Dedicated to Prof. P.T. Frangopol on the occasion of his 75th anniversary

Quantitative Structure-Property Relationship (QSPR) Study of the Hydrophobicity of Phenols and 2-(Aryloxy-α-acetyl)-phenoxathiin Derivatives

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In a preceding study, the molecular hydrophobicity (R_{M0}) was determined experimentally from reverse-phase thin-layer chromatography data for several substituted phenols and 2-(aryloxy-α-acetyl)-phenoxathiin derivatives, obtained from the corresponding phenoxides and 2-(α-bromoacetyl)-phenoxathiin. QSPR correlations for R_{M0} were explored using four calculated molecular descriptors: the water solubility parameter (log S_w), log P, the Gibbs energy of formation (ΔG_f), and the aromaticity index (HOMA). Triparametric correlations do not improve substantially the biparametric correlation of R_{M0} in terms of log S_w and HOMA.

Keywords: Molecular hydrophobicity, phenoxathiin, HOMA, QSPR, Gibbs energy

Phenoxathiin derivatives have numerous biomedical applications such as specific inhibition of monoaminoxidase MAO A (E.C. 1.4.3.4) [1-3], antimicrobial activity [4], antibacterial and bactericidal properties [5]. 2-Aroylbenzofuran-phenoxathiin derivatives, like 2-aroylbenzofurans [6], have potential spasmolytic properties. The fluorescence of phenoxathiins [7-9], and the stability of free radicals obtained from phenoxathiins by oxidation in acid medium [10, 11], have been intensely studied.

In previous papers the synthesis of several classes of new phenoxathiin derivatives was reported [12]. By means of reverse-phase thin-layer chromatography (RP-TLC) the molecular hydrophobicity values (R_{M0}) could be determined experimentally. Using molecular descriptors calculated with the help of Katritzky and Karelson's CODESSA program [13], QSPR studies were reported for several phenols (**1A**–**1F**) and 2-(aryloxy-α-acetyl)-phenoxathiin derivatives (**2A**–**2F**) obtained from the corresponding phenoxides and 2-(α-bromoacetyl)-phenoxathiin [14]. In the present paper we describe correlations using simpler molecular descriptors and we extended the list of phenols to include also formyl-derivatives (**1G**–**1N**). Several corresponding phenoxathiin derivatives (**2G**–**2J**) and 2-benzofuran 2-phenoxathiin ketones (**3**–**5**) are also included. All structutes are presented in figure 1.

