ejpmr, 2016,3(10), 197-202.

SJIF Impact Factor 3.628

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

EXPLORING STRUCTURAL FEATURE OF BENZOTIAZOLE DERIVATIVES EMPLOYING FUJITA–BAN AND HANSCH APPROACH

Rizwan Khan[1]* and Dr. Love Kumar Soni[1]

School of Pharmacy, D.A.V.V., Indore.

***Corresponding Author: Rizwan Khan**

School of Pharmacy, D.A.V.V., Indore.

Article Received on 04/08/2016 **Article Revised on 24/08/2016** **Article Accepted on 13/09/2016**

ABSTRACT

Designing of active compounds of benztriazole derivatives which are highly selective, potent and safe inhibitor of CYP51 enzyme for inhibition of ergosterol pathways for maximum antifungal activity has been done. In our study, we did quantitative structure–activity relationship (QSAR) analysis, based on Fujita–Ban and classical Hansch approach, on benzotriazole derivatives. First, the Fujita-Ban approach has been followed, which revealed the highest activity contribution for the 5- substituted benztriazole derivatives with bulkier group is supported. Further, the Hansch approach confirms that 5- substituted benztriazole derivatives with bulkier group are active. The hydrophobic properties of the various substituent have been found to play major roles in the binding of these compounds with the receptor.

KEYWORDS: Antifungal, Benzotriazole derivatives, Fujita Ben Analysis, QSAR relationship.

INTRODUCTION

The emergence of azole-resistant fungal strains and the increasing incidence of fungal infection associated with unsatisfactory therapeutic treatment in immunocompromized patients have stimulated the search for alternative antifungal drugs with higher potency and broader spectrum of activity. The most common fungal infections affecting immunocompromized individuals from a clinical stand point are candidiasis and aspergillosis.[1,2] Candida albicans is not only a common opportunistic pathogenic yeast of immunodeficient hosts but the mortality rate by life threatening nocosomial infections approaches 35%.[3] On the other hand, invasive aspergillosis is the leading cause of death in leukemia and bone marrow transplant patients, and its infections are rather difficult to treat with the azole antifungal agents currently available.[4] In view of the limited number of therapeutic choices for controlling fungal infections there is at present an urgent need for novel antifungal compounds with a high potency and a broad spectrum of activity.

The triazole antifungal drugs fluconazole[5,6], itraconazole[7], voriconazole[8], ravuconazole[9–11], and posaconazole[12,13] form an important class of antifungal agents. These drugs act by displacing lanosterol from cytochrome P45014aDM and, in this manner, block the biosynthesis of ergosterol, an essential component of the fungal cell membrane.[14,15] Cytochrome P45014aDM oxidatively removes the 14-a-methyl group of lanosterol by using oxygen and NADPH.[16,17] Fluconazole is effective against candidiasis after both oral and parenteral administration but is ineffective against aspergillosis.

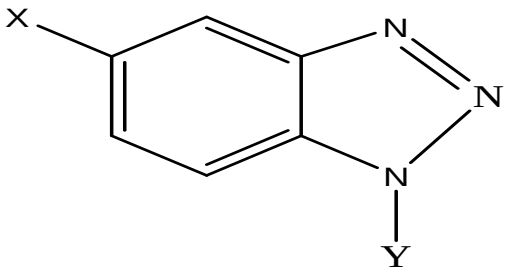


Figure 1: General structure of Benzotriazole used for this study.

QSAR studies of Benzotriazole derivatives have been carried out using Fujita-Ban and Hansch approach. An attempt was made to estimate the de novo contribution of substituents to the activity of the molecules employing Fujita-Ban approach. In addition, a quantitative model has been proposed for describing the factors, influencing the affinity of the drug molecules towards the enzyme.

