Antiallergic Activity of Substituted Benzamides: Characterization, Estimation and Prediction

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Abstract
Antiallergic activity of twenty-three substituted N 4-methoxyphenyl benzamides was model by the use of an original methodology. After sketching out the compounds structure and creating the file with the observed activities, strictly based on compounds structure, the molecular descriptors family was generated and descriptors entered into a multiple linear regression analysis. The multi-varied model with four descriptors proved to render higher ability in estimation (squared correlation coefficient, $r^2 = 0.9986$) as well as in prediction (cross-validation leave-one-out score, $r^2_{cv\text{-}loo} = 0.9956$) of antiallergic activity of compounds, obtained significantly greater correlation coefficient compared with the previously reported model ($p < 0.01$). Characterization of antiallergic activity of substituted N 4-methoxyphenyl benzamides by integration of complex structure information provides a stable and efficient multi-varied model with four descriptors. According with the multi-varied model with four descriptors the antiallergic activity of substituted N 4-methoxyphenyl benzamides is like to be of geometry nature, depending by the number of directly bonded hydrogen's, and the atomic relative mass, being in relation with the partial charge of compounds

Keywords
Molecular Descriptors Family on Structure-Activity Relationships (MDF-SAR), Substituted N 4-methoxyphenyl benzamides, Antiallergic activity, Multiple linear regression (MLR)

Background
Benzamide derivatives, known for their anti-inflammatory and immunomodulatory [1,2], anti-tumoral [3], antipsychotic [4], and antiallergic [5] activities, are drugs widely used in medicine [6].
Twenty-three derivatives of N 4-methoxyphenyl benzamide were previously synthesized and their antiallergic activity was tested using dinitrochlorobenzene by inducing delayed allergy of rat skin in vivo [5]. The inhibitory tumor swell rate (IR) was model by the use of molecular connectivity indices, and the following equation was obtained:

$$\log IR = 3.002 + 0.8909\,{}^4x_p - 1.3465\,{}^5x_p - 13.8234\,{}^6x_{cg} \quad (1)$$

where logIR is inhibitory rate expressed in logarithm scale, and ${}^4x_p$, ${}^5x_p$, ${}^6x_{cg}$ are molecular connectivity indices.
The statistical characteristics of previously reported model [5] are:

$$r = 0.8865,\ F = 23,\ s = 0.572,\ n = 23 \quad (2)$$

where r = correlation coefficient, F = parameter of Fisher-test, s = standard deviation, and n = sample size.
A CoMFA analysis was also applied by Yu-xin Zhou et al. [5] and the following results were obtained:

$$r = 0.990,\ r^2_{cv} = 0.830 \quad (3)$$

where r^2_{cv} = cross-validated correlation coefficient.
The relationship between antiallergic activities of some substituted N 4-methoxyphenyl benzamides and the information obtained from theirs structure was study by the use of an original MDF-SAR methodology. The aim of the research was to analyze the performances of the MDF-SAR methodology in estimation and prediction of antiallergic activities of twenty-three substituted N 4-methoxyphenyl benzamides.

Materials and Methods

N 4-methoxyphenyl benzamides Pharmacology

A number of twenty-three substituted N 4-methoxyphenyl benzamides were included into the study. The generic structure of the substituted N 4-methoxyphenyl benzamides, corresponding substituent(s) of compounds, and inhibitory activity expressed on logarithmical scale are in table 1. In the default cases, $X = Y = Z = T = H$. The inhibitory rate, was calculated by Yu-xin Zhou & all [5] based on the following formula: $(V_1-V_2)/V$ where V_1 is the swell value of tumor of the reference set of rats (treated with hydrocortisone 20 mg) and V_2 the swell value of tumor of the test set of rats (treated with hydrocortisone 100 mg).