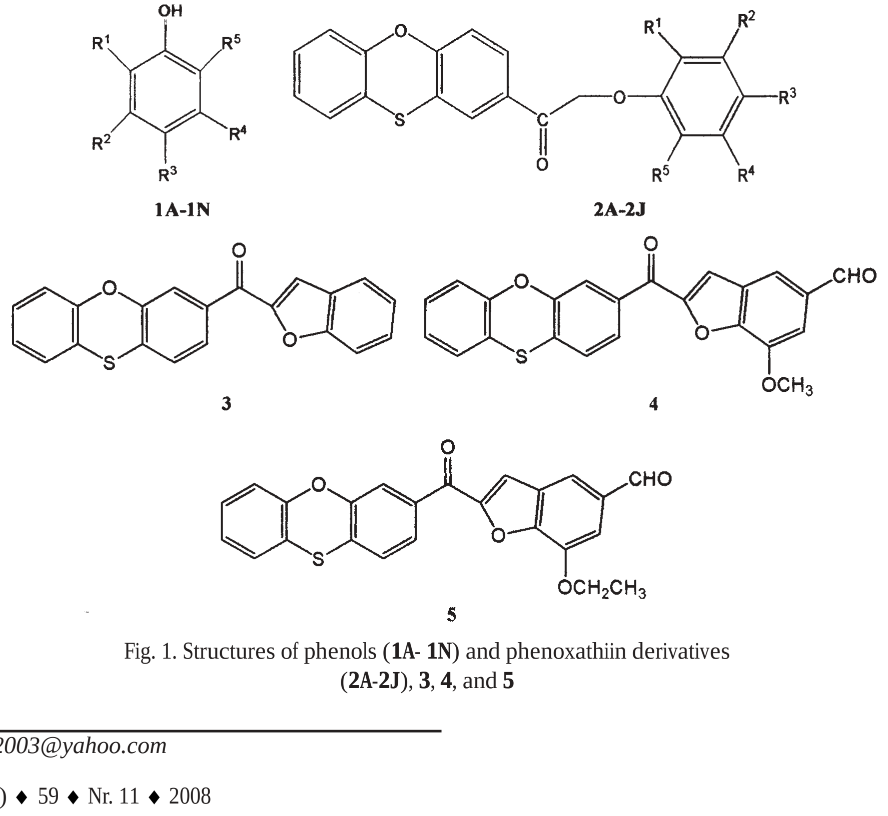
1A-1N
2A-2J
3
4
5

Fig. 1. Structures of phenols (**1A**- **1N**) and phenoxathiin derivatives (**2A-2J**), **3**, **4**, and **5**

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Molecular hydrophobicity

Experimental data (R_f values) from reverse-phase thin-layer chromatography of compounds **1A** – **1N**, **2A** – **2J**, **3** – **5** were converted into molecular hydrophobicity values (R_{M0}) molecular hydrophobicity values by means of equations (1) and (2).

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

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

where R_{M0} is the R_M value extrapolated to zero concentration of organic component in the alcohol-water 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.

Octanol – water partition coefficient and logP

Interactions between water and organic solutes are determined by several constitutional factors of the solute molecules such as the presence of hydrogen-bond donor or acceptor groups, of large nonpolar hydrocarbon residues, of ionizable groups, etc. By studying the partition coefficient (P_{ow}) of many solutes between n-octanol and water, Corwin Hansch introduced log*P* as a universally accepted measure of hydrophobicity or lipophilicity [15]. It can be measured experimentally (e. g. by RP-TLC) [16], or it can be calculated by various methods [17].

Water solubility is a key factor in biological activities of organic non-electrolyte substances, determining availability, distribution, degradation, and accumulation in living cells [18, 19]. Three main factors are involved in determining water solubility [20-26]: (i) entropy of mixing; (ii) differences between interactions of molecules in liquid phase: (water + solute cohesive forces) minus [(water + water cohesive forces) plus (solute + solute cohesive forces)]; (iii) for solid compounds one must also consider solute-solute interaction energies in the ºC). As a result, Yalkowski's equation (3) defines a water solubility parameter S_w by its logarithm [26]:

$$\log S_w = -\log P_{ow} + 0.01(25 - \mathrm{MP}) + 0.5 \qquad (3)$$

This water solubility parameter can be determined experimentally, or estimated by group- or atom-contribution methods [27].

Melting points for compounds that have not been synthesized can be approximated by theoretical calculations, which however give imprecise results [28-30].

Gibbs energy of formation

According to the well-known equation (4), the standard molar Gibbs energy of formation ΔG_f^{298} (abbreviated as ΔG_f) is an additive property that can be obtained from thermodynamic tabulated data using various procedures [31 - 35] or by means of 2D structural parameters and QSPR method [36].

$$\Delta G_f^{298} = \Delta H_f^{298} - T\,\Delta S_f^{298} \qquad (4)$$

The most frequently utilized approach is the group contribution method [31].

Aromaticity parameters

Aromaticity remains a discussion topic [37-39] as proved by a recent controversy between Katritzky and Schleyer on its multidimensionality (resolved by a joint paper) [40]. For benzenoids, properly formulated Clar structures encompass much information [41]. The partitioning of π-electrons between condensed rings of alternant or non-alternant conjugated hydrocarbons provides a rationalization of chemical behavior [42]. The richness of properties exhibited by aromatic heterocyclic compounds is a cornerstone in explaining their essential role in carrying genetic information in living cells and in medicinal chemistry [43].

For converting local or global aromaticity into numbers that can then be used in correlations, many procedures have been advocated. Here we will mention only Bird's, (I_6 index) [44], Schleyer's (NICS indices based on calculated NMR chemical shifts due to ring currents) [45, 46], and Julg's indices [47], which were adopted by many chemists. Julg et al. defined aromaticity indices on the basis of bond lengths on the periphery of aromatic molecules, which (according to the Hellmann-Feynman theorem) [48] reflects the π-electron density, hence the π-electron delocalization. For eliminating some deficiencies of the Julg index, it was defined aromaticity by means of the harmonic oscillator model (HOMA) [49-53]. In this approach, the first term in brackets of equation (5) reflects the energy and the last term the geometric contribution:

$$\mathrm{HOMA} = 1 - \Sigma_i[\alpha\,(R_{opt} - R_{av})^2 + (\alpha / n)\Sigma(R_{av} - R_i)^2] \qquad (5)$$

In equation (5) α is a normalization constant, *n* is the number of bonds involved in the summation, R_{opt}, R_{av}, and R_i are bond lengths for optimal, average, and running (current) bond in the summation. Calculation of HOMA values was effected by using Todeschini's DRAGON program [54].

