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Computational and chromatographic study of hydrophobic properties of hydroxylated 3-phenyl-1-pyrazin-2-ylpropen-1-ones

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Abstract

Hydrophobicity can either be determined experimentally or predicted by means of commercially available programmes. In the studies concerning biological activities of pyrazine analogues of chalcones, 3-(2-hydroxyphenyl)-1-pyrazin-2-ylpropen-1-ones were more potent than the corresponding 3-(4-hydroxyphenyl)-1-pyrazin-2-ylpropen-1-ones. As the difference in lipohilicity may be a factor responsible for the difference in the potency, R_M values of the compounds were determined by RP-TLC and compared with log*P* values calculated by various commercially available programmes. Important discrepancies were found between experimental and computational lipophilicity data. Therefore, we have tried to find a reliable method for calculating R_M values from *in silico* derived molecular parameters. The R_M values obtained with the chromatographic system consisting of Silufol UV 254 plates impregnated with silicon oil as the stationary phase and acetone-citrate buffer (pH =

3) 50:50 (V/V) as the mobile phase correlated well with van der Waals volumes (V_W) and hydration energies (ΔG_{H_2O}) derived of molecular models calculated on RHF/AM1 level.

Key Words: hydroxylated 1-pyrazin-2-ylpropen-1-ones, lipophilicity, RP-TLC, molecular models

Introduction

The discovery and development of a new chemical entity (NCE), that can reach the market as an effective new drug, is a long, arduous and expensive process. According to current estimates, from 30000 compounds synthesized, 2000 enter preclinical development, 200 enter phase I clinical trial, 40 enter phase II clinical trials, 12 enter phase III clinical trials, 8 are approved and only 1 makes a satisfactory return on investment. The physiological effects generated by biologically active substances, including drugs, are a function of the amount of an active compound that actually reaches the „receptor“, which in a general picture can be an enzyme, an ion channel, a receptor protein, a nucleic acid or any other biological macromolecule, and a function of the strength of the interaction at this site or the relevance of the structural changes produced. Because all these are ultimately determined by intermolecular forces, the main determinants of a compound´s biological activity are its relevant structural features and its physicochemical properties [1].

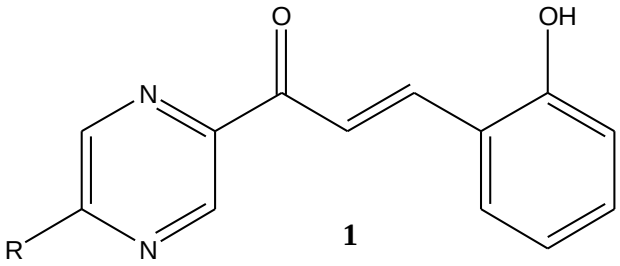
High-throughput screening (HTS) of large compound collections and combinatorial libraries have changed the drug discovery process and put more focus on an early generation of physicochemical, pharmacokinetic, metabolism and safety data (generally called ADMET or ADME/tox data). ADMET data can be estimated by a range of *in vivo* and *in vitro* methods Based on the experimental data, *in silico* models have been developed to predict the most critical properties from molecular structure [2–11].

The logarithm of the partition coefficient between n-octanol and water (log*P*) has often been used to represent molecular lipophilicity, which seems to be a key factor related to the transport process through cell membranes and many other biological events [12]. Experimental

determination of log*P* can be done only after the compounds have been synthesized. That is why several procedures for the estimation of log*P* on an empirical and theoretical basis have been developed during the last years [13–19].

Chalcones (1,3-diphenylprop-2-en-1-ones) are open analogues of flavonoids in which the two aromatic rings are joined by a three carbon, α,β-unsaturated carbonyl system. They have been studied as potential drugs since the 1940´s, and various biological activities, such as antibacterial, antifungal, antiviral, antiprotozoal, anthelmintic, antineoplastic, chemoprotective, gastroprotective, anti-oxidative, cardiovascular, anti-inflammatory and estrogenic, have been reported for them [19–25].

