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RP-HPLC determination of lipophilicity in series of quinoline derivatives

Research Article

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Abstract: In the present paper we describe results on the synthesis and lipophilicity determination of a series of biologically active compounds based on their heterocyclic structure. For synthesis of styrylquinoline-based compounds we applied microwave irradiation and solid phase techniques. The correlation between RP-HPLC retention parameter log *k* (the logarithm of retention factor *k*) and log *P* data calculated in various ways is discussed, as well as, the relationships between the lipophilicity and the chemical structure of the studied compounds.

Keywords: *Lipophilicity • RP-HPLC • Microwave synthesis • Quinoline derivatives*

1. Introduction

The quinoline moiety is present in many classes of biologically active compounds. A number of them have been clinically used as antifungal, antibacterial and antiprotozoic drugs [1,2] as well as antituberculotic agents [3,4]. Some quinoline based compounds showed also antineoplastics, antiasthmatic and antiplatelet activity [5-10]. The acetylcholinesterase inhibitory activity of various quinoline derivatives has been tested for potential treatment of nervous diseases [11].

Styrylquinoline derivatives have gained great attention recently due to their activity as potential HIV integrase inhibitors [12-16]. Our previous study dealing with styrylquinoline derivatives showed that they could also possess also strong antifungal activity [17]. The compounds containing 8-hydroxyquinoline pharmacophore seem especially interesting.

According to the results reported recently some new 8-hydroxyquinoline derivatives possessed interesting antifungal and herbicidal activities [18,19].

Determination of the physico-chemical parameters of biologically active compounds has become more important with an age of rational thinking in drug design [20]. One of the major prerequisites for pharmacological screening and drug development is the prediction of absorption, *e.g.* the transport of a molecule through cellular membranes, *i.e.* bioavailability, fate in the biological system. Drugs cross biological barriers most frequently through passive transport, which strongly depends on their lipophilicity. Therefore hydrophobicity is one of the most important physical properties of biologically active compounds. This thermodynamic parameter describes the partitioning of a compound between an aqueous and an organic phase and can be characterized by the partition coefficient (log *P*) [21,22].

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With new computer methods for log *P* calculation, the possibility of high throughput screening of large combinatorial libraries is possible. However there is still a need for algorithms that are sensitive to various electronic effects and individual structural aspects.

Reversed-phase high performance liquid chromatography (RP-HPLC) methods have become popular and widely used for lipophilicity measurement [23-27]. The general procedure is the measurement of the directly accessible retention time under isocratic conditions with varying amounts of an organic modifier in the mobile phase. The lipophilicity index, log *k*, can be derived from the retention factor *k.*

Our investigation of the spectrum of biological activity of hydroxyquinoline derivatives showed that these compounds can be valuable antifungal and herbicidal agents [17-19]. Antifungal activity seems to be dependent on lipophilicity [17,19]. Some parameters influencing herbicidal activity are molecular size and position of the phenolic moiety in the quinoline nucleus. It is the interaction of the OH–N in the quinoline molecule and protonization the whole molecule that influences lipophilicity of compounds.

These facts inspired us to study the hydrophobic properties of quinoline derivatives prepared in our laboratory in great detail. The aim of this study was to determine the lipophilicity (log *k*) of a new series of biologically active quinoline derivatives. The general formulas of all evaluated quinoline derivatives are shown in Fig. 1. The results obtained are also discussed with lipophilicity (log *P*/Clog *P*) calculated using available computer programs.

2. Experimental Procedures

2.1 Lipophilicity HPLC determination (retention factor *k*/calculated log *k*)

The HPLC separation module Waters Alliance 2695 XE and Waters Photodiode Array Detector 2996 (Waters Corp., Milford, MA, U.S.A.) were used. The chromatographic column Symmetry® C_{18} 5 µm, 4.6×250 mm, Part No. WAT054275, (Waters Corp., Milford, MA, U.S.A.) was used. The HPLC separation process was monitored by Millennium32® Chromatography Manager Software, Waters 2004 (Waters Corp., Milford, MA, U.S.A.). The mixture of MeOH p.a. (55.0%) and H_2O-HPLC – Mili-Q Grade (45.0%) was used as a mobile phase for compounds **1-21** and **25-49**. The mixture of MeOH p.a. (50.0%) and H_2O-HPLC – Mili-Q Grade (50.0%) was used as a mobile phase for compounds **22-24**. H_2O-HPLC, pH = 7.02 (Mili-Q Grade) The total flow rate of the column was 0.9 mL min^{-1}, injection volume of 30 µL, column temperature 30°C and sample temperature 10°C. The detection wavelength was 210 nm. The KI methanolic solution was used for the hold-up time (t_0) determination. Retention times (t_R) were measured in minutes.

The capacity factors *k* were calculated using the Millennium32® Chromatography Manager Software according to the formula $k = (t_R - t_0)/t_0$, where t_R is the retention time of the solute, whereas t_D denotes the hold-up time obtained *via* an unretained analyte. The log *k* values of the individual compounds, calculated from the retention factor *k*, are shown in Tables 1-4.

2.2 Lipophilicity calculations

Log *P* was calculated using the programs CS ChemOffice Ultra ver. 9.0 (CambridgeSoft, Cambridge, MA, U.S.A.) and ACD/LogP ver. 1.0 (Advanced Chemistry Development Inc., Toronto, Canada). Clog *P* values were generated by means of CS ChemOffice Ultra ver. 9.0 (CambridgeSoft, Cambridge, MA, U.S.A.) software. The miLog *P* values were calculated using free tool available at Molinspiration Property Calculation Service website [28-32]. The results are shown in Tables 1-4.