Experimental

The cytochrome P450 14-alpha -sterol demethylase (CYP51) inhibitory activity data of benzotriazole analogues was taken from the reported work of Talele et al.[18] (Fig. 1). The biological activity data (IC50 in nM) was converted to negative logarithmic mole dose (pIC50) to reduce the skewness of data set. Initially, the series was subjected to a Fujita-Ban approach[19] using

regression analysis in order to estimate the de novo contribution of substituents to the activity of the molecules. The Hansch approach was carried out to establish a correlation between the ALR2 inhibitory activity and various substituent constants at positions X and Y of molecule (Fig. 1). Values of the substituent constants like hydrophobic (Rp), steric (molar refractivity or MR), hydrogen acceptor (HA), hydrogen donor (HD), electronic descriptor (field effect or F, resonance effect or R, and Hammett's constant or s) and shape of each substituent (Verloop parameters L and B1–B3) were taken from the published literature.[20, 21]

Stepwise multiple linear regression analysis method was used to perform QSAR analysis employing in-house VALSTAT[22] program. The data was transferred to the statistical program in order to establish a correlation between physicochemical parameters as independent variables and aldose-reductase inhibitory activity as dependent variable. The best model was selected from the various statistically significant equations on the basis of the observed squared correlation coefficient (r2), the standard error of the estimate (SE), Sequential Fischer test (F), inter-correlation among parameter (ICAP), the bootstrapping squared correlation coefficient (r^2 bs), the bootstrapping standard deviation (Sbs), the cross-validated squared correlation coefficient using leave-one-out procedure (q2)[23], chance statistics (evaluated as the ratio of the equivalent regression equations to the total number of randomized sets; a chance value of 0.001 corresponds to a 0.1% chance of fortuitous correlation), outliers (on the basis of Z-score value), predictive residual sum of square (SPRESS), and standard error of predictivity (SDEP).

RESULT AND DISCUSSION

The multivariant regression expression, model I, obtained by Fujita-Ban approach accounts for more than 87.2% variance in activity with de novo contribution of substituent to the activity of the molecules.

Model I

BA= [7.687(± 0.0638933)] +YH [0.0825(± 0.0714349)] +R7a [0.0605(± 0.09584)]

n=11, r=0.763087, r^2=0.582302, variance=0.00145975, std=0.0382067, F=5.5763,FIT=74.3506

Contributions of parameters to the model are:

Contribution of parameters to model is YH : R7a :: 12.2727 : 1

Fujita ben analysis of benzotriazole derivatives shows that the substitution of bulkier group as 7a compound of the series having methyl aniline at position 5 is favorable for the activity. Also the presence of the hydrogen at position 1 is shown positive action by the Model I. De novo contribution of groups also help understanding the binding of benzotriazole derivatives to the receptors by means of hydrogen bond interactions as well as the attachment of the designed molecules to the receptors in the hydrophobic pocket of the target CYP51 enzyme.

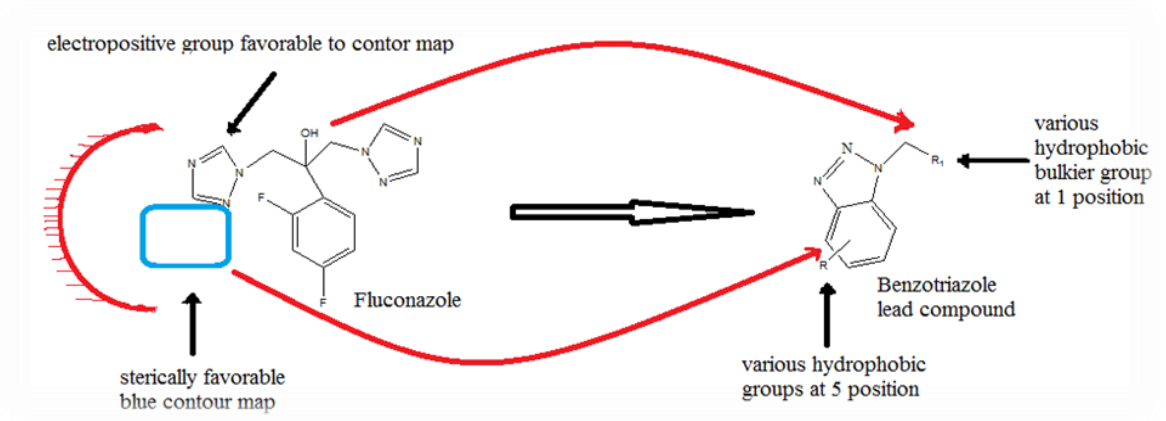


Figure2: Benzotriazole analog design strategy schematic representation.