As a part of studies aimed at finding novel biologically active pyrazine derivatives a number of ring substituted 3-phenyl-1-pyrazin-2-ylprop-2-en-1-ones was prepared and tested for antifungal and antimycobacterial properties [26–28]. The influence of these compounds on photosynthetic processes [26–28] and their platelet-antiaggregatory effects [29] were studied as well. In all types of bioassays, 3-(2-hydroxyphenyl-1-pyrazin-2-ylprop-2-en-1-ones (**1a–1e**) were more potent than the corresponding 3-(4-hydroxyphenyl-1-pyrazin2-ylprop-2-en-1-ones (**2a–2e**). As the difference in lipophilicity could be responsible for the higher potency of 2-OH derivatives, log*P* values of the compounds were calculated by means of commercially available programmes. However, the results obtained with various programmes differed significantly. Therefore we tried to find a more reliable method for the evaluation of lipophilicity, and the results of these efforts are reported in the present paper.



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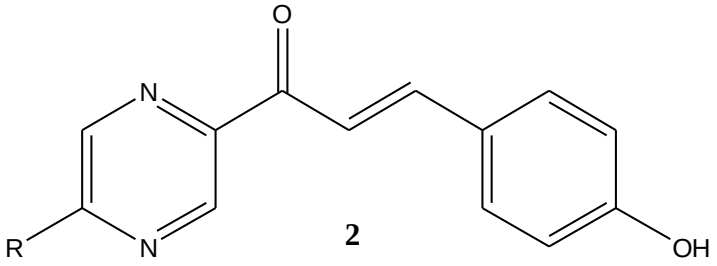

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a: R = H, b: R = *tert*-butyl, c: R = isobutyl, d: R = butyl, e: R = propyl

Results and Discussion

Commercially available programmes generating log*P* from the structure have been widely used recently [17–18]. However, the results are dependent on the size of the training set and the algorithm used for calculation and may not be reliable, especially in the case of *ortho*-substituted compounds where possible intramolecular interactions affecting lipophilicity must be taken in account [30–35]. In the present paper, *ACD/logP v. 1.0* and *v. 8.14* (Advanced Chemistry Development Inc., Toronto, Canada), *HyperChem v. 6.03* (HyperCube Inc., Gainesville, USA) and *ChemBioDraw Ultra v. 11.0* (CambridgeSoft Corporation, Cambridge, USA) were used to calculate log*P* values of hydroxylated 3-phenyl-1-pyrazin-2-ylpropen-1-ones. Table I shows that according to *ACD/logP v. 1.0* 2-OH derivatives (**1a–1e**) are less lipophilic then the corresponding 4-OH derivatives (**2a–2e**), whilst the version 8.14 indicated that 2-OH chalcones (**1a–1e**) are more lipophilic that their 4-OH counterparts (**2a–2e**). *HyperChem* and *ChemBioDraw Ultra* showed no differences in the lipophilicity of the two series. *ChemBioDraw Ultra* enables to calculate Clog*P*, i.e. the n-octanol/water partition coefficient based on established chemical interactions. However, based on this value no difference in lipophilicity of the two series was observed either.

We have therefore decided to verify the results experimentally by means of RP-TLC. Chromatographic systems were chosen on the basis of literature data [31, 36]. Citrate buffer (pH = 3) [37] was used to suppress dissociation of the phenolic groups. The results (hR_MA and hR_MB in Table I) clearly show that 2-OH derivatives (**1a–1e)** are more lipophilic than the corresponding 4-OH derivatives (**2a–2e**). Hence, some intramolecular interactions that are not reflected by commercially available programmes must occur in the molecules of the studied compounds, and the definite conclusions about their lipophilicity should be preferably done on experimental data.

Table I: Molecular parameters and lipophilicity of compounds **1a–1e** and **2a–2e**