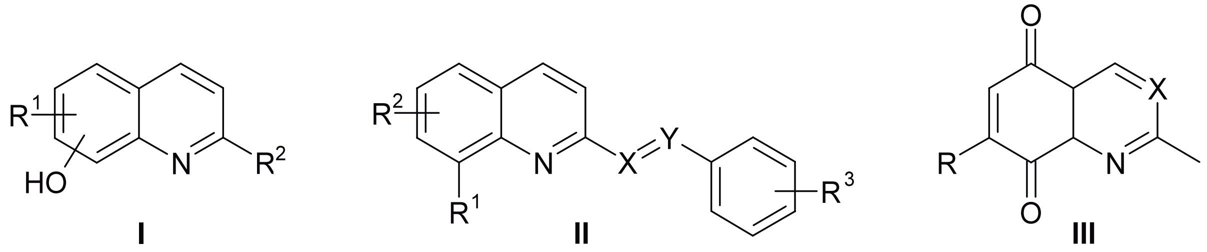
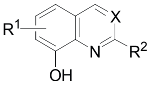


Figure 1. General formulas of all the quinoline/quinazoline derivatives

Table 1. Comparison of the calculated lipophilicities (log *P*/Clog *P*) with the determined log k of compounds **1-21**.



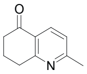
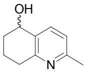
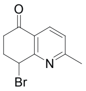
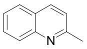
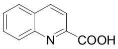
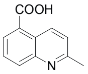
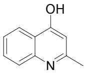
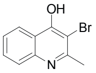
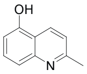
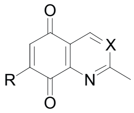
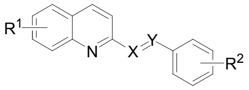
Comp.	R¹	R²	X	log k	log P/Clog P ChemOffice	log P ACD/LogP	miLog P
1				0.1580	1.64 / 1.523	1.88 ± 0.23	1.263
2				0.8233	1.91 / 1.079	1.02 ± 0.22	0.929
3				0.2443	2.03 / 2.076	2.04 ± 0.33	1.778
4				0.6649	2.82 / 2.528	2.54 ± 0.20	1.996
5				0.7125	2.10 / 2.603	2.17 ± 0.25	1.585
33				0.3629	2.38 / 2.579	2.22 ± 0.72	1.823
6				0.0029	0.62 / 0.781	1.18 ± 0.23	2.394
7				0.0996	0.93 / 1.722	2.34 ± 0.38	3.131
8				0.6061	2.43 / 2.577	1.91 ± 0.21	2.032
9	8-OH	CH_3	C	0.6838	2.43 / 2.577	2.33 ± 0.23	1.728
10	5-Br	CH_3	C	1.3142	3.26 / 3.562	3.54 ± 0.38	2.793
11	7-Br	CH_3	C	1.0759	3.26 / 3.282	3.38 ± 0.38	2.490
12	5,7-Br	CH_3	C	1.8054	4.09 / 4.188	4.55 ± 0.43	3.530
13	5-NO_2	H	C	0.5695	1.69 / 2.0836	2.00 ± 0.32	1.942
14	5,7-NO_2	H	C	0.7154	1.80 / 1.919	2.18 ± 0.34	1.776
15	5,7-NO_2	CH_3	C	0.7292	2.50 / 2.418	2.64 ± 0.35	1.829
16	5,7-NO_2	CH_3	N	0.5687	1.67 / 1.486	0.66 ± 1.27	1.829
17	5,7-NH_2	H	C	0.0522	0.12 / 1.344	-0.84 ± 0.34	0.824
18	5,7-NH_2	CH_3	C	0.2707	0.83 / 1.843	-0.38 ± 0.35	0.878
19	5-SO_3H-7-NO_2	H	C	0.1479	0.37 / -0.703	1.70 ± 0.88	-1.191
20	5-SO_3H-7-Br	H	C	0.3786	1.72 / -0.004	2.39 ± 0.91	-0.341
21	5-N=N-2,6-Cl-Ph	H	C	0.9633	5.28 / 5.570	4.72 ± 0.79	5.382

Table 2. Comparison of the calculated lipophilicities (log *P*/Clog *P*) with the determined log *k* of compounds **22-24**. (Different conditions MeOH/H_2O : 50/50).



Comp.	R	X	log k	log P/Clog P ChemOffice	log P ACD/LogP	miLog P
22	-$NHCOCH_3$	C	0.2227	-0.91 / 0.939	1.09 ± 0.75	-0.875
23	-$NHCOCH_3$	N	0.0167	-1.07 / -1.250	0.69 ± 0.75	-0.706
24	-OCH_3	C	0.0907	-0.10 / 1.224	1.60 ± 0.75	-0.037

Table 3. Comparison of the calculated lipophilicities (log *P*/Clog *P*) with the determined log *k* of compounds **25-32**.



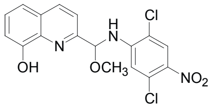
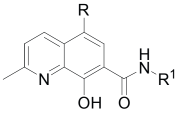
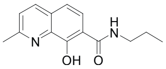
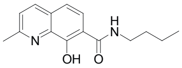
Comp.	R¹	R²	X	Y	log k	log P/Clog P ChemOffice	log P ACD/ LogP	miLog P
25	8-OH	3-Cl	CH	CH	1.5395	4.90 / 5.483	5.08 ± 0.32	4.778
26	8-OH	4-Cl	CH	CH	1.5558	4.90 / 5.483	5.08 ± 0.32	4.802
27	8-OH	4-Br	CH	CH	1.5802	5.17 / 5.633	5.26 ± 0.38	4.934
28	8-OH	4-OH	N	CH	0.8353	3.92 / 3.569	1.24 ± 1.05	3.071
29	8-OH	2-OH	CH	N	0.4308	3.63 / 2.432	1.09 ± 0.79	3.012
30	8-OH	3-OH	CH	N	0.8860	3.63 / 2.432	1.51 ± 0.79	2.776
31	8-OH	4-OH	CH	N	1.0911	3.63 / 2.432	1.32 ± 0.79	2.80
32					1.1766	4.08 / 4.661	4.44 ± 0.43	4.328
34	5-COOH	4-Cl	CH	CH	1.3976	4.85 / 5.485	4.97 ± 0.73	4.897
35	6-COOH	2-Cl	CH	CH	1.4787	4.85 / 5.485	5.02 ± 0.32	4.729
36	7-COOH	3-Cl	CH	CH	1.2858	4.85 / 5.485	4.97 ± 0.73	4.932
37	8-COOH	2-OCH$_3$	CH	CH	1.1922	4.16 / 4.691	3.62 ± 0.35	3.745
38	5,8-COOH	3-Br	CH	CH	1.2171	4.67 / 5.650	4.49 ± 0.80	4.528

Table 4. Comparison of the calculated lipophilicities (log *P*/Clog *P*) with the determined log k of compounds **39-49**.



