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Determination of solubilities in water and 1-octanol of nitrogen-bridgehead heterocyclic compounds.

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Abstract

The solubilities in water and 1-octanol of 22 nitrogen-bridgehead quinazolone derivatives were investigated. The data were determined with a conventional method, with the typical confidence intervals at 95% probability level about $\pm 5\%$ and the precision good enough to evaluate the influence of structural modifications and to compare data with the lipophilicity of molecules. Solubilities in water spanned five orders of magnitude depending on the substituents attached to the ring-system. The solubility in octanol was generally somewhat higher and the range was only three magnitudes. Aqueous solubilities were more sensitive to structural changes than those in octanol. Solubility ratios were computed and fitted to the predictive relationship with two independent variables proposed by Yalkowsky. The equation with solubility ratios gave better results than the one calculated with experimental $\log P$ (partition coefficient) values. That corresponds to the known difference of solubility ratios ($\log SR$) and $\log P$ values, caused mainly by the mutual solubility of two phases in $\log P$ measurements. The solubility ratio and the partition coefficient have the same trend but the values differ significantly. Thus the partition coefficient and the solubility ratio are not recommended for estimation of aqueous solubility ($\log S_w$) data of these compounds. © 1997 Elsevier Science B.V.

Keywords: Aqueous solubility; Solubility in octanol; Solubility ratio; Estimation of $\log P$; Estimation of aqueous solubility; Estimation of lipophilicity through solubility data; Nitrogen-bridgehead compounds

1. Introduction

The solubility of a compound is an important parameter as it has several practical aspects in pharmacy and chemistry, therefore data for many materials are given in handbooks (Weast and Astle, 1980) and pharmacopoeias (USP 23, 1995; Ph. Hg. VII, 1986). Moreover, the aqueous solubility governs the bioavailability of an agent through the influence of absorption, distribution and elimination in the body (Said et al., 1996; Kamlet et al., 1987; Yalkowsky and Valvani, 1980). Octanol solubility, or the ratio of octanol/water solubilities (besides the partition coefficient,

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log P) can characterize transport through membranes and the topical activity of drugs (Yalkowsky and Banerjee, 1992). As is well-known, in most of the cases the equilibrium solubility of a certain compound in various solvents depends primarily on the chemical structure. The theory and determination of solubility in connection with pharmaceutical and therapeutic importance are well summarized elsewhere (Hildebrand and Scott, 1962; Valvani and Yalkowsky, 1980; Dogonadze et al., 1988; Yalkowsky and Banerjee, 1992).

Several authors have made attempts to calculate the solubility from available log P values and other parameters related to structure. A good review is given in the introductory part of a paper by Etzweiler et al. (1995) (references 1–18) besides the description of a new technique for determination of solubility. A theoretically based and experimentally established work has been carried out by Yalkowsky and Valvani (1980). They derived an equation for the calculation of aqueous solubility (log S_w) with 1-octanol/water partition coefficient (log P) and melting point (mp) data:

$$\log S_w = c_1 \times \log P + c_2 \times (\mathrm{mp} - 25) + c_3. \qquad (1)$$

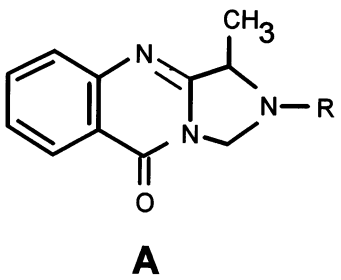
The theoretical parameters are: $c_1 = -1$, $c_2 = -0.01$, $c_3 = 0.8$. The verification of their theory is reviewed (Yalkowsky et al., 1988). Yalkowsky's own and other literature data relevant to the solubility of structurally different compounds prove the theory, only few compounds deviating from the theoretically derived equation. Heat capacity assumptions (Steven et al., 1989; Mishra and Yalkowsky, 1992) and deviation from the ideal activity coefficient (Yalkowsky and Valvani, 1980; Valvani et al., 1981; Yalkowsky and Pinal, 1993) has influence on the estimation of both log S_w and log P values. Those are considered as main factors of bias in parameters of Eq. (1). Several other effects may have influence on this calculation, for example, mutual solubility of two solvents, alteration of solvent composition with increasing amount of substance dissolved, difference of solubility ratios and log P values (Dearden and Bresnen, 1988; Said et al., 1996). Another well-known approach is the calculation of solubility and log P data with solvatochromic parameters. The latter method has a sound theoretical and experimental background too. A good example of its utility for the estimation of solubility and partition data in biological media shows the benefit of it for application in pharmacy and pharmacology (Kamlet et al., 1987).