The series was subjected to stepwise multiple linear regression analysis, in order to develop a 2D-QSAR model between the inhibitory activity of CYP51 enzyme as dependent variable and different, afore-mentioned substituent constants as independent variables. All the regression coefficients were significant at 95% confidence interval. The representative QSAR model's regression coefficients with pertinent statistical parameters are described below.

BA = [7.687(± 0.0385889)] +pi [0.0449489(± 0.0237453)] +YH [0.0440735(± 0.0488761)]

n=11, r=0.920673, r^2=0.847638, variance=0.000532467, std =0.0230752, F=22.2533, FIT=296.71

Q^2 = 0.714044, Spress = 0.0316124, SDEP = 0.0269592

Model II has a good correlation coefficient (r = 0.921). The value of Sequential Fischer test (F = 22.25), which exceeds the tabulated value ($F_{1,12\ a\ 0.025}$ = 6.72) explain the fitness of the model. The addition of the second descriptor pi, hydrophobic constant, in model II is

statistically significant. The positive contribution of pi demonstrates the possible hydrophobic interaction of the substitution of the aromatic ring with the receptor.

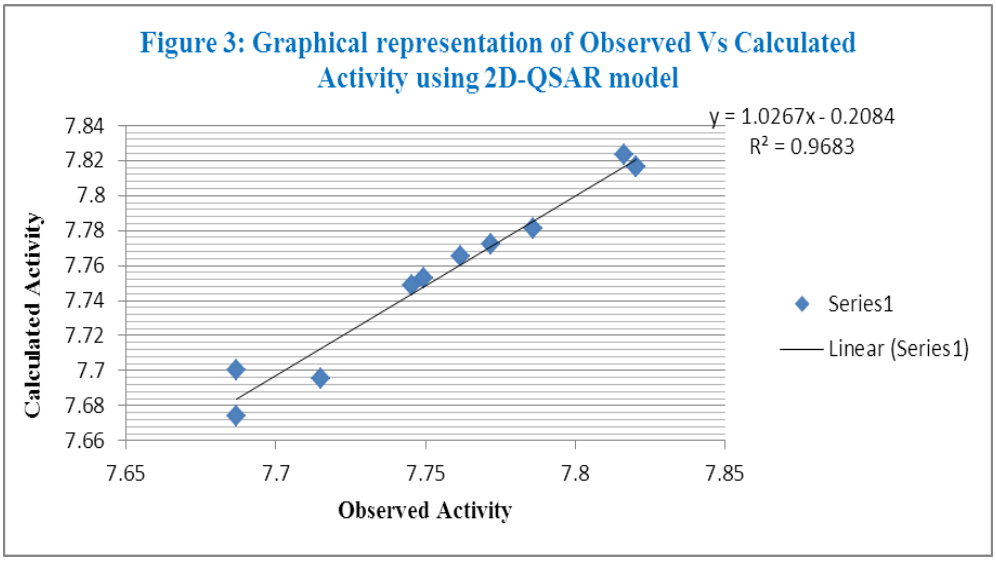
Model III has a high correlation coefficient (r = 0.852) and a low standard error of the estimate (SE = 0.263). The inter-correlation among the parameters is also less (ICAP = 0.3273) as shown in Table 1.

Table 1.

pi	MR	F	R	S	YH	YClM	Y2MA	
pi	1.000000							
MR	0.802107	1.000000						
F	0.689012	0.375735	1.000000					
R	0.707110	0.545267	0.857117	1.000000				
S	0.723499	0.515163	0.924689	0.988640	1.000000			
YH	0.487985	0.712524	0.067733	0.294073	0.199042	1.000000		
YClM	0.327350	0.477976	0.045437	0.197270	0.133522	0.670820	1.000000	
Y2MA	0.327350	0.477976	0.045437	0.197270	0.133522	0.670820	0.100000	1.000000

Table 2. Calculated and predicted pIC50 (by LOO method) of a series using a 2D-QSAR model.

Compd. No	Calculated pIC50	Z value	Predicted pIC50 (LOO)
3	7.7151	1.28994	7.69517
4a	7.77173	-0.296733	7.77246
4b	7.74544	-0.696065	7.74871
4c	7.74948	-0.801998	7.75276
6	7.76162	-1.1716	7.765
7a	7.82027	0.504254	7.8164
7b	7.81622	-1.09936	7.82344
7c	7.82027	0.504254	7.8164
8a	7.78588	1.76732	7.78126
10	7.687	-0.67346	7.7
11	7.687	0.67346	7.674



The value of the Sequential Fischer test (F = 14.609), which exceeds the tabulated value (F2,11 a 0.002 = 13.8) explains the fitness of model.