Compound	logP ACD 1.0	logP ACD 8.14	logP HyperChem	logP ChemBio Draw	ClogP ChemBio Draw	hR_MA	hR_MB	ΔG_{H_2O} kcal/mol	V_W [Å^3]	V_{SA} [Å^3]	S_W [Å^2]	S_{SA} [Å^2]	$hR_MCalc.$
1a	1,61	2.105	2,56	0,94	1.30066	-86	**-33**	-10,9	205,08	688,1	242,99	435,45	**-32**
2a	2,36	1.551	2,56	0,94	1.30066	-79	**-37**	-12,84	204,98	690,25	243,03	440,67	**-39**
1b	3,30	3.793	4,12	3,07	3.12667	19	**12**	-7,41	271,76	880,24	320,52	535,53	**11**
2b	4,05	3.240	4,12	3,07	3.12667	-10	**9**	-9,35	271,77	883,57	320,86	539,24	**5**
1c	3,48	3.975	3,94	2,88	3.25666	-2	**9**	-7,6	272,23	888,69	321,35	545,39	**11**
2c	4,23	3.422	3,94	2,88	3.25666	-16	**2**	-9,53	272,52	892,00	322,59	545,98	**4**
1d	3,66	4.159	4,01	2,97	3.38667	7	**12**	-7,56	272,43	900,08	324,00	552,77	**11**
2d	4,41	3.605	4,01	2,97	3.38667	-10	**5**	-9,5	272,73	904,26	325,34	557,46	**5**
1e	3,13	3.628	3,61	2,55	2.85767	-31	**3**	-8	255,67	846,42	303,25	523,42	**2**
2e	3,88	3.074	3,61	2,55	2.85767	-52	**-9**	-9,94	255,86	849,46	304,85	530,05	**-5**

Although RP-TLC is relatively inexpensive, it still requires a great deal of highly accurate laboratory work. The expression of lipophilicity by properties of molecules that can be obtained from models calculated by quantum-chemical methods is another possibility. In the present study, experimental hR_M values were correlated with van der Waals volume (V_W), solvent accessible volume (V_{SA}), van der Waals surface (S_W), solvent accessible surface (S_{SA}) and hydration energy (ΔG_{H_2O}). The models of the studied compounds were formed on the semi-empirical level, which should be sufficiently accurate for this purpose, and the volumes or the surfaces of the molecules were calculated from the most stable conformation with the lowest energy. The best fit was found between hR_MB and van der Waals volume (V_W), especially in the combination with the hydration energy (ΔG_{H_2O}). The correlation coefficient for this combination of parameters is 0.99110. Slightly worse results were obtained when the solvent accessible volume V_{SA} (with the solvent probe radius 1.4 Å) or surfaces (S_W, S_{SA}) of the calculated molecules were used as independent variables.

Estimating lipophilicity of chalcones using the relationship expressed by the equation (1) thus represents a suitable and even better alternative to some common algorithms based on fragment addition methods.

Experimental

Synthesis of model compounds

Model 3-(2-hydroxyphenyl)-1-pyrazin-2-ylpropen-1-ones **1a-1e** and 3-(4-hydroxyphenyl)-1-pyrazin-2-ylpropen-1-ones **2a-2e** were prepared by the Claisen-Schmidt condensation of the corresponding acetylpyrazines with 2-hydroxybenzaldehyde and 4-hydroxybenzaldehyde, respectively [26].

Calculations of logP by means of commercially available programmes

ACD/logP v. 1.0 (Advanced Chemistry Development Inc., Toronto, Kanada), *HyperChem v. 6.03* (HyperCube Inc., Gainesville, USA) and *ChemBioDraw Ultra v. 11.0* (CambridgeSoft Corporation, Cambridge, USA) that automatically generate log*P* from the structure were used. Log*P* calculated with *ACD/logP v. 8.14* were found in Chemical Abstracts [38]. The results are given in Table I.

Evaluation of lipophilicity by RP-TLC

Two chromatographic systems were used to determine hR_M values ($hR_M = R_M \cdot 100$) :

A: *stationary phase* – Celufol plates (Kavalier, Votice) impregnated by development in 5% solution of octan-1-ol in diethyl ether; *mobile phase* – acetone + citrate buffer (pH = 3) 50:50 (V/V) saturated with octan-1-ol.

B: *stationary phase* – Silufol plates UV 254 (Kavalier, Votice) impregnated by immersion in 5% solution of silicone oil (Lukoil M 200, Lucebni zavody, Kolin) in diethyl ether; *mobile phase* – acetone + citrate buffer (pH = 3) 50:50 (V/V)

Studied compounds were dissolved in methanol (1 mg/ml) and 2 μl were applied on the plate with an interval 1.3 – 1.4 cm between circular spots using micropipette. The starting line was 1.5 cm from the lower edge of the plate. The plates were developed over a path of 12.0 cm in a normal chamber (16 cm × 16 cm × 7 cm) at room temperature, previously equilibrated for 2 h. After development the plates were dried in a gentle stream of air and the spots were visualized in λ = 254 nm UV light by means of a Camag UV lamp. An arithmetic average was calculated from three independent TLC measurements.

