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QSPR Study for the Hydrophobicity of 4–Aryloxy–7–nitrobenzofurazan and 2–Aryloxy–(α–acetyl)–phenoxathiin Derivatives

Adrian Beteringhe,[1] Ana Cristina Radutiu,[1] Marioara Bem,[1] Titus Constantinescu,[1] and Alexandru T. Balaban [2]

[1] Romanian Academy, "Ilie Murgulescu" Institute of Physical Chemistry, Laboratory of Supramolecular Chemistry and Interphase Processes, Splaiul Independentei 202, 060021, Bucharest, Romania
[2] Texas A&M University at Galveston, 5007 Avenue U, Galveston, TX, 77551, USA

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QSPR Study for the Hydrophobicity of 4–Aryloxy–7–nitrobenzofurazan and 2–Aryloxy–(α–acetyl)–phenoxathiin Derivatives

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Abstract

Motivation. The experimental values of the molecular hydrophobicity (R_{M0}) determined for seven phenols and for their newly obtained derivatives, 2–aryloxy–(α–acetyl)–phenoxathiin and 4–aryloxy–7–nitrobenzofurazan compounds, were correlated with the molecular descriptors implementated in the CODESSA program. A quantitative structure–property relationship (QSPR) was established between the experimental R_{M0} values and the hydrophobicity values (logP) calculated by the Hansch method. The QSAR equations with three descriptors obtained by these two methods have good predictive power: with CODESSA descriptors: $N = 20$ compounds, $R = 0.938$, $S = 0.333$, $F = 51.23$, $R^2_{CV} = 0.826$; and with logP and two other terms: $N = 20$, $R = 0.994$, $S = 0.065$, $F = 2067$, $R^2_{CV} = 0.952$.

Method. Molecular descriptors implemented in CODESSA program were used to establish some QSPR models. The QSPR models were validated by the leave–one–out cross validation method.

Conclusions. The correlation between the two hydrophobicity parameters (experimental R_{M0} and calculated logP) demonstrates that molecular surfaces can be modeled satisfactorily using appropriate descriptors.

Keywords. 4–Aryloxy–7–nitrobenzofurazan; 2–aryloxy–(α–acetyl)–phenoxathiin; molecular hydrophobicity R_{M0}; water/*n*–octanol partition coefficient; CODESSA; QSPR; quantitative structure–property relationships.

1 INTRODUCTION

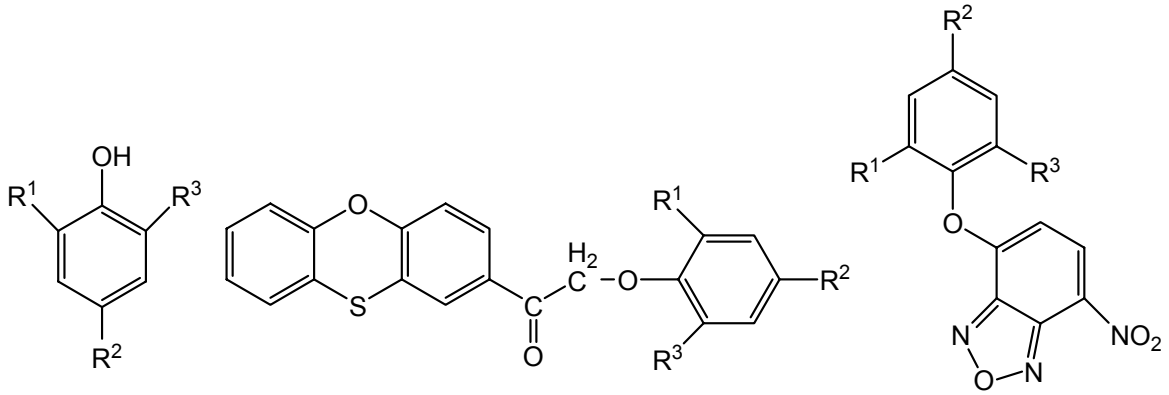
Benzofuroxan (benzo[1,2–*c*]–1,2,5–oxadiazole–2–oxide), furoxan (1,2,5–oxadiazole–2–oxide), furazan (2,1,3–oxadiazole) and benzofurazan (2,1,3–benzoxadiazole) derivatives have been intensely studied in connection with their antifungal, antibacterial (gram–negative and gram–positive), and antiprotozoal properties (*Trichomonas vaginalis*, *Entamoeba histolytica*) [1,2].