Model III was considered the best 2D-model for the data set. The model is used for the internal predictivity of the series (Figs. 3, and Table 2). The value of the leaveone-out cross-validation squared correlation coefficient (q2 = 0.567) predictive residual sum of square (SPRESS = 0.331) and standard error of predictivity (SDEP = 0.293) suggested good predictability. The bootstrapping squared correlation coefficient (r2 bs = 0.799) and smaller bootstrapping standard deviation (Sbs = 0.124) supported the robustness of the model and indicated that no single compound of the series contributed much more to the model. Randomization test (chance *a*0.001) in randomized biological activity data revealed that the results.

Table 3: Benzotriazole analogues for antifungal activity as CYP51 enzyme inhibitor.

Compound no.	Substituents		IC_{50}(nM)	pIC_{50}
	X	Y	55.02	7.7151
2	-COOH	-H	58.38	7.77173
4a	-CO -2-methylaniline	-H	54.07	7.74544
4b	-CO-n- butylamine	-H	54.30	7.74948
4c	-CO-benzylamine	-H	54.91	7.76162
6	$-CH_2Cl$	-H	67.67	7.82027
7a	$-CH_2$ -2-methylaniline	-H	62.47	7.81622
7b	$-CH_2$-n- butylamine	-H	67.67	7.82027
7c	$-CH_2$-benzylamine	-H	66.11	7.78588
8a	$-CH_2$-2-methylphenol	-H	47.26	7.687
10	-H	-chloromethyl	50.19	7.687
11	-H	2-methyl aniline	65.55	7.7151

In conclusion, the present study provides important structural insights in designing of active compounds of benzotriazole derivatives which are highly selective, potent and safe inhibitor of CYP51 enzyme. The quantitative models derived for the study illustrates the significance of the bulkier groups for the drug–enzyme interaction. The results of the study also reveal the necessity of lipophilic functional groups at the aromatic ring.

Figures

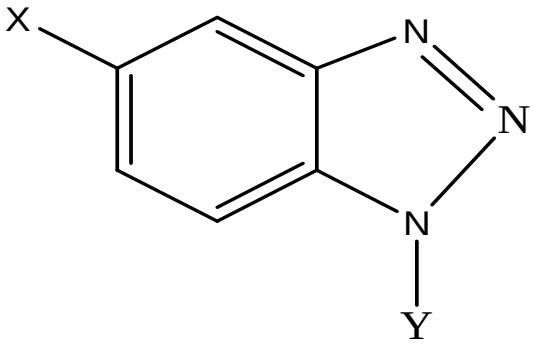


Figure 1: General structure of Benzotriazole used for this study.

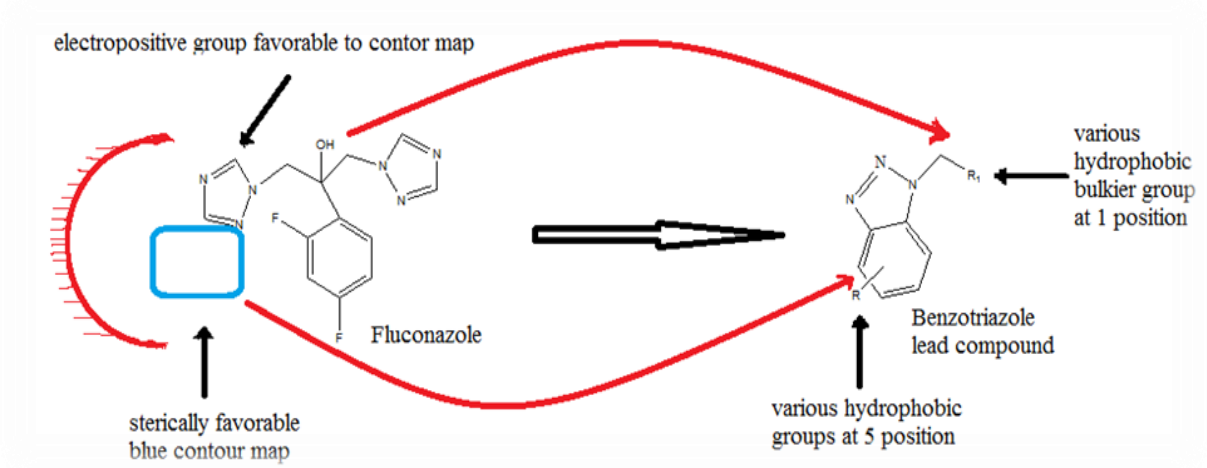


Figure2: Benzotriazole analog design strategy schematic representation.

