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Journal of the Serbian Chemical Society

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J. Serb. Chem. Soc. *73* (10) 967–978 (2008)
JSCS–3778

UDC 577.15:547.53:615.281–188
Original scientific paper

The effect of lipophilicity on the antibacterial activity of some 1-benzylbenzimidazole derivatives

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(Received 27 February, revised 13 May 2008)

Abstract: In the present paper, the antibacterial activity of some 1-benzylbenzimidazole derivatives were evaluated against the Gram-negative bacteria *Escherichia coli*. The minimum inhibitory concentration was determined for all the compounds. Quantitative structure–activity relationship (QSAR) was employed to study the effect of the lipophilicity parameters (log *P*) on the inhibitory activity. Log *P* values for the target compounds were experimentally determined by the "shake-flask" method and calculated by using eight different software products. Multiple linear regression was used to correlate the log *P* values and antibacterial activity of the studied benzimidazole derivatives. The results are discussed based on statistical data. The most acceptable QSAR models for the prediction of the antibacterial activity of the investigated series of benzimidazoles were developed. High agreement between the experimental and predicted inhibitory values was obtained. The results of this study indicate that the lipophilicity parameter has a significant effect on the antibacterial activity of this class of compounds, which simplifies the design of new biologically active molecules.

Keywords: benzimidazole derivatives; lipophilicity; quantitative structure–activity relationship; antibacterial; *in vitro* studies.

INTRODUCTION

The benzimidazole nucleus, which is a useful structure for further molecular exploration and for the development of new pharmaceutical compounds, has been studied intensively. The synthesis of benzimidazoles has received a lot of attention owing to the varied biological activity exhibited by a number of these compounds.[1–7] This class of molecules proved to be very important, as they possess pharmaceutical properties, including antibacterial, against different strains of Gram-positive and Gram-negative bacteria,[8–10] antifungal[3] and herbicidal[11] activity. It is also well-known that these molecules are present in a variety of anal-

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doi: 10.2298/JSC0810967P

gesic,[12] anti-oxidant,[13,14] anti-allergic[15,16] and antitumoral[17] agents. Many derivatives of benzimidazole show antiparasitic[18] and anthelmintic[19] activities. In addition, they were confirmed to have moderate *in vitro* anti-HIV activity.[20,21]

The success with these groups of molecules stimulated the search for new biologically active derivatives. Understanding the role of chemical structure on influencing biological activity is very important.[22,23] Progress in the use of quantitative structure–activity relationship (QSAR) methods has shown the importance of the hydrophobic or lipophilic nature of biologically active molecules. The lipophilicity modifies the penetration of bioactive molecules through the apolar cell membranes. This property is usually characterized by the partition coefficient (log *P*), which is essentially determined from distribution studies of the compound between an immiscible polar and non-polar solvent pair. This quantitative descriptor of lipophilicity is one of the key determinants of pharmacokinetic properties.[24–26] Knowing the exact values for this parameter, it is possible to predict the inhibitory activity of the drugs.

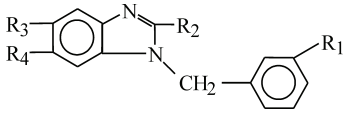
In this context, the aim of the present study was to investigate the activity of different substituted benzimidazoles against the Gram-negative bacteria *Escherichia coli* and to study the quantitative effect of lipophilicity on antibacterial activity. The objective of this study was to develop a rapid and reliable method for predicting the antibacterial activity of this class of molecules, as well as to determine the best log *P* values affording the most significant multilinear QSAR models, which link the structure of these compounds with their inhibitory activity.

EXPERIMENTAL

Modeling of compounds and calculation of lipophilicity parameters

The investigated compounds (Table I) were synthesized by a procedure described earlier.[27] The free on-line JME molecular editor software was used to model these molecules in SMILES (simplified molecular input line entry system) format. The SMILES notation created by the structure drawing program CambridgeSoft's ChemDrawPro was used as chemical structure input for all programs, except HyperChem 7.5 (HyperCube Inc., Version 7.5).[28]

TABLE I. Structural formula of the compounds



Compound	R_1	R_2	R_3	R_4
I-CH_3	CH_3	H	CH_3	CH_3
I-Cl	Cl	H	CH_3	CH_3
I-F	F	H	CH_3	CH_3
I-OCH_3	OCH_3	H	CH_3	CH_3
II-CH_3	CH_3	NH_2	H	H
II-Cl	Cl	NH_2	H	H
II-F	F	NH_2	H	H
II-OCH_3	OCH_3	NH_2	H	H