Results and discussion

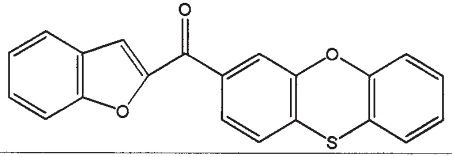
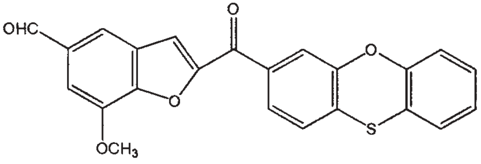
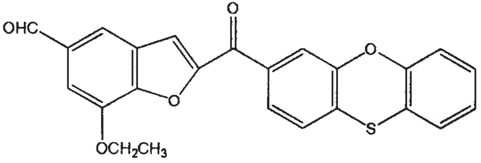
The molecular hydrophobicity data (R_{M0}) for compounds **1** – **5** , calculated from previously measured RP-TLC data [12, 14, 16] according to equation (1) and (2), are presented in table 1. In the same table one may see values of the solubility parameter S_w, Gibbs energy of formation ΔG_f, log*P*, and HOMA aromaticity index. For calculating S_w and ΔG_f values we used the trial version of the program MMP (Molecular Modeling Pro) [55]. Correlations were computed using the Minitab program.

The intercorrelation matrix is presented in figure 2. From it one can see that intercorrelations are fairly high between $\log S_w$ and log*P* (as expected), or between $\log S_w$ and ΔG_f (which is less evident). However, as shown by Randiæ, one can obtain significant results even when one has such fairly high intercorrelations (provided that parameters are not collinear) [56].

Results of monoparametric correlations with R_{M0} show that, as expected, the molecular hydrophobicity presents a better regression in terms of $\log S_w$ ($R^2 = 0.925$) than in terms of log*P* ($R^2 = 0.845$) or ΔG_f ($R^2 = 0.868$). The correlation coefficient for the regression in terms of HOMA is quite low ($R^2 = 0.135$).

However, as seen from figure 3, among biparametric regressions with one of the terms being $\log S_w$, the correlation with HOMA gives somewhat better results. As there is little substantial improvement in statistical data on adding a third parameter, one can consider that the biparametric equation (10) from figure 3 provides a satisfactory model for the molecular hydrophobicity of the phenols and phenoxathiin derivatives described in the present paper. In table 1 one can see the calculated R_{M0} values according to that equation and the residuals, and figure 4 presents a plot of observed values *versus* calculated values according to equation (10).