Dedicated to Professor Lemont B. Kier on the occasion of the 75th birthday.

* Correspondence author; phone: +1–409–741–4313; fax: +1–409–740–4787; E–mail: balabana@tamug.edu.

Recent studies demonstrated that they could inhibit the *in vitro* development of *Trypanosoma cruzi* [3], and *Trypanosoma Americana* (Chagas' Disease) [3]. Nitrobenzofurazan and nitrobenzofuroxan derivatives inhibit the synthesis of polynucleotides in leucocytes [4], resulting in antileukemic and immunosuppressive activity [5], and they can act as reactive probes for characterizing active centers of papain (EC 3.4.22.2) [6], ficain (EC 3.4.22.3) [6] and bromelain (EC 3.4.22.4) [6]. Benzofurazan and benzofuroxan derivatives are used as fluorogenic reagents in the analytical chemistry of amino acids, primary and secondary amines or polypeptides [7–11]. Phenoxathiin derivatives also are biologically active [12–17], and have promising fluorescent properties [18–23]. The hydrophobic/hydrophilic balance of chemical compounds is an important parameter for their biological and physical–chemical applications. Corwin Hansch defined it experimentally in 1962 as logP, the water/*n*–octanol partition coefficient. It can also be measured as by reverse phase thin–layer chromatography (RP–TLC), or it can be calculated by several methods [11,23,24].

Previous papers reported experimental R_{M0} (molecular hydrophobicity) and calculated logP values for 4–aryloxy–7–nitrobenzofurazan [11] and 2–aryloxy–(α–acetyl)–phenoxathiin [23]. In the present paper we report the quantitative structure–property relationships for R_{M0} hydrophobic parameters of seven phenols (**1a–1g**), seven phenoxathiin phenolic ethers (**2a–2g**), and six nitrobenzofurazan ethers (**3a–3e**, **3g**) that are structurally related by the substituents at the phenolic moiety. The group designated as **g** is part of the anti–cancer agent etoposide, and here the 4–methoxy substituent in the 3,4,5–trimethoxyphenolic moiety of etoposide is replaced by a different substituent.



1a-g **2a-g** **3a-e, g**

Figure 1. Structures of phenols **1a**–**1g** and phenolic ether derivatives of phenoxathiin (**2a**–**2g**) and of nitrobenzofurazan (**3a**–**3e**, **3g**)

We present first the QSPR results obtained for R_{M0} values and molecular descriptors using the CODESSA program, and then correlation results between experimental R_{M0} values and calculated logP values using Hansch's molecular fragment approach. The physical meaning of the molecular descriptors involved in the optimized QSPR is discussed in the last section of this paper.

2 MATERIALS AND METHODS

From the experimental RP–TLC data (R_f) [11, 23] one calculates the molecular hydrophobicity R_{M0} using the following equations [25,26]:

$$R_M = \log (1/R_f - 1) \quad (1)$$

$$R_M = R_{M0} + bK \quad (2)$$

where R_{M0} is the extrapolated R_M for zero concentration in the water – organic solvent mixture, and b is the change in the R_M value caused by increasing the concentration (K) of the organic component in the mobile phase. Once we have the molecular hydrophobicity R_{M0} values, we can explore which of the many molecular descriptors provided by the CODESSA 2.7.2 program [27–30] give the best bi– and tri–parametric QSPR models.