TABLE I. Continued

Compound	R_1	R_2	R_3	R_4
III-CH_3	CH_3	NH_2	CH_3	CH_3
III-Cl	Cl	NH_2	CH_3	CH_3
III-F	F	NH_2	CH_3	CH_3
III-OCH_3	OCH_3	NH_2	CH_3	CH_3

The lipophilicity parameters, based on log *P*, for all the compounds were experimentally determined (the "shake-flask" method) and their values calculated using different theoretical procedures from internet data (log P_{Hyper}, CSlog P, milog P, ALOGP, IAlogP, CLOGP, log Kow and XLOGP) (Table II).

TABLE II. Lipophilicity descriptors experimentally determined by "shake-flask" method and those calculated using different software

Cmpd.	Log *P*								
	Experi-mental	Calculated							
		Log P_{Hyper}	CSlog P	milog P	ALOGP	IAlogP	CLOGP	log Kow	XLOGP
I-CH_3	4.85	3.48	4.66	4.32	3.96	4.00	4.80	5.13	4.64
I-Cl	5.05	3.75	4.46	4.55	4.27	4.27	5.01	5.23	4.83
I-F	4.50	2.70	3.85	4.03	3.65	3.34	4.44	4.78	3.85
I-OCH_3	4.28	2.31	4.29	3.93	3.55	3.75	4.22	4.67	4.29
II-CH_3	3.60	2.75	3.06	3.32	3.14	2.70	3.56	3.68	3.44
II-Cl	3.85	2.80	3.48	3.55	3.60	3.06	3.78	3.78	3.62
II-F	3.25	2.42	2.18	3.03	3.08	3.16	3.21	3.33	3.17
II-OCH_3	3.04	2.03	2.85	2.93	2.83	2.57	2.98	3.21	2.92
III-CH_3	4.55	3.06	4.13	4.12	3.85	3.36	4.51	4.77	4.32
III-Cl	4.78	3.01	4.41	4.35	4.18	3.65	4.72	4.87	4.50
III-F	4.20	2.72	3.28	3.84	3.55	2.94	4.16	4.43	4.04
III-OCH_3	3.97	2.34	3.90	3.73	3.46	3.20	3.93	4.31	3.80

"Shake-flask" method

Partition coefficients (*P*) for benzimidazoles between *n*-octanol and phosphate buffer were determined at 25 °C. Before the partitioning of the benzimidazoles, the buffer (0.15 mol L^{-1}, pH 7.4) and *n*-octanol (99 %, Sigma, USA) were saturated with each other. The benzimidazoles were dissolved in ethanol (96 %, Zorka, Serbia) at a concentration of 2 mg mL^{-1} to give the stock solutions. Calibration was performed in exactly the same manner as the partitioning, except that *n*-octanol was not used. The amounts of the sample were chosen so that the absorbance (λ = 252 nm) was between 0.10 and 0.80. The partitioning experiments were performed in the systems *n*-octanol/phosphate buffer 1:20, 1:30, 1:70 and 1:80 (v/v). All the solutions were pipetted into glass vials; the *n*-octanol and stock solution were added with a microliter syringe. The phases were shaken together on a mechanical shaker (Viggo, Sweden) for 30 min, centrifuged (Rotofix, Switzerland) at 2500 rpm for 20 min to afford complete phase separation, and the *n*-octanol phase was removed. The absorbance of the buffer phase was measured using a Shimadzu UV/Vis spectrophotometer (Japan) at 252 nm. Log *P* values were calculated using Eq. (1):

$$\log P = \log\left(\frac{y-x}{x}\frac{V_{\text{buffer}}}{V_{n\text{-octanol}}}\right) \quad (1)$$

where P is partition coefficient, y is total mass of benzimidazole derivative (mg), x is the mass of benzimidazole derivative in the buffer phase after partitioning (mg), V_{buffer} is the volume of phosphate buffer (mL) and $V_{n\text{-octanol}}$ is the volume of *n*-octanol (mL). Each experimental log P value is the average of five determinations.

Calculation methods

A number of different computer programs for the calculation (prediction) of the lipophilicity of chemical compounds, based on their structure, have recently been developed.