The aim of our work was to elaborate a standardized process for exact equilibrium solubility measurements in two solvents. The usefulness of the method was demonstrated by the determination of precise solubilities for new heterocyclic compounds. These data and the trends of solubilities were used to compare the lipophilicity of molecules by analyzing structural changes of derivatives. The ratio of solubilities and partition coefficients are two different, distinct categories, that only in some cases correlate well with each other. In one set of compounds the solubility ratios were compared with partition coefficients to show the difference of these two descriptors. We have paid special attention to the fact that the extent of differences in solubilities can be explained qualitatively by differences in lipophilicities. The structural modifications have simultaneous effects on several physical properties that impact solubilities but the influences of others are not investigated here.

2. Materials and methods

2.1. Materials

The reagents, other compounds and agents met the requirement of Hungarian Pharmacopoeia (Ph. Hg. VII, 1986). The organic solvent 1-octanol (HPLC grade) was purchased from Aldrich. The distilled water was prepared from deionized water by distilling it twice. Careful handling and storage of solvents was ensured to avoid any contamination or decomposition.The compounds determined: substituted 10H-imidazo(2,1-*b*)-quinazoline-10-ones (imidazoquinazolones) and substituted 11H-pyrido(2,1-*b*)-quinazoline-11-ones (pyridoquinazolones) were synthesized (Kökösi et al., 1993), and the purity was investigated by chromatographic methods (Shalaby et al., 1985a,b,c) at our institute. The ring-systems of



A

Fig. 1. The ring-system of imidazoquinazolones (**A**).

the investigated ten variously substituted imidazoquinazolones (**A**) are in Fig. 1, and the substituents are listed in Tables 1 and 2. The two types of nucleus (**B** and **C**) of the 12 pyridoquinazolones are shown in Fig. 2, and the substituents are listed in Tables 1 and 4. The complete list of substituents for all the three ring-systems and their abbreviations used as legends in Figs. 3 and 4 are summarized in Table 1.

2.2. Method

The theoretical considerations were extracted from the work of Dearden and Bresnen (1988), and the practical procedure was a conventional one performed with special care. The mixing was done with 1–2 fold solute excess in a standard silicone-rubber stoppered 5 ml glass ampoule. To 5.0 ml of solvent a required amount of substance was weighed, the ampoule was stoppered well and placed in a double walled container thermostated to 25.0 ± 0.1°C (MLW U15C). The solution was stirred with a Teflon coated iron rod by rotating it with a magnetic stirrer (Heidolph MR1000). Samples were taken out at predetermined intervals (2, 4, 8, 12, 24, 48 h). The required complete separation of solid and solution was done by means of centrifugation ($2000 \times g$) at a controlled temperature for 10 min or by sedimentation. The solution was then allowed to stay undisturbed in the thermostated equipment for a day. The concentrations were determined by ultraviolet (UV) spectroscopy (Hewlett-Packard 8452-A). To draw the sample rapidly, carefully and accurately from the solution phase of the system is the most important step at this measurement. A 5–200 μl Hamilton syringe was inserted in the supernatant clean solution in a manner to avoid disturbance of sedimented solid phase. Three samples were taken at a time out of an equilibrated solution and those were immediately diluted in a previously prepared flask with solvent. The establishment of an equilibrium was checked with repeated sampling until the concentration had not changed significantly ($p < 0.05$) after a new stirring period for 2 h. Each time a complete separation was achieved, samples were taken out of the clean supernatant solution. The standard, routine work was done with 48 h stirring and one day sedimentation before sampling, followed by three or four checks of saturation. Typically four or five consecutive measurements of a single solution and three parallels for a compound were made.

The UV absorption spectra of the compounds were registered and a maximum high wavelength was chosen for determination, typically around 260–300 nm. The molar absorptions were calculated previously in separate experiments from two parallels with six-membered dilution series, made with very small amounts of compound, where the weighing and dilution were made with special care. The compounds substituted with alkyl groups have molar absorptions of about 3500; they are about 5000 for aromatic homologs.

