these compounds (**3–8**) exihibit the highest antifungal activity. Therefore it can be concluded, that the receptor site seems to have an electron donating property. For that reason $\varepsilon_{LUMO}$ values of the compounds studied are of importance to enlighten drug-receptor interactions. It is most likely, that the oxazole ring system is the pharmophoric site of the molecules studied. Since the heterocyclic ring is coplanar with a phenylene moiety but probably a twist angle exists between the phenyl ring and oxazole system; the quantum chemical effects of R substituents on the biological activities should be more pronounced compared to $R_1$ groups. The data of Table 1 generally imply, that electron withdrawing substituents in position-5 improve the biological activity.

Calculations, varying the twist angle (Q) between the benzoxazole moiety and the phenyl ring (which is substituted at position 2) indicate, that with a disappearing coplanarity, the substractive effect of the $\varepsilon_{HOMO}$ and the additive effect of the $\varepsilon_{LUMO}$ values, contributing to the activity against *Candida albicans*, decrease. The results of these investigations can be helpful for a further understandings of the interactions between the receptor site and the antifungal-active compounds.

## References

[1] W. J. Bywater, W. R. Coleman, O. Kamm and H. H. Meritt: J.Am.Chem.Soc., **67,** 905 (1945).

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

[3] C. H. Cashin, D. W. Dunwell, D. Evans, T. A. Hicks and E. A. Kitchen: J. Med. Chem., **18,** 53 (1975).
[4] H. D. Cossey, R. N. Gartside and F. F. Stephens: Arzneim. Forsch./Drug. Res., **16,** 33 (1966).
[5] D. Evans, D. W. Dunwell and T. A. Hicks: J. Med. Chem., **18,** 1158 (1975).
[6] R. D. Haugwitz, R. G. Angel, G. A. Jacops, B. V. Maurer, V. L. Narayanan, L. R. Cruthers and J. Szanto: J. Med. Chem., **25,** 969 (1982).
[7] R. Rips, M. Lachaize, O. Albert and M. Dupont: Chim. Ther., **6,** 126 (1971).
[8] W. Shulze, W. Gutsche and W. Jungstand: Arzneim.-Forsch., Drug. Res., **15,** 1235 (1965).
[9] C. O. Wilson, O. Gisvold and R. F. Doerge: „Textbook of Organic Medicinal and Pharmaceutical Chemistry“, J. P. Lippincott Company, Philadelphia, 421 (1971).
[10] G. M. Holder, P. J. Little, A. J. Ryan and T. R. Watson: Biochem. Pharmacol. **25,** 2747 (1976).
[11] D. Davis and C. Lo: Phytopathology, **44,** 680 (1954).
[12] E. Sener, S. Özden, I. Yalçın, T. Özden, A. Akın, S. Yıldız, FABAD: J. Pharm. Sci. **11,** 190 (1986).
[13] I. Yalçın, E. Sener, T. Özden, S. Özden, A. Akın, S. Yıldız, FABAD: J. Pharm. Sci., **11,** 257 (1986).
[14] S. Özden, T. Özden, E. Sener, I. Yaļcın, A. Akın, S. Yıldız, FABAD: J. Pharm. Sci. **12,** 39 (1987).
[15] E. Sener, I. Yalçın, S. Özden, T. Özden, A. Akın and S. Yıldız: DOGA TU J. Med. and Pharm. **11**, 391 (1987).
[16] F. R. Gould: „Biological Correlations – The Hansch Approach“
T. Fujita: „Extrathermodynamic Structure-Activity Correlations“
Adv. in Chem. Series 114, American Chemical Society p. 1–19, Washington D. C. 1972.
[17] C. Hansch and T. Fujita: J. Amer. Chem. Soc. **86,** 1616 (1964).
[18] C. Hansch: Accounts Chem. Res. **2,** 232 (1969).
[19] I. Motoc and M. Viteazu: Match, **11,** 169 (1980).
[20] I. Motoc and Dragomir-Flimonescu: Match, **12,** 127 (1981).
[21] C. Hansch, A. Leo and C. Church: J. Med. Chem. **12,** 766 (1969).
[22] P. Ahmad, C. A. Fyfe and A. Mellors: Biochem. Pharmacol., **24,** 1103 (1975).
[23] Q. R. Quayle: Chem. Rev. **53,** 439 (1953).
[24] C. Hansch, A. Leo, S. H. Unger, K. H. Kim, D. Nikaitani and E. J. Lien: J. Med. Chem., **16,** 1207 (1973).
[25] E. Heilbronner and H. Bock: „The HMO Model and Its Applications“ John Wiley and Sons, New York (1976).
[26] A. Streitwieser Jr.: „Molecular Orbital Theory for Organic Chemists“ John Wiley and Sons Inc., New York (1961).
[27] R. Franke: Theoretical Drug Design Methods, Akademie-Verlag, Berlin, 25 (1984).
[28] N. Draper and H. Smith: „Applied Regression Analysis“, John Wiley and Sons Inc., New York (1966).
[29] D. Salvatore: „Statistics and Econometrics“, McGraw Hill, New York (1982).