Comp.	R	R¹	log k	log P/Clog P ChemOffice	log P ACD/ LogP	miLog P
39	H	-CH$_2$Ph	0.2812	3.31 / 4.840	3.75 ± 0.80	2.821
40	H	-CH$_2$Ph-4-F	0.3389	3.47 / 4.983	3.80 ± 0.85	2.984
41	H	-CH(CH$_3$)Ph-4-F	0.3720	3.78 / 5.2918	4.15 ± 0.85	3.544
42	-NO$_2$	-CH(CH$_3$)Ph-4-F	0.4283	3.42 / 5.2237	4.47 ± 0.85	3.733
43	H	-CH$_2$Ph-4-CH$_3$	0.3903	3.79 / 5.339	4.21 ± 0.80	3.269
44	H	-CH$_2$Ph-4-OCH$_3$	0.2843	3.18 / 4.759	3.67 ± 0.81	2.877
45	H	-CH$_2$CH$_2$Ph	0.2404	3.59 / 4.969	4.17 ± 0.80	3.226
46	H	-CH$_2$CH$_2$Ph-4-F	0.3342	3.74 / 5.112	4.22 ± 0.84	3.390
47	H	-CH$_2$CH$_2$CH$_2$CH$_2$Ph	0.5075	4.00 / 5.348	5.06 ± 0.79	4.015
48	H		0.1109	2.91 / 5.991	4.04 ± 1.13	2.532
49	H		0.1208	3.01 / 6.303	4.26 ± 1.12	2.802

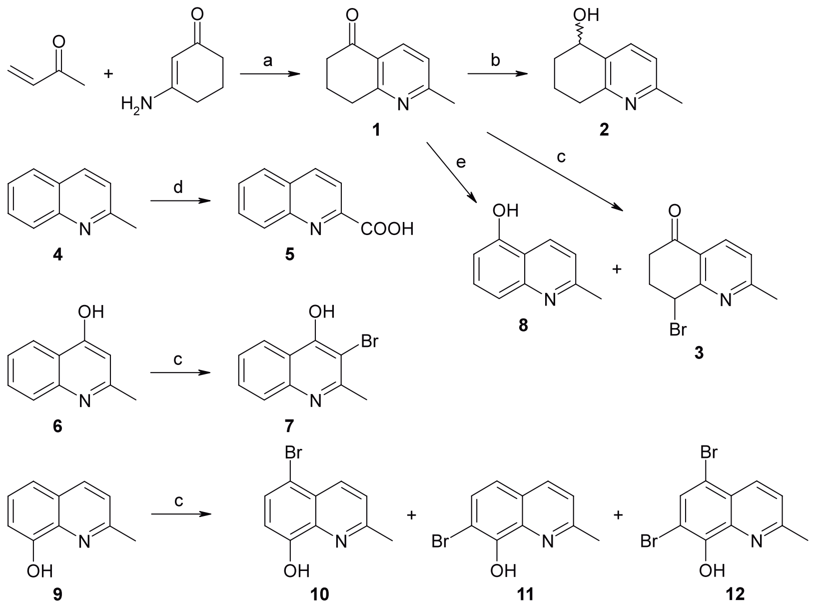
3. Results and Discussion

3.1 Chemistry

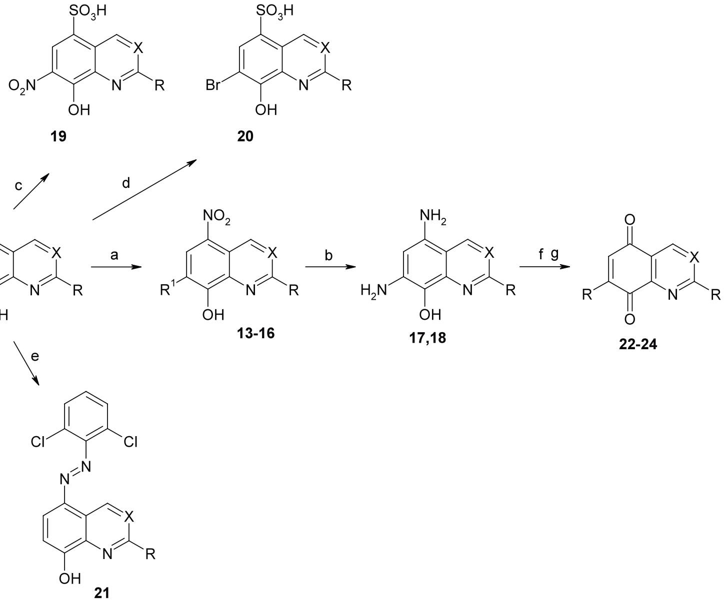
All of the synthesized compounds were derived from quinoline.

The chemistry and physico-chemical properties of quinoline have been described very well [33]. The synthesis of compounds **1-12** is shown in Scheme 1. New and/or more advantageous preparations of some compounds were described recently [18]. The main starting material **1** was obtained by means of condensation between but-3-en-2-one with 3-aminocyclohex-2-enone. Ketone **1** was reduced with Synhydride® to give racemic secondary alcohol **2**.