3 RESULTS

3.1 QSPR Results with two CODESSA descriptors

The optimal multilinear regression with two descriptors is:

$$R_{M0} = -241.6\ (\pm 105.9) - 0.117(\pm 0.013)\ HACA + 62.05(\pm 10.75)\ MVCA$$
$$N = 20 \quad R = 0.938 \quad S_{PRESS} = 0.333 \quad F = 51.23 \quad Qf = 2.817 \quad R^2_{CV} = 0.826 \quad (3)$$

where *HACA* is H–acceptor charged surface area (quantum–chemical partial charge) and *MVCA* is the maximum valency of a carbon atom. The CODESSA program uses *AMPAC* quantum–chemical results for these two descriptors. The charge distribution for hydrogen–bond acceptors is based on Mulliken's definition of atomic charges: $\delta_A = Z_A - \Sigma_i P_{ii}$ where Z_A is the nuclear charge of atom A, and the summation of Mulliken populations P_{ii} is carried out for all atomic orbitals of atom A, N is the number of data points, R denotes the correlation coefficient, S is the standard deviation of the fit, F is the Fisher test, and Qf is the quality factor. In Table 1 and Figure 2 we present the experimental [11,23] and estimated values (biparametric Eq. (3)) of the molecular hydrophobicity R_{M0}.

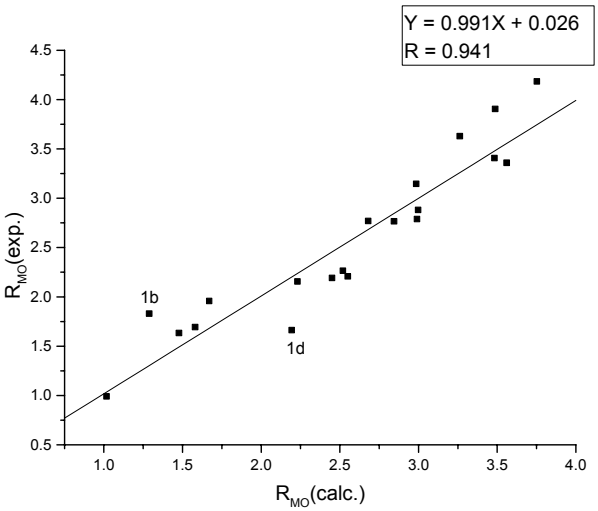
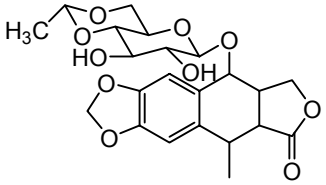
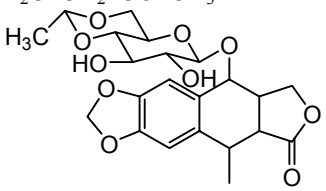
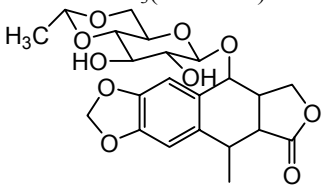


Figure 2. Plot of experimental vs. calculated molecular hydrophobicity (R_{M0}) values for phenols **1a–g**, aryloxy–phenoxathiin derivatives **2a–g**, and 4–aryloxy–7–nitrobenzofurazan derivatives **3a–e**, **3g** obtained with CODESSA program (biparametric Eq. (3)).

Table 1. Experimental and estimated molecular hydrophobicity (R_{M0}) values for phenols **1a–g**, 2–aryloxy–(α–acetyl)–phenoxathiin derivatives **2a–g** and 4–aryloxy–7–nitro–benzofurazan **3a–e**, **3g** derivatives obtained with CODESSA program (biparametric eq. 3)