Table 1
The substituents and their abbreviations attached to ring-systems **A**, **B** and **C**

R-		Serial number at ring-system		
Name	Abbreviation	**A**	**B**	**C**
Methyl-	Me	1	11	19
Ethyl-	Et	2	12	20
Hydroxyethyl-	HOEt	3	—	—
n-Propyl-	Pr	4	13	21
n-Butyl	Bu	5	—	—
Phenylmethyl-	PhMe	6	14	22
Phenylethyl-	PhEt	7	—	—
Phenyl-	Ph	8	15	—
p-Methylphenyl-	MePh	9	—	—
p-Methoxyphenyl-	MeOPh	10	16	—
p-Ethoxyphenyl-	EtOPh	—	17	—
p-Chlorphenyl-	ClPh	—	18	—

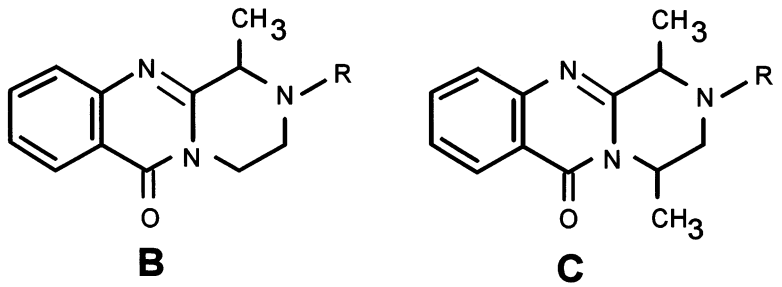


Fig. 2. The two-ring systems of pyridoquinazolones (**B** and **C**).

In cases when only small amounts of sample available or when the compound can be dissolved very well in a solvent, the whole procedure can be done using 1.0 ml of solvent under the same circumstances described, only the sampling must be made with much more care. For quinazolones only the methyl-imidazoquinazolone (1) in water and butyl-imidazoquinazolone (5) in 1-octanol dissolve to such a high extent, that the experiments could be done using 1.0 ml of solvent, all the others were determined with the standard procedure using 5.0 ml of solvent.

3. Results and discussion

3.1. Solubility data of imidazoquinazolones in water and 1-octanol

Ten derivatives of imidazoquinazolones were investigated and seven of those were soluble in water, namely the alkyl (1–5) and the aralkyl homologs (6,7). In three compounds the aromatic ring is attached directly to the heterocyclic ring (8–10); these have a very low aqueous solubility. The octanol solubilities are better and all the compounds have measurable values.

Solubility data, confidence intervals at the 95% probability level (in mol/dm^3) and numbers of measurements (n) are summarized in Table 2. The solubilities are given according to the corresponding confidence intervals, but tendencies can be followed more easily in Fig. 3.

Aqueous solubility markedly decreases with increasing size of the substituents of these molecules. Among the alkyl homologs, from the methyl (1) to the propyl derivative (4), by lengthening the alkyl chain by a methylene group the solubility is lowered by an order of magnitude. An OH substituent at the end of ethyl side chain causes some increase in polarity, therefore solubility of the hydroxyethyl derivative (3) is higher than that of ethyl homolog (2). The butyl homolog (5) has a slightly better solubility than the propyl derivative (4) and only these two have the same magnitude. The somewhat higher solubility of the butyl derivative indicates that other physical parameters change parallel with the increase of lipophilicity and this has an effect on aqueous solubility too. Another order of magnitude decrease is observed with aromatic ring containing derivatives (6,7), that are nearly independent of connecting alkyl chain lengths. This decrease in the magnitude of solubility is continued when the aromatic ring is attached directly to the ring-system (8–10). The latter three could be estimated only in order of magnitude, as their saturated solutions have absorbances at the limit of determination. The decrease in water solubility strictly follows the increase of lipophilicity of these molecules, except for the butyl derivative (5).

Solubilities in 1-octanol do not show such differences as is observed in water and nearly all values are higher than those obtained for aqueous media. The better solubility can be explained by the nonpolar character of the compounds and the special apolar/polar, but mainly nonpolar property of octanol (Hildebrand et al., 1970). The order of solubility of alkyl homologs is: methyl > ethyl > propyl < butyl ($1 > 2 > 4 < 5$), the same as in water. From the methyl to the propyl derivatives, an increase in lipophilicity decreases solubil-

Table 2
Equilibrium solubilities of imidazoquinazolones in water and 1-octanol

Ring-system: **A**		Water solvent			1-Octanol solvent		
Serial number	R-	Solubility mol/dm^3	Confidence interval ($\pm$)	n	Solubility mol/dm^3	Confidence interval ($\pm$)	n
1	Methyl-	1.06	0.06	12	0.42	0.04	20
2	Ethyl-	0.0205	0.0002	12	0.23	0.04	15
3	Hydroxyethyl-	0.0294	0.0002	15	0.055	0.001	20
4	*n*-Propyl-	0.0021	0.0001	15	0.115	0.007	15
5	*n*-Butyl-	0.0085	0.0002	15	1.44	0.09	20
6	Phenylmethyl-	0.00009	0.00001	12	0.216	0.002	15
7	Phenylethyl-	0.00005	0.00001	12	0.065	0.003	15
8	Phenyl-	$\leq$0.00001	—	6	0.0048	0.0004	12
9	*p*-Methylphenyl-	$\leq$0.00001	—	6	0.0042	0.0001	12
10	*p*-Methoxyphenyl-	$\leq$0.00001	—	6	0.0046	0.0002	15