Table 1. Characteristics of studied substituted N 4-methoxyphenyl benzamides and their inhibitory activity

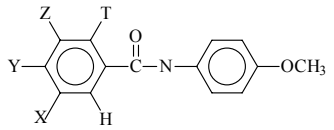

Abb.	Substituent	logIR
com_01	Y = Z = OH	0.13
com_02	X = T = OH	0.07
com_03	T = F	-0.06
com_04	Y = Cl	-0.12
com_05	$Y = NO_2$	0.05
com_06	$Y = CH_2CH_3$	0.03
com_07	Y = *t*-Bu	0.07
com_08	Y = *t*-Pro	0.00
com_09	$T = OCH_2COOH$	-0.09
com_10	$Y = Z = CH_2$-mophlinyl; X = OH	-4.00
com_11	Y = OH; Z = CH2-mophlinyl	-4.00
com_12	$X = Z = NH_2$	0.03
com_13	$Y = OCH_3$	0.05
com_14	$T = OCH_3$	0.03
com_15	$X = Y = Z = OCH_3$	-0.06
com_16	$T = OCH_2Ph$	-0.80
com_17	$T = OCH_2CHCH_2$	-0.04
com_18	$Z = OC_4H_9$	-0.39
com_19	$Y = OC_8H_{17}$	0.11
com_20	$Y = OCH_2CHCH_2$	-0.34
com_21	T = SH	-0.18
com_22	Z = SH	-0.25
com_23	Y = SH	0.07

MDF-SAR methodology

The MDF-SAR methodology applied on substituted N 4-methoxyphenyl benzamides consisted of the following steps [7]:

1: Sketch out 3D structure of each substituted N 4-methoxyphenyl benzamides compounds by the use of HyperChem software [8];

2: Create of the file with measured Antiallergic Activity (logIR) of substituted N 4-methoxyphenyl benzamides compounds;

3: Generate the molecular descriptors family (MDF) members for substituted N 4-methoxyphenyl benzamides compounds [9,10]. All twenty-three compounds were used in generation of the molecular descriptors family. The algorithm of generation the molecular descriptors family was strictly based on compounds structure. The process of molecular descriptors family generation was followed by a filtration in which there were deleted from databases identical descriptors by imposing a significance selector equal with 10^{-9} (the redundant information was clear away). The

name of each molecular descriptor refers its calculation mode and includes: compound geometry or topology (the 7th letter), atomic property (cardinality, number of directly bonded hydrogen's, atomic relative mass, atomic electronegativity, group electronegativity, partial charge - the 6th letter), the atomic interaction descriptor (the 5th letter), the overlapping interaction model (the 4th letter), the fragmentation criterion (the 3rd letter), the molecular selector (the 2nd letter), and the linearization function applied in molecular descriptor generation (the 1st letter).
4: Find and identify the MDF-SAR models.
5: Validation of the obtained MDF-SAR models were performed through computing the cross-validation leave-one-out correlation score (r^2_{cv}) [11]. The cross-validation leave-one-out correlation score was compute by exclusion one time and applying to all sample one compound from dataset, rebuilding the MDF-SAR model and estimation of excluded compound activity based on MDF-SAR model.
6: Analyze the selected MDF-SAR models through: squared correlation coefficients, statistical parameters of estimation and prediction analysis, model stability analysis (the differences between squared correlation coefficient and cross-validation leave-one-out score - the lowest value correspond to the most stable model), and correlated correlation analysis [12] by comparing the results of the MDF-SAR models with previously reported models.

Results
The best performing multi-varied MDF-SAR models (one with two-descriptors and one with four descriptors) are:

- MDF-SAR model with two-descriptors: $\hat{Y}_{2d} = -8.8\cdot10^{-3}-5.1\cdot10^{-5}\cdot isDRtHg+0.13\cdot iHMMtHg$ (4)
- MDF-SAR model with four-descriptors: $\hat{Y}_{4d} = -0.15+9\cdot10^{-4}\cdot imMRkMg-0.32\cdot imMDVQg-5.2\cdot10^{-5}\cdot isDRtHg+0.14\cdot iHMMtHg$ (5)

where $\hat{Y}_{2d}$ respectively $\hat{Y}_{4d}$ are estimated log IR by the MDF-SAR model with two, respectively with four molecular descriptors, and *isDRtHg*, *iHMMtHg*, *imMRkMg*, *imMDVQg* are molecular descriptors. Statistical characteristics of the MDF-SAR models are presented in table 2 and 3.