No	R^1	R^2	R^3	R_{M0} (obs.)	R_{M0} (calc.)	Resid.
1a	H	H	H	1.948	1.676	–0.272
1b	OCH_3	H	H	1.821	1.295	–0.526
1c	OCH_3	H	OCH_3	1.623	1.484	–0.139
1d	OCH_3	CH_2–CH=CH_2	H	1.653	2.201	0.548
1e	OCH_3	HC=CH–CH_3(*cis*+*trans*)	H	2.255	2.526	0.271
1f	H	H_2C–CH_2–CO–CH_3	H	0.981	1.024	0.043
1g	OCH_3		OCH_3	1.683	1.587	–0.096
2a	H	H	H	3.137	2.992	–0.145
2b	OCH_3	H	H	2.871	3.004	0.133
2c	OCH_3	H	OCH_3	2.779	2.997	0.218
2d	OCH_3	CH_2–CH=CH_2	H	3.895	3.494	–0.401
2e	OCH_3	HC=CH–CH_3(*cis*+*trans*)	H	4.174	3.759	–0.415
2f	H	H_2C–CH_2–CO–CH_3	H	3.397	3.489	0.092
2g	OCH_3		OCH_3	2.756	2.851	0.095
3a	H	H	H	2.197	2.557	0.360
3b	OCH_3	H	H	2.182	2.457	0.275
3c	OCH_3	H	OCH_3	2.146	2.237	0.091
3d	OCH_3	CH_2–CH=CH_2	H	3.620	3.269	–0.351
3e	OCH_3	HC=CH–CH_3(*cis*+*trans*)	H	3.350	3.567	0.217
3g	OCH_3		OCH_3	2.760	2.687	–0.073

3.2 QSPR Results with Three CODESSA Descriptors

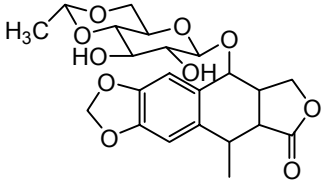
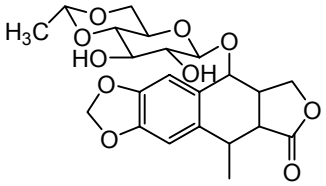
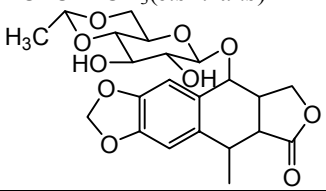
The QSPR model with three descriptors is:

$$R_{M0} = -3.280\ (\pm 0.458) - 109.4(\pm 13.67)\ MPCH + 0.064(\pm 0.004)\ PPSA3 + 0.339(\pm 0.051)\ MRECCB \quad (4)$$

$$n = 20 \quad R = 0.979 \quad S_{PRESS} = 0.198 \quad F = 105.6 \quad Qf = 4.949 \quad R^2_{CV} = 0.932$$

where *MPCH* is the minimum partial charge for a hydrogen atom (Zefirov's partial charge), *PPSA3* denotes the atomic charge weighted PPSA (quantum–chemical partial charge) and *MRECCB* is the minimum resonance energy for a C–C bond. In Table 2 and Figure 3 we present the experimental [11,23] and estimated values (triparametric Eq. (4)) of the molecular hydrophobicity R_{M0}.

Table 2. Experimental and estimated molecular hydrophobicity (R_{M0}) values for phenols **1a–g**, aryloxy–phenoxathiin derivatives **2a–g** and 4–aryloxy–7–nitrobenzofurazan **3a–e**, **3g** derivatives obtained with CODESSA program (triparametric Eq. (4))