Log P_{Hyper}. The computer program HyperChem 7.5 predicts log P values using the atom-additive method according to Ghose, Prichett and Crippen.[29] The program lists atom contributions for each atom type and calculates the log P value summing up all the atom contributions.

CSlog P. This program is based on topological structure descriptors and electropological state (E-state) indices.[30]

milog P. The milog P 1.2 program calculates log P values as the sum of group contributions and correction factors.[31]

ALOGP. The ALOGPS 2.1 package includes programs to predict lipophilicity and aqueous solubility of chemical compounds. The method is based on atom-type E-state indices and the associative neural network modeling was developed by Tetko *et al.*[32] This method combines electronic and topological characters to predict lipophilicity of the analyzed molecules.

IAlogP. This is another calculation program which predicts lipophilicity of chemical compounds using neural network algorithms and Molconn-Z indices, including E-state indices for atom types.[33]

CLOGP. The CLOGP 4.0 program is based on the fragmental method developed by Leo and Hansch[34] and has become the standard in the field of rational drug design.

LogKOW. The KoWWin program calculates log P values of organic compounds using the atom/fragment contribution (AFC) method developed by Syracuse Research Corporation (SRC).[35]

XLOGP. The XLOGP 2.0 is a computer program based on additive atomic contributions and calculates log P values according to Wang, Fu and Lai.[36,37]

The complete regression analysis, including linear, non-linear and multi-linear regression (MLR), were carried out by PASS 2005, GESS 2006, NCSS Statistical Software.[38]

Antibacterial investigations

All the 1-benzylbenzimidazole derivatives were evaluated for their *in vitr*o growth inhibitory activity against Gram-negative bacteria *Escherichia coli* (ATCC 25922). Antibacterial activities of the compounds were tested by the disc-diffusion method under standard conditions using Mueller-Hinton agar medium as described by NCCLS.[39] The investigated isolate of bacteria was seeded in tubes with nutrient broth (NB). The seeded NB (1 cm^3) was homogenized in tubes with 9 cm^3 of melted (45 °C) nutrient agar (NA). The homogenous suspension was poured into Petri dishes. Discs of filter paper (diameter 5 mm) were placed on the cool medium. After cooling on the formed solid medium, 2×10^{-5} dm^3 of the investigated compounds were added by micropipette. After incubation for 24 h at 25–27 °C, the diameters of the inhibition (sterile) zone (including disc) were measured (in mm). A diameter of the inhibition zone greater than 8 mm indicates the tested compound was active against the microorganism. Every test was performed in triplicate.

Minimum inhibitory concentration (*MIC*) was determined by the agar dilution method according to guidelines established by the NCCLS standard M7-A5.[40] The *MIC* value of tested benzimidazoles is defined as the lowest concentration of the compound at which no growth of the strain was observed in a period of time and under specified experimental conditions. Stock solutions of the compounds were prepared in dimethylformamide (DMF). Further dilutions were performed with distilled water. The concentration range of the compounds tested

was between 6.25–50 μg ml^{-1}. The inoculated plates were then incubated at 35 °C for 16–20 h. A control using DMF without any test compound was included. There was no inhibitory activity in the wells containing only DMF. The *MIC* values of the benzimidazoles tested were obtained as μg ml^{-1}. For further QSAR analyses, the negative logarithms of molar *MIC*s (log ($1/c_{MIC}$)) were used. In order to classify the antibacterial activity comparisons were established with antibacterial agents currently employed in therapeutic treatment. The *MIC*s were compared with those of ampicillin and gentamicin, which were screened under similar conditions as the tested compounds.

RESULTS AND DISCUSSION

The values of antibacterial activity of the benzimidazole derivatives against the tested Gram-negative bacteria are summarized in Table III. The screening results revealed that the investigated compounds expressed inhibitory activity against *Escherichia coli*. Compounds with a high log $1/c_{MIC}$ (or low *MIC*) are the best antibacterials.