Table 2. Statistical characteristics of MDF-SAR models for antiallergic activity of substituted N 4-methoxyphenyl benzamides

Characteristic (notation)	***Value***	
Number of variable (v)	2	4
Correlation coefficient (r)	0.9942	0.9986
Squared correlation coefficient (r^2)	0.9884	0.9973
Adjusted squared correlation coefficient (r^2_{adj})	0.9872	0.9967
Standard error of estimated (s_{est})	0.1300	0.0664
Fisher parameter (F_{est})	848*	1638*
Cross-validation leave-one-out (loo) score ($r^2_{cv\text{-}loo}$)	0.9864	0.9956
Fisher parameter for loo analysis (F_{pred})	725*	1007*
Standard error for leave-one-out analysis (s_{loo})	0.1405	0.0847
Model stability ($r^2 - r^2_{cv(loo)}$)	0.0019	0.0016

* $p < 0.001$

The experimental values (logIR) and values predicted by MDF-SAR models with two ($\hat{Y}_{2d}$), respectively with four-descriptors ($\hat{Y}_{4d}$) and previously reported model ($\hat{Y}_{CoMFA}$) are in figure 1.
The absolute differences between estimated by models ($\hat{Y}_{2d}$, $\hat{Y}_{4d}$, and $\hat{Y}_{CoMFA}$) and measured (logIR) antiallergic activities of substituted N 4-methoxyphenyl benzamides were used in order to obtain the best estimation (figure 2).

Table 3. Regression analysis of the MDF-SAR models

	StdError	***t Stat***	***95%CI$_{coefficient}$***

MDF-SAR model with four descriptors			
Intercept	0.037	-3.985*	[-0.224, -0.0693]
imMRkMg	0.000	6.917*	[0.0006, 0.0012]
imMDVQg	0.042	-7.628*	[-0.411, -0.2337]
isDRtHg	$7 \cdot 10^{-7}$	-77.12*	$[-5.4 \cdot 10^{-5}, -5 \cdot 10^{-5}]$
iHMMtHg	0.002	64.03*	[0.1345, 0.1437]
MDF-SAR model with two descriptors			
Intercept	0.031	-0.288*	[-0.073, 0.0552]
isDRtHg	$1 \cdot 10^{-6}$	-40.719*	$[-5.4 \cdot 10^{-5}, -5 \cdot 10^{-5}]$
iHMMtHg	0.003	36.678*	[0.1226, 0.1374]