No	R^1	R^2	R^3	R_{M0}(obs.)	R_{M0}(calc.)	Resid.
1a	H	H	H	1.948	1.942	–0.006
1b	OCH_3	H	H	1.821	1.759	–0.062
1c	OCH_3	H	OCH_3	1.623	1.654	0.031
1d	OCH_3	CH_2–CH=CH_2	H	1.653	1.730	0.077
1e	OCH_3	HC=CH–CH_3(*cis*+*trans*)	H	2.255	2.046	–0.209
1f	H	H_2C–CH_2–CO–CH_3	H	0.981	1.151	0.170
1g	OCH_3		OCH_3	1.683	1.704	0.021
2a	H	H	H	3.137	2.777	–0.360
2b	OCH_3	H	H	2.871	2.801	–0.070
2c	OCH_3	H	OCH_3	2.779	3.068	0.289
2d	OCH_3	CH_2–CH=CH_2	H	3.895	3.847	–0.048
2e	OCH_3	HC=CH–CH_3(*cis*+*trans*)	H	4.174	4.070	–0.104
2f	H	H_2C–CH_2–CO–CH_3	H	3.397	3.481	0.084
2g	OCH_3		OCH_3	2.756	2.750	–0.006
3a	H	H	H	2.197	2.312	0.115
3b	OCH_3	H	H	2.182	2.126	–0.056
3c	OCH_3	H	OCH_3	2.146	2.122	–0.024
3d	OCH_3	CH_2–CH=CH_2	H	3.620	3.427	–0.193
3e	OCH_3	HC=CH–CH_3(*cis*+*trans*)	H	3.350	3.717	0.367
3g	OCH_3		OCH_3	2.760	2.815	0.055

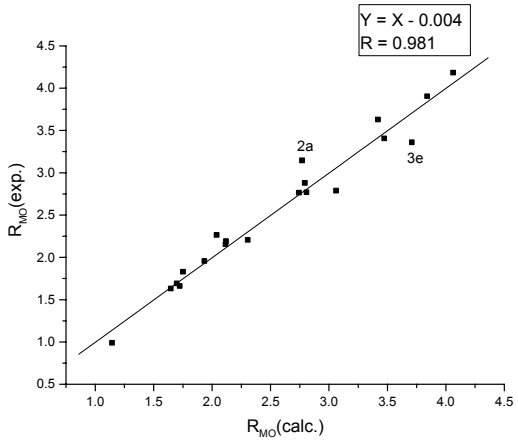


Figure 3. Plot of experimental vs. calculated molecular hydrophobicity (R_{M0}) values for phenols **1a–g**, 2–aryloxy–(α–acetyl)–phenoxathiin derivatives **2a–g** and 4–aryloxy–7–nitro–benzofurazan **3a–e**, **3g** derivatives obtained with the CODESSA program (triparametric Eq. (4)).

3.3 Correlation between Experimental Molecular Hydrophobicity R_{M0} and the Calculated LogP Values using Hansch's Molecular Fragment Approach

For computing logP values one may choose either Hansch's fragment constants *f* [31,32], or the summation of lipophilicity (π) values. One can use the R_{M0} parameter for computing logP, according to literature data [11,23,33–37]. Reviews for linear correlations between R_{M0} and logP (obtained from fragment constants *f* or π values) are available [38–41].

In the present paper we present a relationship between the experimental R_{M0} values and the calculated logP *via* Hansch fragment constants *f*, as shown in Eq. (5):

$$R_{M0} = \log P + (-1)^{3-s} \cdot 10^{-(s+1)} \cdot \log(MR - ST) - FS$$
$$N = 20 \quad R = 0.994 \quad S_{PRESS} = 0.065 \quad F = 2067 \quad Qf = 15.23 \quad R^2_{CV} = 0.952 \tag{5}$$

where R_{M0} is the experimental molecular hydrophobicity, logP is the hydrophobicity calculated via Hansch fragment constants, *s* is the number of non–hydrogen phenolic substituents (R^1, R^2, R^3), MR is the molecular refraction, ST is the surface tension, and FS is the substituent factor (an indicator variable that has value 0 when the phenolic moiety has an odd number *s* of substituents, and the value –0.074 for an even number *s* of substituents).