Table 1
DATA FOR THE PHENOLS AND PHENOXATHIIN DERIVATIVES

No.	R^1	R^2	R^3	R^4	R^5	HOMA	logS_w	ΔG_f	log$P$	R_{M0} (exp.)	R_{M0} (calc.) Eq. (10)	Resid.
1A	H	H	H	H	H	0.474	-0.675	-32.94	1.51	1.948	1.638	0.310
1B	OMe	H	H	H	H	0.503	-0.399	-139.2	1.34	1.821	1.305	0.516
1C	OMe	H	H	H	OMe	0.519	-0.123	-245.4	1.16	1.623	1.032	0.591
1D	OMe	H	CH_2-CH=CH_2	H	H	0.492	-1.562	-35.68	2.73	1.653	2.200	-0.547
1E	OMe	H	CH=CH-CH_3	H	H	0.544	-1.562	-43.30	2.65	2.255	1.962	0.293
1F	H	H	$(CH_2)_2$-CO-CH_3	H	H	0.486	-0.362	-137.8	1.48	0.981	1.356	-0.375
1G	OMe	H	CHO	H	H	0.549	0.248	-233.9	1.05	0.108	0.625	-0.517
1H	OEt	H	CHO	H	H	0.544	-0.281	-231.5	1.55	0.715	1.032	-0.317
1I	OMe	H	CHO	H	OMe	0.539	0.248	-239.9	0.88	0.083	0.671	-0.588
1J	OMe	H	H	CHO	H	0.571	0.524	-346.1	1.05	0.108	0.324	-0.216
1K	CHO	H	H	H	H	0.533	-0.027	-133.7	2.01	0.823	0.898	-0.075
1L	OMe	H	CHO	H	CHO	0.581	0.895	-340.6	1.55	0.318	0.009	0.309
1M	OEt	H	CHO	H	CHO	0.581	0.366	-332.2	2.04	0.682	0.394	0.288
1N	OH	H	CHO	H	CHO	0.575	1.286	-389.0	1.24	-0.251	-0.246	-0.005
2A	H	H	H	H	H	0.511	-3.291	226.2	5.50	3.137	3.368	-0.231
2B	OMe	H	H	H	H	0.520	-2.820	120.0	5.07	2.871	2.985	-0.114
2C	OMe	H	H	H	OMe	0.525	-2.349	13.82	4.93	2.779	2.620	0.159
2D	OMe	H	CH_2-CH=CH_2	H	H	0.525	-3.983	223.5	6.46	3.895	3.807	0.088
2E	OMe	H	CH=CH-CH_3	H	H	0.530	-3.983	215.9	6.38	4.174	3.784	0.390
2F	H	H	$(CH_2)_2$-CO-CH_3	H	H	0.514	-2.978	121.4	5.48	3.397	3.127	0.270
2G	OMe	H	CHO	H	H	0.529	-2.173	19.30	4.79	2.694	2.474	0.220
2H	OEt	H	CHO	H	H	0.529	-2.702	27.72	5.28	2.881	2.858	0.023
2I	OMe	H	CHO	H	OMe	0.527	-2.173	19.30	4.65	2.516	2.483	0.033
2J	OMe	H	H	CHO	H	0.534	-1.702	-86.91	4.79	2.301	2.109	0.192
3						0.538	-4.104	332.7	6.03	3.265	3.835	-0.570
4						0.554	-3.181	125.8	5.83	3.182	3.092	0.090
5						0.550	-3.710	134.2	6.32	3.327	3.494	-0.167

	logP	HOMA	logS_w	ΔG_f	R_{M0}
logP	1.000	-0.103	-0.956	0.891	0.845
HOMA	-0.103	1.000	0.292	-0.417	0.135
logS_w	-0.956	0.292	1.000	-0.970	0.925
ΔG_f	0.891	-0.417	-0.970	1.000	0.868
R_{M0}	0.845	0.135	0.925	0.868	1.000

Fig. 2. Intercorrelation matrix between all variables for phenols and phenoxathiins

Monoparametric correlations

R_{M0} vs. logS_w:

$$R_{M0} = -0.748(\pm 0.042)\log S_w + 0.849 \qquad (6)$$

$N = 27$ $R^2 = 0.925$ SD = 0.364 F = 308.5 R^2 cross-validated = 0.876

R_{M0} vs. ΔG_f:

$$R_{M0} = 0.006(\pm 4.722\cdot 10^{-4})\,\Delta G_f + 2.285 \qquad (7)$$

$N = 27$ $R^2 = 0.868$ SD = 0.482 F = 164.9 R^2 cross-validated = 0.804

R_{M0} vs. log$P$:

$$R_{M0} = 0.576(\pm 0.049)\log P - 0.027 \qquad (8)$$

$N = 27$ $R^2 = 0.845$ SD = 0.522 F = 137.1 R^2 cross-validated = 0.795

R_{M0} vs. HOMA:

$$R_{M0} = -17.79(\pm 9.023)\mathrm{HOMA} + 11.44 \qquad (9)$$

$N = 27$ $R^2 = 0.135$ SD = 1.237 F = 3.888 R^2 cross-validated = 0.095

Biparametric correlations

R_{M0} vs. logS_w and HOMA:

$$R_{M0} = -4.565(\pm 2.676)\text{HOMA} - 0.726(\pm 0.042)\log S_w + 3.312 \qquad (10)$$

$N = 27$ $R^2 = 0.933$ SD = 0.351 F = 167.4 R^2cross-validated = 0.865

R_{M0} vs. logS_w and ΔG_f:

$$R_{M0} = -0.758(\pm 0.179)\log S_w - 9.224\cdot 10^{-5}(\pm 1.001\cdot 10^{-5})\,\Delta G_f + 0.827 \qquad (11)$$