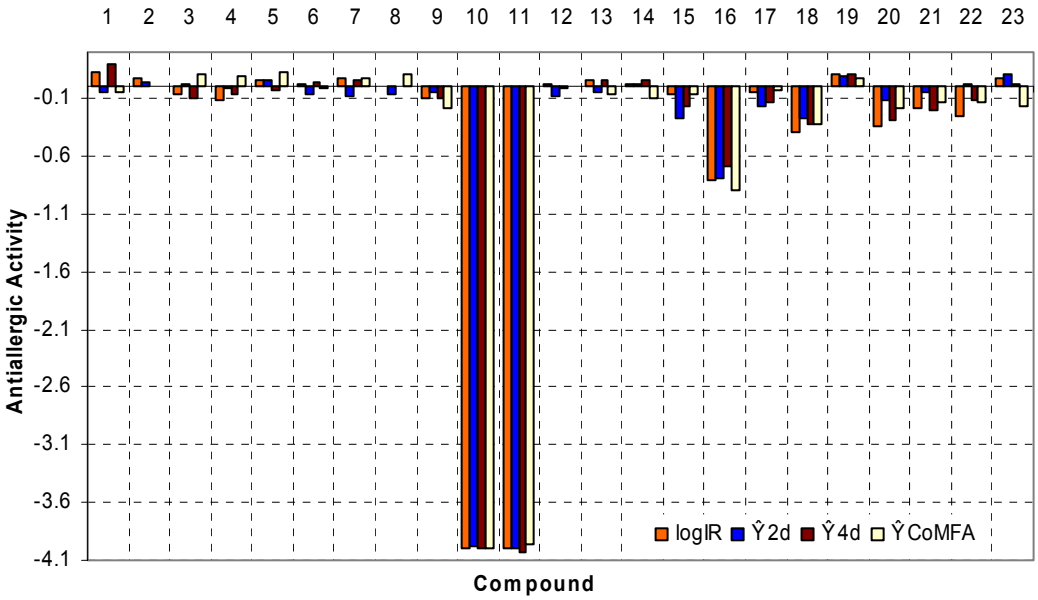

Figure 1. Measured antiallergic activity (logIR) and estimated by MDF-SAR, respectively CoMFA models

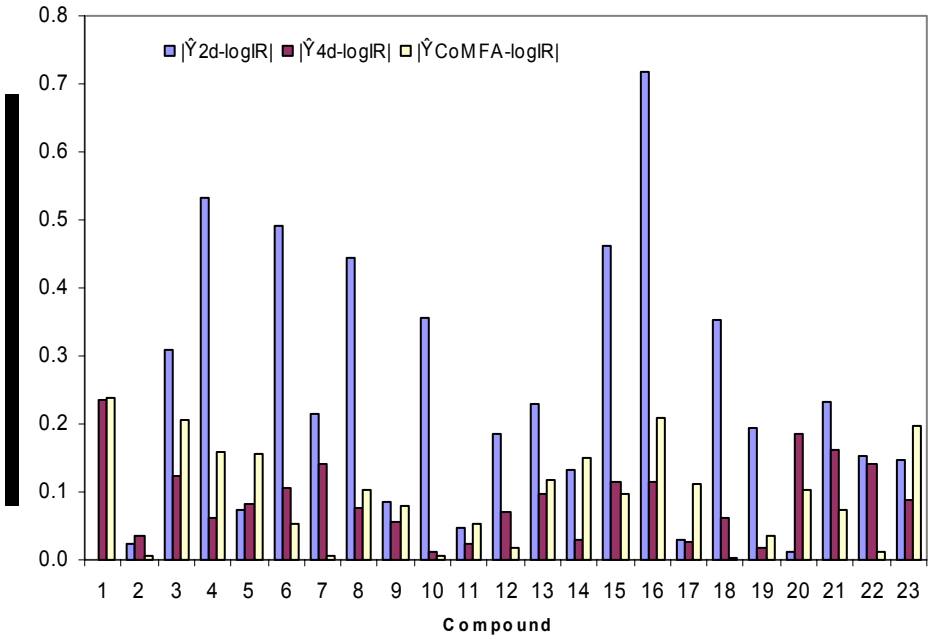

Figure 2. Measured (logIR) and estimated activities of compounds using MDF-SAR models and previously reported CoMFA model

In eleven out of twenty-three cases, the best estimation is obtained by multi-varied MDF-SAR model with four descriptors (see figure 3).