The molecular refraction according to the Lorentz–Lorenz formula, Eq. (6) [42,43], and the surface tension, Eq. (7), were calculated using the ChemSketch 8.0 Freeware [44]:

$$MR = (n^2 - 1 / n^2 + 1) \cdot (MW / d) \tag{6}$$

$$ST = (\partial G / \partial A)_{P,T} \tag{7}$$

where *n* is the index of refraction, *MW* is the molecular weight, *d* is the density, *G* is the Gibbs free energy and *A* is the area. In Table 3 and Figure 4 we present the calculated logP values and the experimental [11, 23] and calculated values of the molecular hydrophobicity R_{M0} according to Eq. (5).

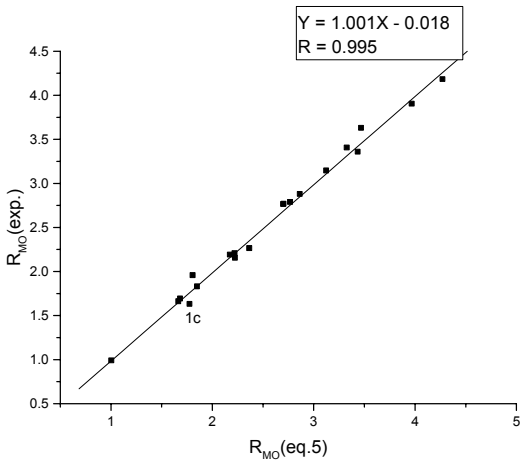
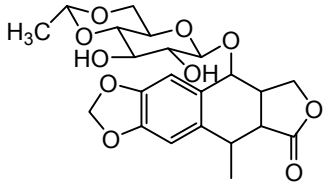
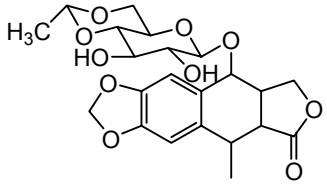
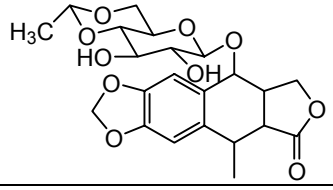


Figure 4. Experimental vs. estimated, Eq. (5), molecular hydrophobicity (R_{M0}) values for phenols **1a–g**, 2–aryloxy–(α–acetyl)–phenoxathiin derivatives **2a–g**, and 4–aryloxy–7–nitrobenzofurazan derivatives **3a–e**, **3g**.

Table 3. Structural parameters, calculated logP values, experimental and calculated R_{M0} values, Eq. (5), for phenols **1a–g**, 2–aryloxy–(α–acetyl)–phenoxathiin derivatives **2a–g** and 4–aryloxy–7–nitrobenzofurazan **3a–e**, **3g**

No	R^1	R^2	R^3	s*	MR	ST	logP	R_{M0}(obs.)	R_{M0}(calc.)	Resid.
1a	H	H	H	0	48.13	40.9	1.900	1.948	1.814	–0.134
1b	OCH_3	H	H	1	44.81	38.6	1.850	1.821	1.857	0.036
1c	OCH_3	H	OCH_3	2	45.49	37.2	1.710	1.623	1.783	0.160
1d	OCH_3	CH_2–CH=CH_2	H	2	48.72	36.5	1.600	1.653	1.672	0.019
1e	OCH_3	HC=CH–CH_3(*cis*+*trans*)	H	2	50.70	38.9	2.300	2.255	2.372	0.117
1f	H	H_2C–CH_2–CO–CH_3	H	1	46.97	41.8	1.005	0.981	1.012	0.031
1g	OCH_3		OCH_3	3	172.6	64.2	1.690	1.683	1.690	0.007
2a	H	H	H	0	95.22	56.7	3.290	3.137	3.131	–0.006
2b	OCH_3	H	H	1	101.9	54.0	2.854	2.871	2.870	–0.001
2c	OCH_3	H	OCH_3	2	108.6	51.9	2.703	2.779	2.775	–0.004
2d	OCH_3	CH_2–CH=CH_2	H	2	115.8	50.4	3.903	3.895	3.975	0.080
2e	OCH_3	HC=CH–CH_3(*cis*+*trans*)	H	2	117.8	52.0	4.207	4.174	4.279	0.105
2f	H	H_2C–CH_2–CO–CH_3	H	1	120.8	51.9	3.316	3.397	3.334	–0.063
2g	OCH_3		OCH_3	3	244.0	69.8	2.705	2.756	2.706	–0.050
3a	H	H	H	0	68.56	66.2	2.265	2.197	2.227	0.030
3b	OCH_3	H	H	1	72.24	60.9	2.170	2.182	2.180	–0.002
3c	OCH_3	H	OCH_3	2	78.92	56.9	2.160	2.146	2.232	0.086
3d	OCH_3	CH_2–CH=CH_2	H	2	86.15	54.5	3.470	3.620	3.475	–0.145
3e	OCH_3	HC=CH–CH_3(*cis*+*trans*)	H	2	88.13	56.8	3.370	3.350	3.442	0.092
3g	OCH_3		OCH_3	3	209.3	75.4	2.710	2.760	2.711	–0.049