$N = 27$ $R^2 = 0.925$ SD = 0.370 F =148.1 R^2 cross-validated = 0.862

R_{M0} vs. logS_w and log$P$:

$$R_{M0} = -0.743(\pm 0.147)\log S_w + 0.118(\pm 0.039)\log P + 0.843 \qquad (12)$$

$N = 27$ $R^2 = 0.918$ SD = 0.371 F =148.1 R^2 cross-validated = 0.872

R_{M0} vs. HOMA and log$P$:

$$R_{M0} = 0.558(\pm 0.036)\log P - 13.31(\pm 2.808)\text{HOMA} + 7.126 \qquad (13)$$

$N = 27$ $R^2 = 0.913$ SD = 0.382 F =138.7 R^2 cross-validated = 0.856

R_{M0} vs. ΔG_f and log$P$:

$$R_{M0} = 0.003(\pm 8.930\cdot 10^{-4})\,\Delta G_f + 0.271(\pm 0.086)\log P + 1.212 \qquad (14)$$

$N = 27$ $R^2 = 0.899$ SD = 0.413 F =117.1 R^2 cross-validated = 0.854

R_{M0} vs. HOMA and ΔG_f:

$$R_{M0} = 1.285(\pm 0.915)\text{HOMA} + 0.006(\pm 5.292\cdot 10^{-4})\,\Delta G_f + 1.604 \qquad (15)$$

$N = 27$ $R^2 = 0.869$ SD = 0.479 F = 79.55 R^2cross-validated = 0.808

Triparametric correlations

R_{M0} vs. HOMA, logS_W and log$P$:

$$R_{M0} = -7.552(\pm 3.347)\text{HOMA} - 0.474(\pm 0.181)\log S_w + 0.201(\pm 0.140)\log P + 4.584 \qquad (16)$$

$N = 27$ $R^2 = 0.938$ SD = 0.343 F =117.2 R^2 cross-validated = 0.930

R_{M0} vs. HOMA, logS_w, and ΔG_f:

$$R_{M0} = -6.964(\pm 3.224)\text{HOMA} - 0.970(\pm 0.192)\log S_w - 0.002(\pm 0.001)\,\Delta G_f + 4.111 \qquad (17)$$

$N = 27$ $R^2 = 0.937$ SD = 0.345 F =115.4 R^2 cross-validated = 0.930

Eq. 3. R_{M0} vs. logS_w, ΔG_f, and log$P$:

$$R_{M0} = -0.758(\pm 0.322)\log S_w - 8.942\cdot 10^{-5}(\pm 1.795\cdot 10^{-5})\Delta G_f + 4.439\cdot 10^{-4}(\pm 1.396\cdot 10^{-4})\log P + 0.825 \qquad (18)$$

$N = 27$ $R^2 = 0.925$ SD = 0.374 F =94.62 R^2 cross-validated = 0.874

Fig. 3. Mono-, bi-, and triparametric correlations of the molecular hydrophobicity

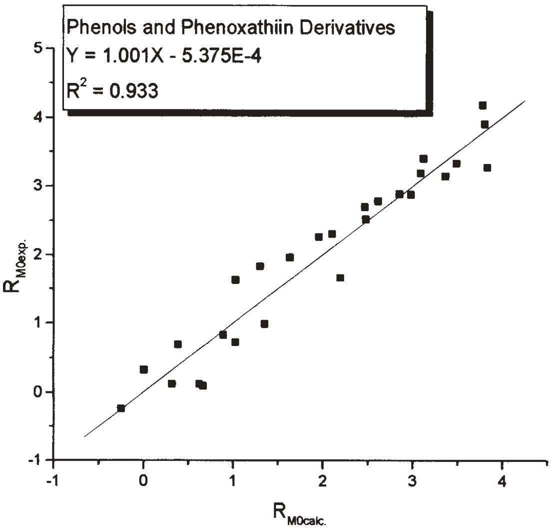


Fig. 4. Plot of experimental vs. computed molecular hydrophobocity according to equation (10)

Conclusions

Experimentally measured hydrophobicities (R_{M0}) of several newly synthesized phenoxathiin derivatives and of phenols with congeneric structures have been correlated with simple calculated parameters: the water solubility parameter (logS_w), log$P$, the Gibbs energy of formation (ΔG_f), and the aromaticity index (HOMA). For the biparametric equation (10) in terms of log S_w and HOMA, a correlation factor $R^2 = 0.933$ was obtained, and adding one or two of the other parameters did not improve substantially the correlation.