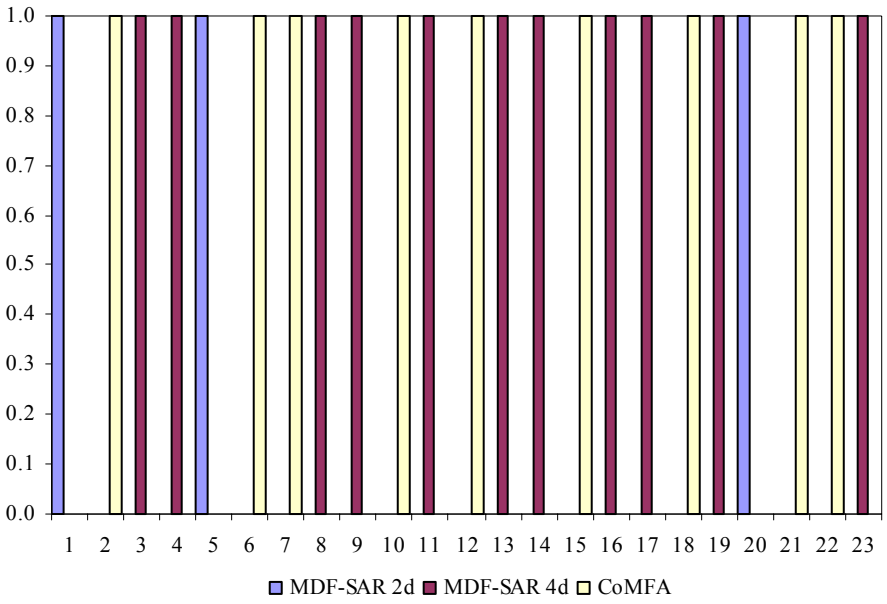

Figure 3. Best estimation antiallergic activity by MDF-SAR and CoMFA models

The comparison of MDF-SAR models with previously reported CoMFA model was performed by applying a correlated correlation analysis and the results are presented in table 4.

Table 4. The results of comparison between MDF-SAR model with four descriptors and previously reported CoMFA model

Characteristic	**Value**	
Number of descriptors used in MDF SAR model	2	4
r(logIR, $\hat{Y}_{MDF\text{-}SAR}$)	0.9941	0.9986
r(logIR, $\hat{Y}_{CoMFA}$)	0.9952	0.9952
r($\hat{Y}_{MDF\text{-}SAR}$, $\hat{Y}_{CoMFA}$)	0.9945	0.9943
Steiger's Z parameter	-0.5113	2.7974*

* $p < 0.05$

Discussions

Antiallergic activity of twenty-three substituted N 4-methoxyphenyl benzamides was characterized by the use of an original methodology, based on complex structure information of the compounds in order to explain associated biological activity.

Two multi-varied MDF-SAR models, one with two descriptors and other with four descriptors, proved to obtained performances in antiallergic activity estimation and prediction. The MDF-SAR models are statistically significant at a significance level less than 0.001 (see table 2).

The MDF-SAR model with two descriptors uses two molecular descriptors which take into consideration the geometry (***g***) and the number of directly bonded hydrogen's (***H***) of compounds (see Eq. 4). Almost ninety-nine percent of variation in antiallergic activity of substituted N 4-methoxyphenyl benzamides can be explainable by its linear relation with *isDRtHg* and *iHMMtHg* descriptors. The correlation coefficient obtained by the MDF-SAR model with two descriptors is not statistical significant different by the previously reported CoMFA model (see table 4) at a significance level of 5%. The performance of the MDF-SAR model with two descriptors is sustained by the correlation coefficient and the squared of the correlation coefficient ($r = 0.9942$, $r^2 = 0.9942$, table 2); the stability of the model is proved by the very lower value of the differences between squared correlation coefficient and cross-validation leave-on-out squared correlation coefficient. The cross-validation leave-one-out score ($r^2_{cv\text{-}loo} = 0.0019$) sustain the stability of the MDF-SAR model with two descriptors and its prediction abilities.