Radical oxidative bromination of ketone **1** using N-bromosuccinimide (NBS) yielded compounds **3** and **8**, nevertheless compound **8** was also obtained also by means of oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).



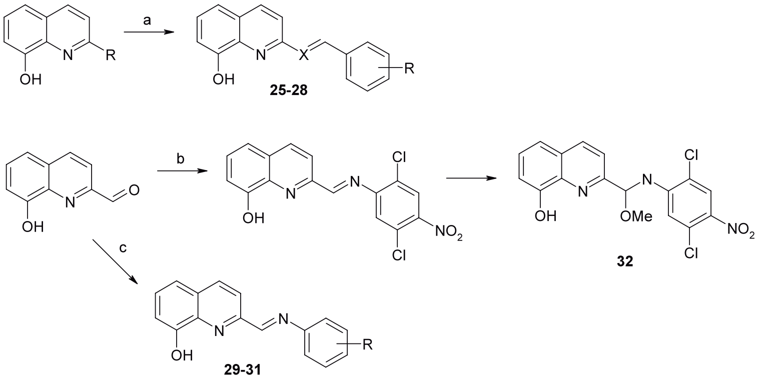
Scheme 1. Synthesis of compounds **1**-**12**: (a) DMF; (b) Synhydride, toluene; (c) NBS, dibenzoyl peroxide, CCl_4; (d) SeO_2, dioxan; (e) DDQ, dioxan.



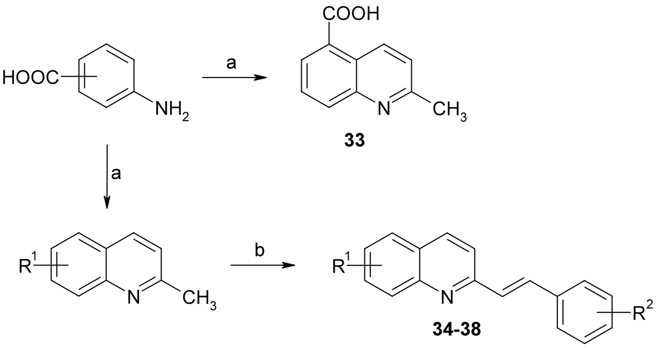
Scheme 2. Synthesis of compounds **13**-**24**: (a) HNO_3/H_2SO_4, 0°C; (b) H_2/Pd; (c) $AcOH/NHO_3$; (d) $Br_2/MeOH$; (e) 2,6-dichloroaniline/$NaNO_2/HCl$, 5°C; (f) AcOH; (g) $K_2Cr_2O_7$; (h) MeOH, heat.

Compounds **4**, **6** and **9** were further starting materials. Quinaldine (**4**) was oxidized using SeO_2 to acid **5**. Compounds **6** and **9** were oxidatively brominated using NBS and dibenzoyl peroxide to give compounds **7**, **10-12** [18].

8-Hydroxyquinoline, 8-hydroxyquinaldine and 8-hydroxyquinazoline were used as starting compounds in synthesis of drugs **13-24**, see Scheme 2. Nitration of these compounds yielded **13-16**. Subsequent hydrogenation yielded diamino derivatives **17**, **18**. These compounds in the next steps gave quinolinediones derivatives **22-24**. Methanolysis of **22** performed in hot MeOH generated compound **24**. Compounds **19**, **20** were obtained from 5-sulfo-8-hydroxyquinoline by gentle nitration or bromination respectively. The direct introduction of a diazonium salt derived from 2,6-dichloroaniline in 8-hydroxyquinaldine resulted in compound **21** [17,19]. A more comprehensive study on quinolinedione derivatives has been recently described [34,35].



Scheme 3. Synthesis of compounds **25**-**32**: (a) aldehydes, SiO_2, microwave irradiation (R=NH_2; 4-hydroxybenzaldehyde, benzene, reflux 2 h; (b) 2,5-dichloro-4-nitro-aniline, MeOH, piperidine; (c) aniline, benzene, reflux 2 h.



Scheme 4. Preparation of styrylquinoline derivatives **33**-**38**: (a) crotonaldehyde, HCl; (b) aldehyde, microwave irradiation.

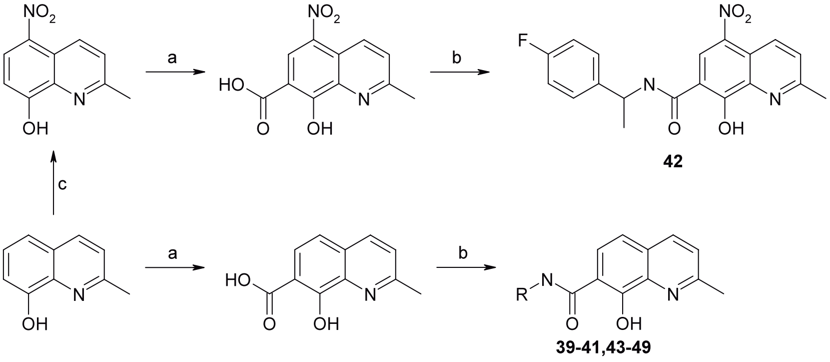
Compounds **25-27** were obtained from 8-hydroxyquinaldine and the appropriate aldehydes using microwave assisted methods [14]. Azaanalogues of styrylquinolines **29-31** were obtained by means of condensation of 8-hydroxyquinoline-2-carbaldehyde with the appropriate aniline in dry benzene. Compound **28** was obtained according to this procedure from 2-amino-8-hydroxyquinoline and 4-hydroxybenzaldehyde. 8-Hydroxyquinoline-2-carbaldehyde with 2,5-dichloro-4-nitroaniline in methanol generated a Schiff base, which was transformed to compound **32**, see Scheme 3 [17,19,36].