* The parameter *s* indicates the number of substituents on the phenolic group.

4 DISCUSSIONS AND CONCLUSIONS

Tables 1, 2, and 3 have presented experimental and calculated R_{M0} values for phenols **1a–g**, 2–aryloxy–(α–acetyl)–phenoxathiin derivatives **2a–g**, and 4–aryloxy–7–nitrobenzofurazan derivatives **3a–e**, **3g**. The accompanying Figures 2, 3, and 4, as well as the high R^2 values indicate a satisfactory correlation between the experimental and calculated values.

The biparametric model for the hydrophobicity R_{M0}, Eq. (3), depends on the quantum–chemical descriptor *HACA*, defined as the sum of solvent accessible surface area of hydrogen bonding acceptor atoms in the molecule. The triparametric model (Eq. 4) also depends on a quantum–chemical descriptor, namely *PPSA3*. In both cases, such parameters describe interactions between the molecular surfaces and the surrounding solvent molecules. One should note that several books

and monographs on QSAR and QSPR have been published recently [45–49].

The correlation between the two hydrophobicity parameters (experimental R_{M0} and calculated logP) according to Eqs. (5)–(7) has better statistical results than Eq. (4). However, one should take into account that that Eq. (5) contains two indicator variables and more than three "hidden" descriptors, although it is a three–parameter equation.

One can therefore argue that hydrophobicity for the two classes of compounds examined in the present paper can be modeled satisfactorily using appropriate molecular descriptors.

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Biographies

Adrian Beteringhe is a graduate student at the "C. D. Nenitzescu'' Institute of Organic Chemistry of the Romanian Academy (supervisor Dr. P. Filip). Research areas: QSPR/QSAR studies of biologically active compounds.

Ana Cristina Radutiu is a graduate student at the Department of Organic Chemistry, Faculty of Chemistry, University Bucharest (supervisor Prof. I. Baciu). Research areas: aromatic compounds with specific physico–chemical properties.

Marioara Bem is a graduate student at the Department of Organic Chemistry, Faculty of Industrial Chemistry, Polytechnic University Bucharest (supervisor Prof. F. Badea). Research areas: syntheses of fluorogenic and fluorescent organic compounds.

Titus Constantinescu, Ph. D. in organic chemistry, is a principal research fellow at the "I. G. Murgulescu" Institute of Physical Chemistry of the Romanian Academy. Major research areas: supramolecular chemistry, molecular modeling, and syntheses of organic compounds with specific physico–chemical properties.

Alexandru T. **Balaban**, titular member of the Romanian Academy, is now a tenured Professor of Organic Chemistry at the Texas A&M University at Galveston, USA. Research areas: aromatic heterocyclic compounds, gene transfer agents, stable free radicals, carbon nanostructures, topological indices for QSAR/QSPR, chemical applications of graph theory.