TABLE III. Summary of the antibacterial screening

Compound	*MIC* / μg ml^{-1}	Log ($1/c_{MIC}$)
I-CH_3	6.25	4.602
I-Cl	6.25	4.637
I-F	6.25	4.609
I-OCH_3	12.5	4.328
II-CH_3	12.5	4.278
II-Cl	12.5	4.314
II-F	25.0	3.981
II-OCH_3	50.0	3.704
III-CH_3	6.25	4.627
III-Cl	6.25	4.659
III-F	12.5	4.333
III-OCH_3	12.5	4.352
Ampicillin	12.5	4.446
Gentamicin	0.780	5.787

In order to identify the effect of lipophilicity on the inhibitory activity, QSAR studies of title compounds were performed. A set of benzimidazoles consisting of 12 molecules was used for the generation of a multilinear regression model. The reference drugs were not included in the generation of the model as they belong to a different structural series. An attempt was made to find the structural requirement for the inhibition of Gram-negative *E. coli* using the QSAR Hansch approach on benzimidazole derivatives. To obtain the quantitative effects of the structural parameters of benzimidazole derivatives on their antibacterial activity, QSAR analysis with nine different partition coefficients (log *P*) was operated. First, the correlation of each one of the log *P* values with each other was calculated. The resulting correlation matrix is represented in Table IV. As is indicated, the calculated partition coefficients were in good correlation with each other, especially milog P, CLOGP, XLOGP and log Kow, as well as the experimentally obtained log *P* value.

TABLE IV. Correlation (r) matrix for the lipophilicity descriptors used in this study

Procedure	"shake-flask"	Log P_{Hyper}	CSlog P	milog P	ALOGP	IAlog P	CLOGP	log Kow	XLOGP
"shake-flask"	1	0.8019	0.9030	0.9971	0.9619	0.8439	0.9998	0.9842	0.9689
Log P_{Hyper}		1	0.6199	0.7800	0.8337	0.7190	0.8052	0.7194	0.7913
CSlog P			1	0.9176	0.8550	0.7921	0.8997	0.9170	0.8906
milog P				1	0.9654	0.8434	0.9969	0.9844	0.9928
ALOGP					1	0.8390	0.9609	0.9092	0.9469
IAlog P						1	0.8437	0.8419	0.8513
CLOGP							1	0.9847	0.9979
log Kow								1	0.9894
XLOGP									1

Usually, lipophilicity parameters are linearly related to pharmacological activity (*MIC*s), but in the more general case, this relationship is not linear.[41,42] Therefore, a complete regression analysis was made including linear, quadratic and cubic relationships. It is apparent from the data presented in Table V that the fitting equations improved when resorting to higher order (second or third order) polynomials.

TABLE V. Correlation coefficients (r) calculated for the relationship between log $1/c_{MIC}$ and different log P values

Procedure	Log $(1/c_{MIC}) = a\log P + b$	Log $(1/c_{MIC}) = a\log P^2 + b\log P + c$	Log $(1/c_{MIC}) = a\log P^3 + b\log P^2 + c\log P + d$
"shake-flask"	0.9384	0.9626	0.9664
Log P_{Hyper}	0.7628	0.8450	0.8490
CSlog P	0.8206	0.8211	0.8478
milog P	0.9282	0.9500	0.9549
ALOGP	0.9077	0.9486	0.9493
IAlog P	0.7032	0.7646	0.7757
CLOGP	0.9389	0.9640	0.9672
log Kow	0.9053	0.9246	0.9443
XLOGP	0.8706	0.9226	0.9359

Data from Table V indicates that only two of the aforementioned log P values are highly correlated with the measured activity. However, the introduction of a second parameter improved the statistical indices of the QSAR models but the best QSAR models were obtained with three variables with second order polynomials. The resulting models are as follows:

$$\text{Log}\,(1/c_{MIC}) = 0.140\text{CLOGP}^2 + 0.103\text{log Kow}^2 - 0.491\text{XLOGP}^2 - 0.302C\log P - 1.191\text{log Kow} + 3.756\text{XLOGP} - 0.632 \quad (2)$$

$$n = 12;\ r = 0.9855;\ s = 0.0744;\ F = 28$$

$$\text{Log}\,(1/c_{MIC}) = 0.939\text{milog P}^2 - 0.881\text{CLOGP}^2 + 0.136\text{XLOGP}^2 - 7.366\text{milog P} + 8.136\text{CLOGP} - 1.437\text{XLOGP} + 3.851 \quad (3)$$

$$n = 12;\ r = 0.9845;\ s = 0.0782;\ F = 24.818$$

$$\text{Log}\,(1/c_{MIC}) = 0.762\text{ALOGP}^2 + 0.736\text{log Kow} - 1.453\text{XLOGP}^2 -$$

$$- 5.246\text{ALOGP} - 6.145 \log \text{Kow} + 11.544\text{XLOGP} + 3.277 \quad (4)$$
$$n = 12;\ r = 0.9843;\ s = 0.0775;\ F = 25.326$$