Microwave assisted organic synthesis was used to obtain the group of styrylquinoline-like compounds **34-38**, see Scheme 4, while necessary quinaldines were synthesized from aromatic amines according to the Scraup synthesis *e.g.* compound **33** [19,37].

Compounds **39-49** were synthesized according to the procedure showed below [38,39]. The Kolbe-Schmidt reaction was used to generate the carboxylic acids which further reacted with the appropriate amine in presence of ethyldimethylaminopropyl carbodiimide (EDCI) to afford an amide. In case of **48**, **49** diamine and twofold of quinaldic acid were used, see Scheme 5.

3.2 Lipophilicity

Chromatographic behaviour and hydrophobicity of quinoline derivatives have not been previously studied to a large extent. Only some QSAR or RP-TLC studies of variously substituted quinolines or substituted 4(1H)-quinolinones have been reported [40,41]. A number of chromatographic studies of diazine hydrophobicity were found. Some groups used a C_{18} chromatographic column with a methanol–water mobile phase to obtain log k_W, *i.e.* the retention factor extrapolated to 0% organic modifier, as an alternative to log *P* [42]. The log k_w is obtained by performing several measurements varying the ratio of water to organic solvent. Nevertheless, determination of log k_w has some disadvantages. Determination of log k_w is time consuming due to a number of measurements before the calculation of log k_w [43]. The conditions (non-buffered mobile phase) were chosen with respect to conditions of biological systems, which are performed mostly under neutral (pH ~ 7) or weakly acidic conditions. Molecules are transported through cellular membranes in organisms in similar environments. The lipophilicity data can be strongly influenced by intramolecular interactions under the applied chromatographic conditions [44-47].



Scheme 5. Synthesis of compounds **39**-**49**: (a) KOH, CO_2; (b) amine, EDCI; (c) HNO_3/H_2SO_4, 0°C.

Therefore, in this study, the measurements were performed using methanol to water (55:45) as the mobile phase. Log *k* derived from RP-HPLC retention factors and computational log *P* values are given in Tables 1-4.

Hydrophobicities (log *P*/Clog *P* values) of all the studied compounds were calculated using available programs and measured by means of RP-HPLC determined retention factors *k* (log *k*). The results are shown in Tables 1-4. All of the hydrophobicity data of the individual compounds are illustrated in Figs. 2-4 and they are ordered according to increasing experimental log *k* values.

Log *P* is the logarithm of the partition coefficient in a biphasic system (*e.g*. *n*-octanol/water), defined as the ratio of a compound concentration in both organic/inorganic phases. The log *P* is, according to definition determined for the uncharged species of the drug. Clog *P* values represent the logarithm of the n-octanol/water partition coefficient based on established chemical interactions. Log *k* is the logarithm of the retention factors (*e.g*. capacity factor *k*) in chromatographic approaches, which is related to the partitioning of a compound between a mobile and a (pseudo-) stationary phase. The procedure is most frequently performed under isocratic conditions with an organic modifier in the mobile phase using an end-capped non-polar C_{18} stationary RP column. Log *k* can be used as the lipophilicity index converted to log *P* scale [24]. An excellent review on the effect of the stationary and mobile phase has been published by van der Waterbeemd *et al*. [22] and, more recently, by Claessens *et al*. [25].

Lipophilicity computing software can usually calculate log *P* and Clog *P*. Log *P* is calculated for the uncharged molecules. Note that compounds presented in this work may exist preferably in the ionic or zwitterionic form(s). In these cases traditional methods of computing log *P* can provide errors and misleading values. The software calculates log *P* as lipophilicity contributions/increments of individual atoms, fragments and pair of interacting fragments in the chemical structure, *i.e*. increments of carbon and hetero atoms, aromatic systems and functional groups. Every software calculates lipophilicity contributions according to different internal databases/libraries. Therefore values of computed lipophilicities are dependent on the used software, and the values for individual compounds may be different. This fact as well as various ionic/zwitterionic forms and intramolecular interactions may cause differences between computed and experimentally determined lipophilicities. It should be noted that for compounds discussed in this paper with values of log *P* obtained using different software, the log *P* values correlate to each other with r^2=0.6. With this in mind, it is very difficult to perform any SAR predictions on the basis of such data.

The results obtained for the compounds **1**-**49** show that the experimentally determined lipophilicities (log *k* values) are lower than those indicated by the calculated log *P*/Clog *P*, see Tables 1-4 and Schemes 2-4. The program ChemOffice has not resolved various lipophilicity values of individual positional isomers, *e.g*. compounds **10**, **11** or **29**-**31**, respectively. The program calculating the miLog *P* values did not resolve hydrophobicities of individual isosters, see compounds **15** and **16**.

All compounds showed differences between experimental and calculated lipophilicity values which are probably caused by interactions of the substituents with heteroatoms in the individual compounds. The lipophilicity of all the discussed 8-hydroxyquinoline derivatives may be modified by an intramolecular hydrogen bond between the quinoline nitrogen and the phenolic moiety. The lipophilicity of further hydroxyquinoline derivatives may be modified by the keto-enol tautomerism, see Schemes 3, 4 [48].