References

1. HARFENIST, M., McGEE, P. C. D., REEVES, M., WHITE, H. L., J. Med. Chem. **41**, 1998, p. 2118

2. WHITE, H. L., SCATES, P. W., Drug Dev. Res., **25**, 1992, p. 191

3. HARFENIST, M., JOYNER, C. T., MIZE, P. D., WHITE, L. A., J. Med. Chem., **37**, 1994, p. 2085

4. MAIOR, O., GAVRILIU, D., STOIA, S., South. Braz. J. Chem., **3**, 1995, p. 79

5. EVERITT, E., SULLIVAN, M., J. Wash. Acad. Sci., **30**, 1940, p.457

6. BUU-HOÏ, N., SAINT-RUF, G., LOC, T. B., XUONG, N. D., J. Chem. Soc., 1957, p. 2593

7. MISCHIE, A., MAIOR, O., BADEA, F., VASILESCU, M., CALDARARU, H.,CARAGHEORGHEOPOL, A., SOCOTEANU, R., PENCU, G., CONSTANTINESCU, T., Rev. Roum. Chim., **46**, nr. 2, 2001, p. 107

8. CONSTANTINESCU, T., MISCHIE. A., MAIOR, O., BADEA, F., VASILESCU, M., CAPROIU, M. T., SOCOTEANU, R., NOURESCU, D., Rev. Roum. Chim., **45**, 2000, p. 1009