The statistical quality of the resulting models, as depicted in Eqs. (2)–(4), is given by the correlation coefficient, r, the standard error of estimation, s, and the probability factor related to the F-ratio, F. It is noteworthy that all these equations were derived using the entire data set of compounds (n = 12) and no outliers were identified. The F-values obtained in Eqs. (2)–(4) are statistically significant at the 99 % level, since all the calculated F values are higher than the tabulated values.

To estimate the quality with regards to predictive ability of this model, the cross-validation statistical technique was applied. This is the most common validation technique, where a number of modified data sets are created by deleting, in each case, one or smaller group of objects from the data in such a way that each object is taken away once and only once. For each reduced data set, the model is calculated, and responses for the deleted objects are predicted from the model. The simplest and most general cross-validation procedure is the leave-one-out technique (LOO technique). The estimation of the models quality was based on cross-validated parameters *viz*., the predicted residual sum of squares, *PRESS*, the total sum of squares deviation, *SSY*, the uncertainty of prediction, S_{PRESS}, the cross-validated correlation coefficient, r^2_{CV}, and the adjusted correlation coefficient, r^2_{adj} (Table VI).

TABLE VI. Cross-validation parameters

Equation	*PRESS*	*SSY*	*PRESS*/*SSY*	S_{PRESS}	r^2_{CV}	r^2_{adj}
(2)	0.1633	0.9417	0.1734	0.1166	0.8266	0.9366
(3)	0.2114	0.9417	0.2245	0.1327	0.7755	0.9285
(4)	0.2037	0.9417	0.2163	0.1303	0.7837	0.9299

PRESS is an important cross-validation parameter as it is a good approximation of the real predictive error of the models. Its value being less than the *SSY* indicates whether a model predicts better than chance and whether it can be considered statistically significant. Thus, in view of this, all the three proposed models are statistically significant. Furthermore, to be a reasonable QSAR model, the *PRESS*/*SSY* ratio should be less than 0.40. The data presented in Table VI indicate that this ratio is < 0.23 for all the developed models. From the *PRESS* and *SSY*, the r^2_{CV} and S_{PRESS} statistics can be easily calculated:

$$r^2_{\text{CV}} = 1 - PRESS/SSY \quad (5)$$

$$S_{PRESS} = \sqrt{\frac{PRESS}{n}} \quad (6)$$

The high r^2_{CV} values observed for all the proposed QSAR models are indicative of their reliability in the prediction of inhibitory activity. However, the only way to estimate the true predictive power of a model is to test its ability to predict accurately the biological activities of compounds. In order to verify the predictive power of the developed models, the predicted log ($1/c_{MIC}$) values of the

investigated benzimidazoles were calculated using Eqs. (2)–(4) and compared with the experimental values. Based on the magnitude of the residue, there is a close agreement between the observed and calculated inhibitory activities (Table VII). Furthermore, plots of the linear regression predicted log $1/c_{MIC}$ values against the observed log ($1/c_{MIC}$) values also favor the models expressed by Eqs. (2)–(4) (Fig. 1).

TABLE VII. Predicted log ($1/c_{MIC}$) values of the benzimidazoles tested against *E. coli*

Compound	Predicting equations and residues					
	Eq. (2)	Residue	Eq. (3)	Residue	Eq. (4)	Residue
I-CH_3	4.595	0.007	4.590	0.012	4.573	0.029
I-Cl	4.637	0.000	4.638	–0.001	4.628	0.009
I-F	4.625	–0.016	4.618	–0.009	4.616	–0.007
I-OCH_3	4.343	–0.015	4.389	–0.061	4.388	–0.060
II-CH_3	4.185	0.093	4.212	0.066	4.285	–0.007
II-Cl	4.334	–0.020	4.284	0.030	4.300	0.014
II-F	3.986	–0.005	4.004	–0.023	4.017	–0.036
II-OCH_3	3.727	–0.023	3.717	–0.013	3.709	–0.005
III-CH_3	4.573	0.054	4.648	–0.021	4.557	0.070
III-Cl	4.657	0.002	4.651	0.008	4.712	–0.053
III-F	4.435	–0.102	4.327	0.006	4.336	–0.003
III-OCH_3	4.342	0.010	4.342	0.010	4.347	0.005