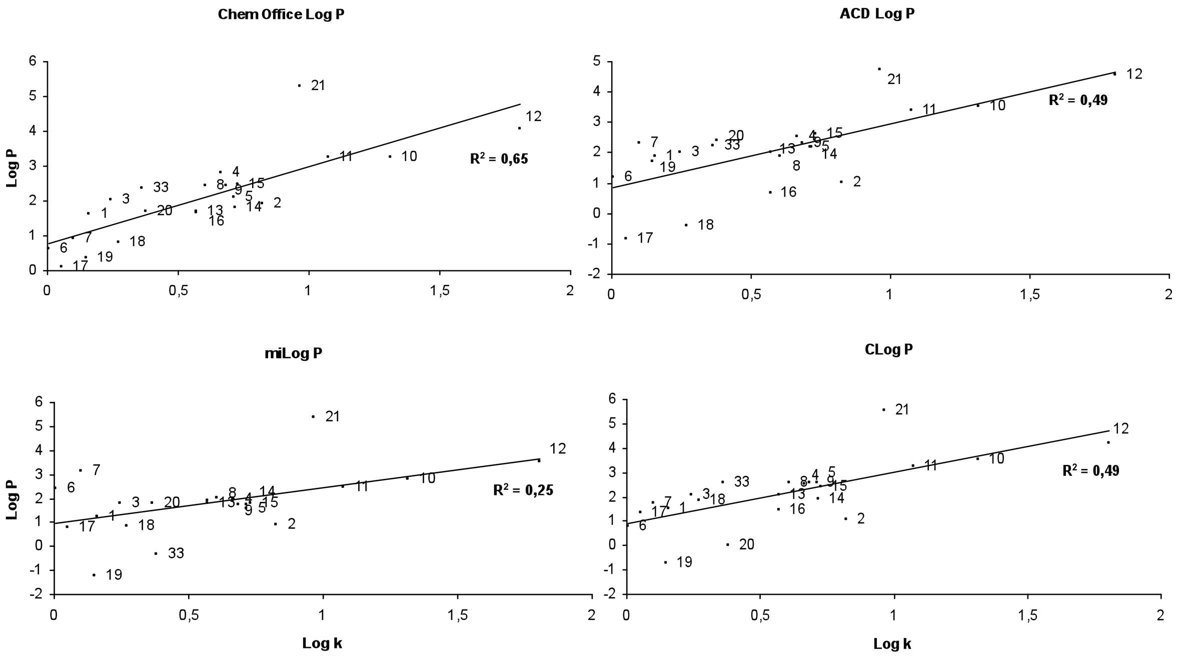


Figure 2. Comparison of the calculated log *P*/Clog *P* data using the three programs with the experimentally found log k values of compounds **1**-**21.** The compounds are ordered according to increasing experimental log *k* values.

Low hydrophobicity of quinolinediones derivatives **22**-**24** (Table 2) forced us to use different lipophilicity measurement conditions (MeOH/H_2O : 50/50). When conditions of MeOH to H_2O : 55/45 were used, the compounds were eluted from the column within hold-up time. The lowest lipophilicity was expected for these compounds of all the quinoline derivatives. This fact is probably caused by the presence of the diketone moiety as well as the second nitrogen atom in the quinoline ring.

The results of the compounds **1**-**21** (Fig. 2) show that the experimentally determined log *k* values correlate best with the lipophilicity data (log *P*) computed using ChemOffice software (r^2=0.65). In This set of compounds **21** is an anomaly and correlation without this structure can be improved (r^2=0.77 for ChemOffice). Other programs did not give reasonable data for this compound (correlation below 0.5) and miLog *P* provided the worst result (r^2=0.2).

As expected, compound **12** possessed the highest hydrophobicity, while unexpectedly compound **6** showed the lowest lipophilicity. This compound exists as 2-methyl-1H-quinolin-4-one, see Scheme 4. This fact corresponds with the following results, keto derivative **1** possesses lower lipophilicity than hydroxy derivative **2**. As expected, bromo derivatives **3** and **7** showed higher hydrophobicity than the unsubstituted compounds **1** and **6**. A large difference between all the experimental and calculated lipophilicity parameters could be observed for the compounds **2** and **8**. Hydroxy derivative **2** shows higher lipophilicity according to log *k* than 2-methylquinolin-5-ol (**8**) but according to the calculated data compound **8** seems to be much more hydrophobic.

According to all the calculated and experimental data a carboxylic acid moiety in position $C_{(5)}$, compound **33**, decreases the lipophilicity much more than carboxylic acid moiety in position $C_{(2)}$, compound **5**. Quinaldine (**4**) is less hydrophobic than quinaldine acid (**5**) according to experimental log *k*, contrary to all the calculated data.

The quinaldine phenolic derivatives **6** and **8** showed lower lipophilicity than quinaldine (**4**), only 8-hydroxyquinaldine (**9**) possessed higher hydrophobicity. Unsubstituted 8-hydroxyquinaldine (**9**) showed a log *k* value in the middle of the series of the compounds **9-21**. Compound **17** showed the lowest lipophilicity within this series.

Compounds substituted by bromine atoms or azoderivatives showed the highest lipophilicity in the series of the discussed compounds. Diamino substituted compounds **17** and **18** possess lower lipophilicity than dinitro substituted compounds **14** and **15**, as expected. Quinoline derivatives **14** and **16** show lower hydrophobicity than quinaldine derivatives **15** and **18**. Subsequent substitution by the second nitrogen atom