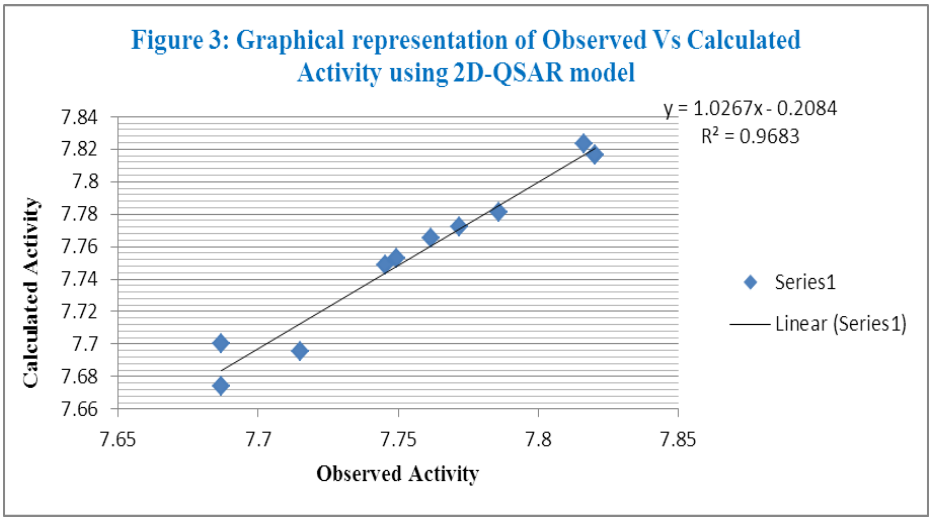


Table 1

pi	MR	F	R	S	YH	YClM	Y2MA	
pi	1.000000							
MR	0.802107	1.000000						
F	0.689012	0.375735	1.000000					
R	0.707110	0.545267	0.857117	1.000000				
S	0.723499	0.515163	0.924689	0.988640	1.000000			
YH	0.487985	0.712524	0.067733	0.294073	0.199042	1.000000		
YClM	0.327350	0.477976	0.045437	0.197270	0.133522	0.670820	1.000000	
Y2MA	0.327350	0.477976	0.045437	0.197270	0.133522	0.670820	0.100000	1.000000

Table 2. Calculated and predicted pIC50 (by LOO method) of a series using a 2D-QSAR model.

Compd. No	Calculated pIC50	Z value	Predicted pIC50 (LOO)
3	7.7151	1.28994	7.69517
4a	7.77173	-0.296733	7.77246
4b	7.74544	-0.696065	7.74871
4c	7.74948	-0.801998	7.75276
6	7.76162	-1.1716	7.765
7a	7.82027	0.504254	7.8164
7b	7.81622	-1.09936	7.82344
7c	7.82027	0.504254	7.8164
8a	7.78588	1.76732	7.78126
10	7.687	-0.67346	7.7
11	7.687	0.67346	7.674

Table 3: Benzotriazole analogues for antifungal activity as CYP51 enzyme inhibitor.

Compound no.	Substituents		IC_{50}(nM)	pIC_{50}
	X	Y	55.02	7.7151
2	-COOH	-H	58.38	7.77173
4a	-CO -2-methylaniline	-H	54.07	7.74544
4b	-CO-n- butylamine	-H	54.30	7.74948
4c	-CO-benzylamine	-H	54.91	7.76162
6	$-CH_2Cl$	-H	67.67	7.82027
7a	$-CH_2$ -2-methylaniline	-H	62.47	7.81622
7b	$-CH_2$-n- butylamine	-H	67.67	7.82027
7c	$-CH_2$-benzylamine	-H	66.11	7.78588
8a	$-CH_2$-2-methylphenol	-H	47.26	7.687
10	-H	-chloromethyl	50.19	7.687
11	-H	2-methyl aniline	65.55	7.7151