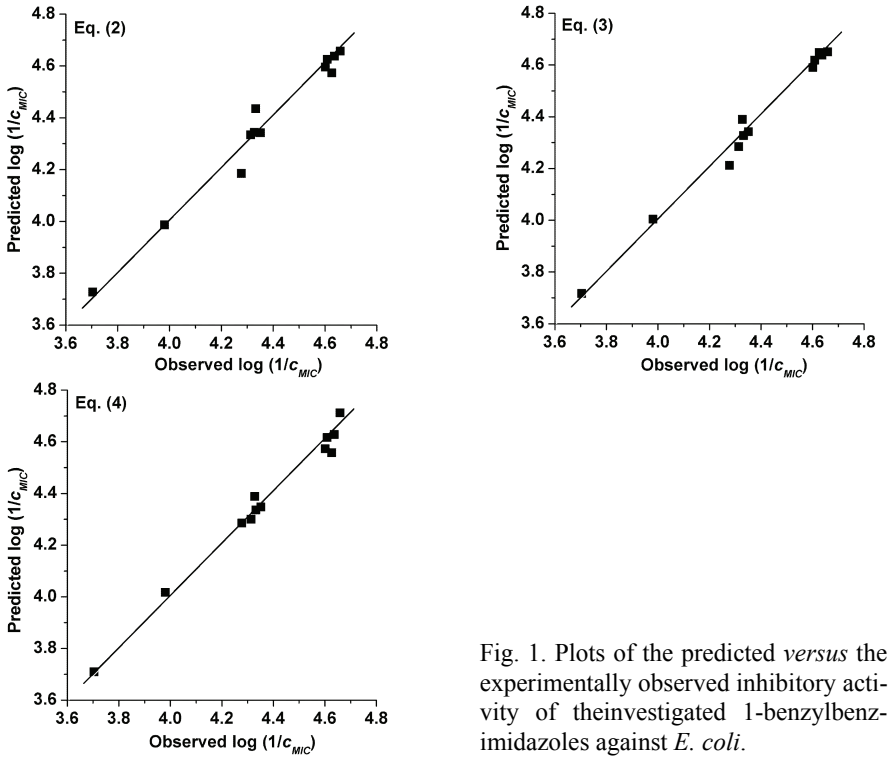


Fig. 1. Plots of the predicted *versus* the experimentally observed inhibitory activity of theinvestigated 1-benzylbenzimidazoles against *E. coli*.

In order to investigate the existence of a systemic error in the development of the QSAR models, the residuals of the predicted log ($1/c_{MIC}$) values were plotted against the observed log ($1/c_{MIC}$) values (Fig. 2). The propagation of the residuals on both sides of zero indicates that no systemic error exists in the development of regression models, as suggested by Jalali-Heravi and Kyani.[43]