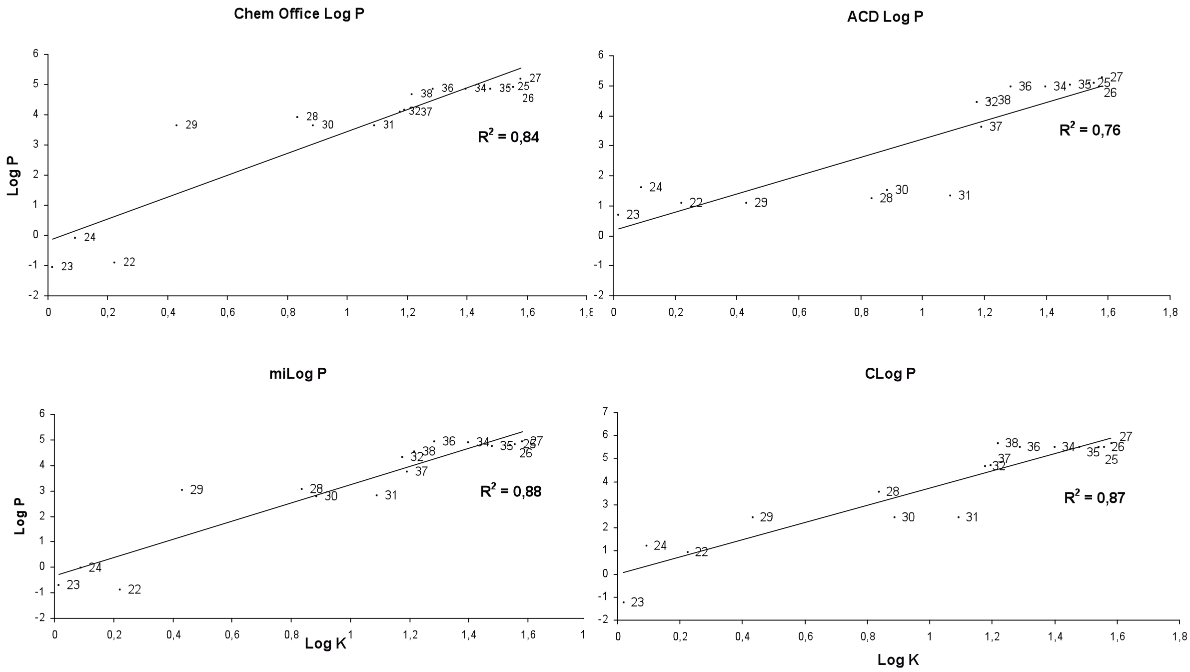


Figure 3. Comparison of the calculated log *P*/Clog *P* data using the three programs with the experimentally found log k values of compounds **25-38.** The compounds are ordered according to increasing experimental log *k* values.

in the position $C_{(3)}$ causes a decrease in lipophilicity, see compounds **15** and **16**. The sulfonic moiety in compounds **19** and **20** causes significant decrease in hydrophobicity, as expected.

7-Bromo-2-methylquinolin-8-ol (**11**) shows lower lipophilicity than 5-bromo-2-methylquinolin-8-ol (**10**). This fact may be probably caused by an interaction of the $C_{(7)}$-bromine substitution with $C_{(8)}$-phenolic moiety.

The electronic effects from the bromine atom in the $C_{(7)}$ position compared to the electronic effects of bromine in the $C_{(5)}$ position differ in their influence on the vicinal phenolic oxygen [45-46] and influence the resultant lipophilicity of compound **11**. These differences cannot be explained more precisely on the basis of the results presented here. Similarly the differences observed for compounds **6**, **8** and **9** seem to be the effect of hydrogen bonding (**8** *vs.* **9**) or tautomeric forms (**6** *vs.* **8**, **9**).

A large difference between the experimental and calculated lipophilicity parameters could be observed for compound **21**. Azoderivative **21** according to all the calculated data seems to be the most hydrophobic within this series which is in contrary with log *k.* This can be only explained by a strong tendency to form a less hydrophobic 5,8-diene- tautomeric structure, as we reported recently [17].

The results of compounds **25-38** (Scheme 2) show that the experimentally determined log *k* values correlate best with milog *P* values calculated according to the molinspiration service. ACD/LogP provided the poorest results for this set of compounds. Structure **29** is an anomaly and correlation without this compound gives and R^2 = 0.95 for miLogP and an R^2 = 0.92 for ChemOffice.

The experimental lipophilicity parameters specify lipophilicity within individual series of compounds **25-27** (3-Cl, 4-Cl, 4-Br), as well as **29-31** (2-OH, 3-OH, 4-OH). Compounds **29-31** possess much less lipophilicity than other styrylquinoline derivatives. This fact is caused by the presence of the nitrogen atom in the olefinic linker. 2-[(2-Hydroxyphenylimino)methyl]quinolin-8-ol (**29**) is much less lipophilic than indicated by the calculated lipophilicity. This fact is probably caused by the interaction of the imine nitrogen with the phenolic moiety in the styryl part of the molecule. Log *k* of **29** equals half of the values of compound **28** or **30** while their calculated log *P* are approximately the same. From this point it can be assumed, that the difference between calculated and measured lipophilicity is caused by two intramolecular hydrogen bonding centres in **29**.

As expected, carboxylic acids of the styrylquinoline derivatives showed lower lipophilicity than