REFERENCES

1. J.P. Latge, Clin. Microbiol. Rev., 1999; 12: 310–350.
2. J.N. Steenbergen, A. Casadevall, J. Clin. Microbiol., 2000; 38: 1974–1976.
3. L. Romani, F. Bistoni, P. Puccetti, Trends Microbiol., 2002; 10: 508–514.
4. R.A. Calderone, W.A. Fonzi, Trends Microbiol., 2001; 9: 327–335.
5. J.H. Rex, M.G. Rinaldi, M.A. Pfaller, Antimicrob. Agents Chemother., 1995; 39: 1–8.
6. J.H. Rex, M.A. Pfaller, J.N. Galgiani, M.S. Bartlett, A. Espinel-Ingroff, M.A. Ghannoum, M. Lancaster, F.C. Odds, M.G. Rinaldi, T.J. Walsh, A.L. Barry, Clin. Infect. Dis., 1997; 24: 235-247.
7. J. Van Cutsem, F. Van Gerven, P.A.J. Janssen, in: R.A. Fromtling (Ed.), Recent Trends in the Discovery, Development and Evaluation of Antifungal Agents, Prous, Barcelona, 1987; 177–192.
8. R.P. Dickinson, A.S. Bell, C.A. Hitchcock, S. Narayanaswami, S.J. Ray, K. Richardson, P.F. Troke, Bioorg. Med. Chem. Lett., 1996; 6: 2031–2036.
9. K. Hata, J. Kimura, H. Miki, T. Toyosawa, M. Moriyama, K. Katsu, Antimicrob. Agents Chemother., 1996; 40: 2237–2242.
10. K. Hata, J. Kimura, H. Miki, T. Toyosawa, M. Moriyama, K. Katsu, Antimicrob. Agents Chemother., 1996; 40: 2243–2247.
11. Y. Kaku, A. Tsuruoka, H. Kakinuma, I. Tsukada, M. Yanagisawa, T. Naito, Chem. Pharm. Bull., 1998; 46: 1125–1129.
12. A. Cacciapuoti, D. Loebenberg, E. Corcoran, F. Menzel Jr., E.L. Moss Jr., C. Norris, M. Michalski, K. Raynor, J. Halpern, C. Mendrick, B. Arnold, B. Antonacci, R. Parmegiani, T. Yarosh-Tomaine, G.H. Miller, R.S. Hare, Antimicrob. Agents Chemother., 2000; 44: 2017–2022.
13. A.K. Saksena, V.M. Girijavallabhan, H. Wang, Y.T. Liu, R.E. Pike, A.K. Ganguly, Tetrahedron Lett., 1996; 37: 5657–5660.
14. Y. Aoyama, Y. Yoshida, R. Sato, J. Biol. Chem., 1984; 259: 1661–1666.
15. Y. Aoyama, Y. Yoshida, Biochem. Pharmacol., 1987; 36: 229–235.
16. J.M. Trzaskos, W.D. Bowen, A. Shafiee, R.T. Fischer, J.L. Gaylor, J. Biol. Chem., 1984; 259: 13402–13412.
17. P. Fresneau, M. Cussac, J. Morand, B. Szymonski, et al., J. Med. Chem., 1998; 41: 4706–4715.
18. Pallav D. Patel, Maulik R. Patel, Bela Kocsis, Erika Kocsis, Steven M. Graham, Andrew R. Warren, Stacia M. Nicholson, Blase Billack, Frank R. Fronczek, Tanaji T. Talele, European Journal of Medicinal Chemistry., 2010; 45: 2214–2222.
19. T. Fujita, T. Ban, J. Med. Chem., 1971; 14: 148–152.
20. C. Hansch, A. Leo, Substituent constants for correlation analysis in chemistry and biology, John Wiley & Sons, New York, 1979.
21. B. Skagrberg, D. Bonelli, G. Clarnenti, C. Ebert, Quant Struc. – Act. Relat., 1989; 8: 32–38.
22. A. K. Gupta, B. M. Arockia, S. G. Kaskhedikar, Indian. J. Pharm. Sci., 2004; 66: 396402.
23. H. Kubinyi, Hansch analysis and related approaches, VCH, Weinheim, New York, 1993.