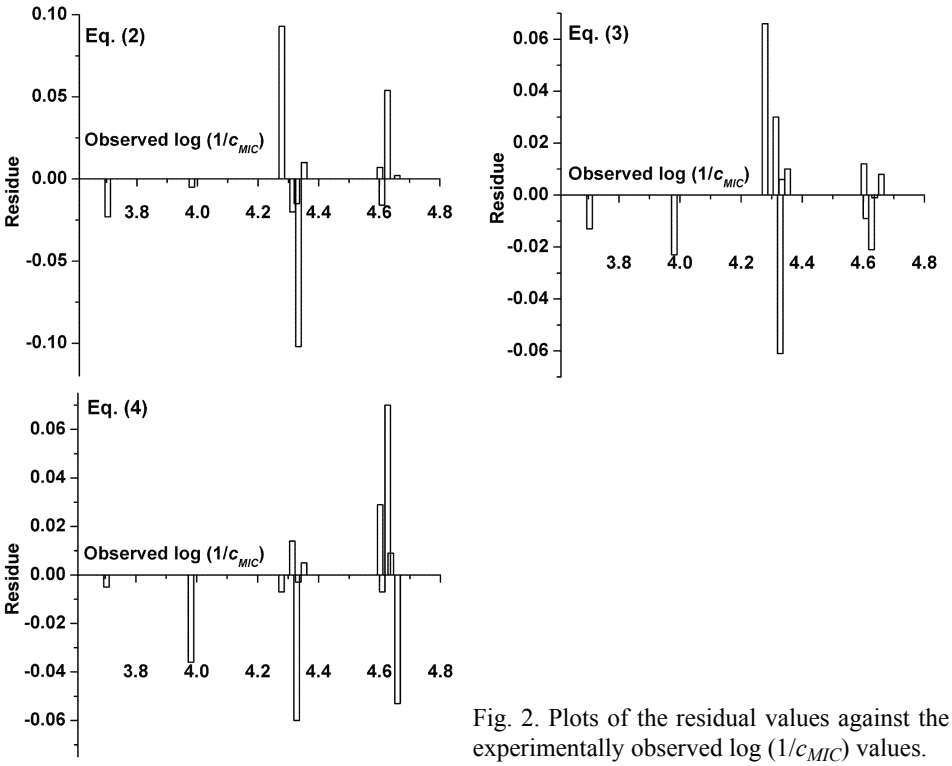


Fig. 2. Plots of the residual values against the experimentally observed log ($1/c_{MIC}$) values.

From the three above presented models, it can be concluded that a strong influence of the partition coefficient, log *P*, is important for antibacterial activity and this parameter is usually related to the pharmacological activity.[41,44] This evidence was clearly described in the lipid theory advanced by Meyer and Overton. According to this theory, log *P* is a measure of hydrophobicity, which is important not only for the penetration and distribution of a drug, but also for the interaction of the drug with receptors. Therefore, it can be suggested that lipophilic properties should be checked in the design of potent antibacterial agents as they are deciding factors for their activity.

CONCLUSIONS

From the results discussed above, it can be concluded that the investigated 1-benzylbenzimidazole derivatives showed *in vitro* inhibitory activity against the

Gram-negative bacteria *Escherichia coli*. QSAR analyses were employed to study the quantitative effects of the lipophilicity of the benzimidazoles on their antibacterial activity. Different lipophilicity parameters were experimentally determined by the "shake-flask" method and calculated using eight different software products. A complete regression analysis was performed in which linear, quadratic and cubic relationships between the log *P* values and the antibacterial activity (log ($1/c_{MIC}$)) were employed. The fitting equations improved when higher order (second or third order) polynomials were used. Three high quality non-linear structure–activity models were derived between the log ($1/c_{MIC}$) and three different log *P* values. The obtained mathematical models were used to predict the inhibittory activity of the investigated benzimidazoles and close agreement between the experimental and predicted values was found. The low residual activity and high cross-validated r^2 values (r^2_{CV}) observed indicate the predictive ability of the developed QSAR models. It indicates that these models can be successfully applied to predict the antibacterial activity of this class of molecules. It can be concluded that the partition coefficient, log *P*, has a strong influence on the antibacterial activity and this parameter is usually related to pharmacological activity.

Acknowledgement. These results are the part of the project No. 142028, supported by the Ministry of Science of the Republic of Serbia.

И З В О Д

УТИЦАЈ ЛИПОФИЛНОСТИ НА АНТИБАКТЕРИЈСКУ АКТИВНОСТ НЕКИХ ДЕРИВАТА БЕНЗИМИДАЗОЛА

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У овом раду испитана је антибактеријска активност неких деривата 1-бензилбензимидазола на грам-негативну бактерију *Escherichia coli*. Испитивани бензимидазоли *in vitro* показују антибактеријску активност и за сва једињења је одређена минимална инхибиторна концентрација. Применом QSAR (quantitative structure–activity relationship) анализе испитане су зависности између инхибиторне активности и параметара липофилности, log *P*. За испитивана једињења, log *P* вредности су одређене експерименталном "shake-flask" методом и израчунате су помоћу осам различитих рачунарских програма. Методом вишеструке регресије испитане су корелације између log *P* вредности и антибактеријске активности деривата бензимидазола. Резултати су продискутовани на основу статистичких података. Развијени су најприхватљивији математички модели за предвиђање антибактеријске активности у оквиру испитиване серије бензимидазола. Добијено је веома добро слагање између експериментално одређених и предвиђених вредности инхибиторних активности. Резултати ових испитивања показују да параметар липофилности има значајан утицај на антибактеријску активност испитиване класе једињења, што олакшава дизајнирање нових биолошки активних молекула.

(Примљено 27. фебруара, ревидирано 13. маја 2008)

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