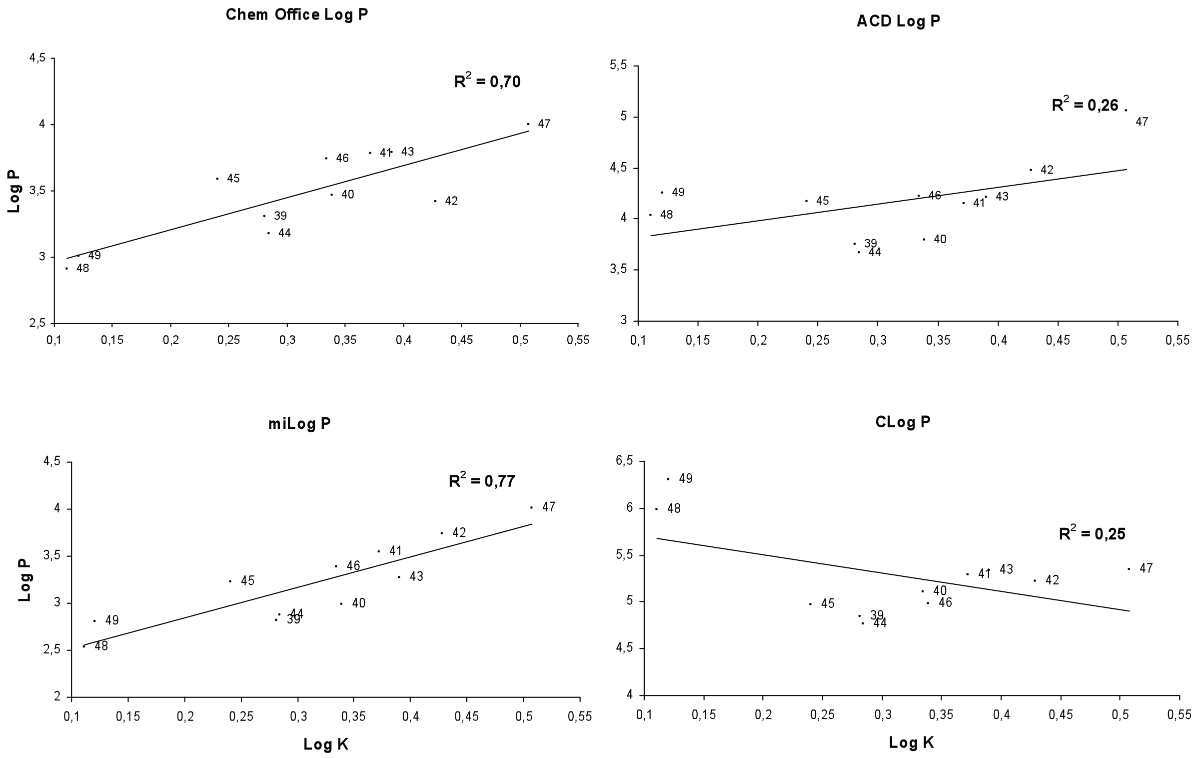


Figure 4. Comparison of the calculated log *P*/Clog *P* data using the three programs with the experimentally found log k values of compounds **39**-**49.** The compounds are ordered according to increasing experimental log *k* values.

styrylquinolines **25**-**27**. Compounds **37** and **38** showed the lowest hydrophobicity than other carboxylic acid derivatives due to substitution by a methoxy moiety in the phenyl ring (compound **36**) or the presence of two carboxylic acid groups in quinoline (compound **38**).

The structure-lipophilicity relationships of compound **32** cannot be discussed in connection with other compounds due to large differences in its substituents.

The results of compounds **39**-**49** (Fig. 4) show that the experimentally determined log *k* values correlate approximately with the computed miLog *P* (R^2=0.77) data and log *P* values using ChemOffice software (R^2=0.7). Clog *P* values calculated by ChemOffice software and ACD/LogP program do not agree with the target compounds **39**-**49** (r^2 <<0.5). It is notewothy that in the results from ACD and ClogP, compounds **48** and **49** can be regarded as anomalies. Especially the Clog *P* values for those structures which are much higher than the measured lipophilicity.

The lipophilicity (log *k* data) of the substituents in the amide part of the molecules increases from benzyl (**45**) < phenyl (**39**) < n-propylphenyl (**47**), as expected. Lower lipophilicity of the benzyl substituent than the phenyl substituent was also described in [49]. Compound **47** possessed the highest hydrophobicity within this series.

Lipophilicity (log *k* data) of phenyl substituents increases H < OCH_3 < F < CH_3. Great differences between the experimental and calculated lipophilicity parameters could be observed for compounds **45** and **44**. Compound **45** (benzyl derivative) showed low lipophilicity, but according to the calculated data it seems to be much more hydrophobic. The compound **44** (4-methoxyphenyl derivative) possesses higher lipophilicity than derived from the calculated data.

Low lipophilicity of both dimers 48 and 49 is interesting. Both dimers showed the lowest hydrophobicity (log *k* data) contrary to the calculated data. However it is noteworthy here that for compounds **39**-**47** differences between measured and calculated lipophilicities are roughly the same. This suggests that one major effect plays a crucial role for all compounds in this group. This is likely due to hydrogen bonding between $C_{(8)}$-OH and the carbonyl C=O and consequently keto-enol tautomerism as should be expected [50-52]. For compounds **48** and **49**, where two such groups exist, the discussed differences are nearly twofold (**39** and **45** *vs.* **48** and **49**).

4. Conclusions

Forty-nine quinoline based compounds possessing significant antifungal and herbicidal activities as well as interesting HIV-integrase inhibiting activity were prepared. Hydrophobicity (log *k*) of all the target compounds was determined by means of RP-HPLC methods for lipophilicity measurement. All the compounds can be divided into four groups according to their structure. Lipophilicity of hydroxyquinoline derivatives may be modified by keto-enol tautomerism. The keto-form of the hydroxyquinolines resulted in a decrease of lipophilicity compared with enol-form. The lipophilicity of all the discussed 8-hydroxyquinoline derivatives is modified by an intramolecular hydrogen bond between the quinoline nitrogen and the phenolic moiety. As was shown, log *k* correlates relatively poorly with calculated lipophilicity of compounds within each series. Nevertheless, it can be assumed that the calculated values of log *P* correlate best within congeneric series of structurally similar compounds. For styrylquinolines correlation of log *k* and calculated lipophilicity reach reasonable levels (r^2 above 0.9). The more diverse the set of compounds, the worse the correlation. This can be seen in the first series. Intramolecular effects such as hydrogen bonding and tautomeric forms can also affect lipophilicity. Popular computer programs that provide tool for calculating log *P* cannot recognize specific strutural features and generate poor results. In quinoline based hydroxylated compounds these effects play a crucial role. The lipophilicity data we have obtained confirm strong influence of intramolecular interactions. All the discussed compounds show relatively low lipophilicity. General structures of small 8-hydroxyquinoline derivatives and styrylquinolines substituted by bromine atoms possess the highest hydrophobicity, compared with the compounds substituted by sulfonic or amino moieties. N-substituted carbamoyl groups show low lipophilicity as well. An introduction of the second nitrogen atom to the position $C_{(3)}$ of the quinoline ring (quinazoline isoster) or the presence of the nitrogen atom in the olefinic linker of styrylquinolines or the quinone moeity itself, causes a decrease in lipophilicity. Experimentally determined log *k* data determine lipophilicity within the series of compounds.

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