Generating hR_M values from quantum-chemical calculations

Quantum-chemical calculations were run on a PC computer using software *HyperChem v. 6.03* (HyperCube Inc., Gainesville, USA). The models of compounds were formed on RHF/AM1 level. The most stable conformations of unsubstituted compounds **1a** and **2a** were optimized by conformational analysis using random variation of dihedral angles. The other derivatives were designed on the basis of these models. Van der Waals volume (V_W) and surface (S_W) and solvent accessible volume (V_{SA}) and surface (S_{SA}) were calculated using the grid method described by

Bodor et al. [39] using the atomic radii of Gavezotti [40] and solvent probe radius 1.4 Å. Hydration energy (ΔG_{H_2O}) was calculated by the method published by Ooi and co-workers [41].

Correlation and regression analyses of the QSAR study were run on a PC computer using the Microsoft Excel program. Multiple regression analyses, which involve finding the best fit of dependent variable (experimental hR_M value) to a linear combination of independent variables (descriptors), were performed by the least squares method. In the equations, the figures in the parentheses are the standard errors of the regression coefficients, n is the number of compounds, r is the multiple correlation coefficient, r^2 is the determination coefficient, F is the significance test (F-test) and s is the standard error of estimate. F test values are for all equations statistically significant at the 1 % level of probability of error. The following relationships were derived:

$$hR_MB = 0.46884(\pm 0.05515)\ V_W + 3.43769(\pm 0.87764)\ \Delta G_{H_2O} - 90.6477(\pm 21.17342)$$

$$n = 10\ \ s = 2.73458\ \ r = 0.99110\ \ r^2 = 0.98228\ F = 194 \qquad (1)$$

$$hR_MB = 0.6413(\pm 0.05551)\ V_W - 166.553(\pm 14.25742)$$

$$n = 10\ \ s = 4.56998\ \ r = 0.97131\ \ r^2 = 0.94344\ F = 133 \qquad (2)$$

$$hR_MA = 0.85874(\pm 0.2769)\ V_W + 6.68074(\pm 4.40621)\ \Delta G_{H_2O} - 183.527(\pm 106.3017)$$

$$n = 10\ \ s = 13.7291\ \ r = 0.94042\ \ r^2 = 0.88439\ F = 27 \qquad (3)$$

$$hR_MB = 0.14812(\pm 0.02088)\ V_{SA} + 3.79807(\pm 1.00428)\ \Delta G_{H_2O} - 92.2793(\pm 25.57208)$$

$$n = 10\ \ s = 3.21577\ \ r = 0.98767\ \ r^2 = 0.97549\ F = 139 \qquad (4)$$

$hR_MB = 0.38713(\pm0.04912)\ S_W + 3.62912(\pm0.92478)\ \Delta G_{H_2O} - 86.3381(\pm22.29547)$

$n = 10\ \ s = 2.92825\ \ r = 0.98979\ \ r^2 = 0.97968\ F = 169$ (5)

$hR_MB = 0.53956(\pm0.05031)\ S_W - 166.121(\pm15.31503)$

$n = 10\ \ s = 4.89993\ \ r = 0.96694\ \ r^2 = 0.93497\ F = 115$ (6)

$hR_MB = 0.25494(\pm0.04474)\ S_{SA} + 4.35402(\pm1.15894)\ \Delta G_{H_2O} - 95.0886(\pm32.26099)$

$n = 10\ \ s = 3.87511\ \ r = 0.98205\ \ r^2 = 0.96442\ F = 95$ (7)

$hR_MB = 0.38319(\pm0.04698)\ S_{SA} - 202.187(\pm24.53688)$

$n = 10\ \ s = 6.29546\ \ r = 0.94481\ \ r^2 = 0.89267\ F = 67$ (8)

The equation with the highest correlation coefficient (1) was then used to generate hR_MCalc. For the results see Table I.

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