Looking at the MDF-SAR model with two descriptors it can be say that the antiallergic activity of studied compounds is of molecular geometry and is strongly depend on the number of directly bonded hydrogen's.
Analyzing the cross-validation leave-one-out scores, it can be said that multi-varied MDF-SAR model with four descriptors is the best performing MDF-SAR model. Almost one hundred percent of variation in antiallergic activity of substituted N 4-methoxyphenyl benzamides can be explainable by its linear relation with four molecular descriptors. Both descriptors used in MDF-SAR model with two descriptors can be found again on model with four descriptors; the other two descriptors consider the geometry of the molecule (***g***), atomic relative mass (***M***) and the partial charge (***Q***) as atomic property with role in antiallergic activities.
Looking at the multi-varied MDF-SAR model with four descriptors it can be observed that the antiallergic activities of studied compounds is positive correlated with *imMRkMg* and *iHMMtHg* descriptors and negative correlated with *imMDVQg* and *isDRtHg* descriptors. The values of squared correlation coefficient ($r^2 = 0.9973$) demonstrate the goodness of fit of the multi-varied MDF-SAR model with four descriptors (see tables 2 and 3, figures 2 and 3). The power of the MDF-SAR model with four descriptors in prediction of antiallergic activity of substituted N 4-methoxyphenyl benzamides compounds is demonstrate by the cross-validation leave-one-out correlation score ($r^2_{cv(loo)} = 0.9956$). The stability of the MDF-SAR model with four descriptors is give by the difference between the squared correlation coefficient and the cross-validation leave-one-out correlation score ($r^2 - r^2_{cv(loo)} = 0.0016$). Analyzing multi-varied MDF-SAR model with four descriptors it can be said that antiallergic activities of substituted N 4-methoxyphenyl benzamides strongly depend on the geometry of the compounds and is in relation with number of directly bonded hydrogen's, atomic relative mass and partial charge of compounds.
Correlated correlations analysis results (see table 4) demonstrate that the multi-varied MDF-SAR model with four descriptors obtained a significantly greater correlation coefficient compared with the previously reported CoMFA.
Starting with knowledge learned from the studied set of substituted N 4-methoxyphenyl benzamides, antiallergic activity of new compound from the same class can be predict by the use of an original software [13]. After the user draw the chemical structure of the new compound and saved it as *.hin file, the software is able to predict the antiallergic activity of new substituted N 4-methoxyphenyl benzamides compound in real time, without any experiments.

Conclusions

Modeling the antiallergic activity of substituted N 4-methoxyphenyl benzamides by integration of complex structural information provide a stable and performing MDF-SAR model with four variables, allowing to make remarks about relation between structure of compounds and their activities.
The antiallergic activity of substituted N 4-methoxyphenyl benzamides is like to be of geometry nature, depending by the number of directly bonded hydrogen's, and the atomic relative mass, being in relation with the partial charge of compounds.

Acknowledgement

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Activitatea Anti-Alergică a Derivaților de Benzamide: Caracterizare, Estimare şi Predicție

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Rezumat
Activitatea antialergică a unui eşantion de douăzeci şi trei de derivaţi N 4-methoxyphenyl benzamide a fost caracterizată, estimată şi prezisă prin folosirea unei metode originale. Familia descriptorilor moleculari care a stat la baza obţinerii modelelor a fost generată strict pe baza structurii compuşilor, după crearea structurii tri-dimensionale a acestora şi a fişierului cu activitatea anti-alergică măsurată. Modelul multi-variat cu patru descriptori s-a dovedit a abilităţi atât în estimarea (r^2 = 0.9986) cât şi în prezicerea ($r^2_{cv\text{-}loo}$ = 0.9956) activităţii anti-alergice a compuşilor studiaţi, obţinând un coeficient de corelaţie semnificativ mai mare în comparaţie cu modelul raportat în literatura de specialitate ($p < 0.01$). Caracterizarea activităţii anti-alergice a derivaţilor N 4-methoxyphenyl benzamide prin integrarea informaţiilor structurale complexe, oferă un model cu patru variabile stabil şi eficient. Activitatea anti-alergică a derivaţilor N 4-methoxyphenyl benzamide este de natură geometrică, depinde de numărul legăturilor directe de hidrogen şi masa atomică relativă, fiind în relaţie cu sarcina parţială.
Cuvinte cheie: Familia de descriptori moleculari, Relaţii structură-activitate (MDF-SAR), derivaţi N 4-methoxyphenyl benzamide, Activitate anti-alergică, Regresie liniară multiplă

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