9. IONESCU, S., GAVRILIU, D., MAIOR, O., HILLEBRAND, M., J. Photochem. Photobiol. A: Chemistry, **124**, 1999, p. 67
10. STOLZE, K., MASON, R. P., Chem. Biol. Interactions**, 77**, 1991, p. 283
11. SHINE, J., SMALL, R. J., J. Org. Chem., **30**, 1965, p. 2140
12. BETERINGHE, A., RADUTIU, A. C., BEM, M., CONSTANTINESCU, T., BALABAN, A. T., Internet Electron. J. Mol. Des., **5**, 2006, p. 237
13. KATRITZKY, A. R., PERUMAL, S., PETRUKHIN, R., KLEINPETER, E., J. Chem. Inf. Comput. Sci., **41**, 2001, p. 569
14. RADUTIU, A. C., BACIU, I., CAPROIU, M. T., DRAGHICI, C., NICOLAE, A., CONSTANTINESCU, T., BALABAN, A. T., Arkivoc, **xiii**, 2007, p. 8
15. HANSCH, C., MALONEY, P. P., FUJITA, T., MUIR, R. M., Nature, **194**, 1962, p. 178
16. RADUTIU, A. C., BACIU, I., CAPROIU, M. T., DRAGHICI, C., NICOLAE, A., CONSTANTINESCU, T., BALABAN, A. T., Rev. Roum. Chim., **51**, 2006, p. 653
17. LEO, A., HANSCH, C., ELKINS, D., Chem. Rev., **71**, 1971, p. 525
18. VAISHNAV, D. D., BOETHLING, R. S., BABEU, L., Chemosphere, **16**, 1987, p. 695
19. ZAROOGIAN, G. E., HELTSHE, J. F., JOHNSON, M., Environ. Toxicol. Chem., **4**, 1985, p. 3
20. YALKOWSKY, S. H., VALVANI, S. C., J. Pharm. Sci., **69**, 1980, p. 912
21. YALKOWSKY, S. H., J. Pharm. Sci., **70**, 1981, p. 971
22. RAN, Y., YALKOWSKI, S. H., J. Chem. Inf. Comput. Sci., **41**, 2001, p. 354
23. PETERSON, D. L., YALKOWSKI, S. H., J. Chem. Inf. Comput. Sci., **41**, 2001, p. 1531
24. RAN, Y., HE, Y., YANG, G., JOHNSON, J. L. H., YALKOWSKI, S. H., Chemosphere, **48**, 2002, p. 487
25. YANG, G., RAN, Y., YALKOWSKI, S. H., J. Pharm. Sci., **91**, 2002, p. 517
26. SANGHVI, T., JAIN, N., YANG, G., YALKOWSKI, S. H., QSAR Comb. Sci., **22**, 2003, p. 258
27. KLOPMAN, G., WANG, S., BALTHASAR, D. M., J. Chem. Inf. Model., **32**, 1992, p. 474
28. DEARDEN, J. C., Environ. Toxicol. Chem., **22**, 2003, p. 1696
29. KATRITZKY, A. R., LOBANOV, V. S., KARELSON, M., Chem. Soc. Rev., **24**, 1995, p. 279
30. KATRITZKY, A. R., JAIN, R., LOMAKA, A., PETRUKHIN, R., MARAN, U., KARELSON, M., Crystal Growth & Design, **1**, 2001, p. 261
31. JOBACK, K. G., REID, R. C., Chem. Eng. Comm., **57**, 1987, p. 233
32. KLINCEWICZ, K. M., REID, R. C., AIChE J., 30, **1984**, p. 137
33. LYMAN, W. J., REEHL, W. F., ROSENBLATT, D. H., Handbook of Chemical Property Estimation Methods, American Chemical Society, Washington, DC, 1990
34. HORVATH, A. L., Molecular Design, Elsevier, Amsterdam, 1992
35. MARRERO, J., GABI, R., Fluid Phase Equilibria, **183-184**, 2001, p. 183
36. YAN, A., J. Chem. Inf. Model., **46**, 2006, p. 2299
37. MINKIN, V. I., GLUKHOVTSEV, M. N., SIMKIN, B. Y., Aromaticity and Antiaromaticity. Electronic and Structural Aspects, Wiley-Interscience, New York, 1994
38. BALABAN, A. T., BANCIU, M., CIORBA, V., Annulenes, Benzo-, Hetero-, Homo-Derivatives and Their Valence Isomers, Vol. I–III, CRC Press, Boca Raton, Florida, 1986
39. BERGMANN, E. D., PULLMAN, B., Aromaticity, Pseudo-Aromaticity and Anti-Aromaticity, Israel Academy of Science and Humanities: Jerusalem, 1971
40. CYRANSKI, M. K., KRYGOWSKI, T. M., KATRITZKY, A. R., SCHLEYER, P. V. R., J. Org. Chem., **67**, 2002, p. 1333
41. CLAR, E., The Aromatic Sextet, Wiley, London, 1972
42. BALABAN, A. T., RANDIC, M., J. Math. Chem., **37**, 2005, p. 443; New J. Chem., **28**, 2004, p. 800; J. Chem. Inf. Comput. Sci., **44**, 2004, p. 50, 1701
43. BALABAN, A. T., ONICIU, D. C., KATRITZKY, A. R., Chem. Rev., **104**, 2004, p. 2777
44. BIRD, C. W., Tetrahedron, **41**, 1985, p. 1409
45. SCHLEYER, P. V. R., MAERKER, C., DRANSFELD, H., JIAO, H., HOMMES, N. J. R. V. E., J. Am. Chem. Soc., 118, **1996**, p. 6317
46. SCHLEYER, P. V. R., MONOHARAR, M., WANG, Z., KIRAN, B., JIAO, H., PUCHTA, R., HOMMESS, N. J. R. V. E., Org. Lett., **3**, 2001, p. 2465
47. JULG, A., FRANCOIS, Ph., Theor. Chim. Acta, **7**, 1967, p. 249
48. FEYNMAN, R. P., Phys. Rev., **56**, 1939, p. 340
49. KRUSZEWSKI, J., KRYGOWSKI, T. M., Tetrahedron Lett., **36**, 1972, p. 3839
50. KRYGOWSKI, T. M., CYRANSKI, M. K., Tetrahedron, **52**, 1996, p. 1713
51. KRYGOWSKI, T. M., CYRANSKI, M. K., CZARNOCKI, Z., HÄFELINGER, G., KATRITZKY, A. R., Tetrahedron, **56**, 2000, p. 1783
52. KRYGOWSKI, T. M., STEPIEN, B. T., CYRANSKI, M. K., Int. J. Mol. Sci., **6**, 2005, p. 45
53. KRYGOWSKI, T. M., CIESIELSKI, A., BIRD, C. W., KOTSCH, A., J. Chem. Inf. Comput. Sci., **35**, 1995, p. 203
54. Dragon Evaluation for Windows (Software for Molecular Descriptor Calculations), Version 5.4, 2006, Talete srl, http://www.talete.mi.it/
55. Molecular Modeling Pro, Version 6.1.0 trial, www.norgwyn.com
56. RANDIC, M., New J. Chem., 15, **1991**, p. 517; J. Chem. Inf. Comput. Sci., 31, **1991**, p. 311

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