ity. The pronounced higher solubility of the butyl derivative (5) can be explained with an increased apolar–apolar interaction between the solute side chain and solvent, which results in increased solvation with octanol. It indicates again that other physical parameters change parallel with the increase of lipophilicity that have an effect on solubility in octanol too. For homologs where a benzene ring is attached through a short alkyl chain to the heterocyclic ring (6,7), a minute lowering tendency can be observed in solubility as the molecule becomes more lipophilic. The phenylmethyl and phenylethyl derivatives (6,7) have nearly the same solubilities as the ethyl and propyl homologs (2,4). The latter means that an increase of the side chain with a methylene group (methyl $\rightarrow$ ethyl; ethyl $\rightarrow$ propyl) has almost the same effect on solubility in octanol as substitution of the methyl or ethyl derivative with a benzene ring (methyl $\rightarrow$ phenylmethyl; ethyl $\rightarrow$ phenylethyl) at ring-system (**A**). Those derivatives, where an aromatic ring is connected directly to the heterocyclic ring (8–10) have nearly two orders of magnitude less solubility than other ones, due to increased lipophilicity. The values are practically the same for the three derivatives investigated.

A special interaction exists with octanol in the hydroxyethyl derivative (3): the polar OH group decreases the solubility compared with the ethyl homolog (2). It is an opposite tendency to that in water, and this can be explained by unfavorable solvation of polar compounds by octanol. The latter is a consequence of an increase in polarity by inserting an OH group in the molecule. This assumption is supported by the fact that partitioning data ($\log P_{exp}$) determined experimentally (Hankó-Novák et al., 1983) and the computed solubility ratios ($\log SR = \log S_{octanol} - \log S_{water}$) have the same trends. Data of Table 3 is used to compute a regression line:

$$\log P_{exp} = 2.59 \times \log SR - 1.64, \quad (2)$$

$$n = 7; r = 0.91; F_{1,5} = 24{,}8$$

Mathematically this is a very good fit at a 99% probability level, but the residuals always have to be checked. Those differences in Table 3 exceed the accuracy of $\log P$ determination, therefore Eq. (2) is considered only as an approximate tendency. This proves solubility data interpretations by way of difference of structure and lipophilicity of molecules. The equation points only to a trend as can be seen directly by comparing determined ($\log P_{exp}$) and calculated ($\log SR$)data (see Table 3). The differences are high and in half of the cases, are comparable with the determined values. This proves, that $\log P$ values may not be calculated from solubility data practically, and support the observations that solubility ratios differ from $\log P$ values in several cases (Dearden and

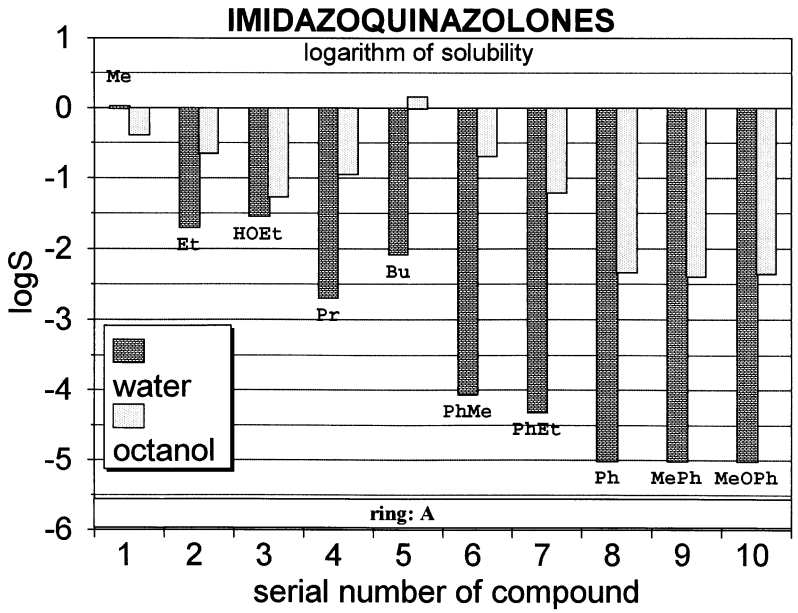


Fig. 3. Solubilities of imidazoquinazolones (mol/dm^3) in logarithmic units.

Bresnen, 1988; Said et al., 1996). This data clearly shows that the equality of the determined and calculated values can considered as exceptions. This can be explained easily with differences in the two techniques, reviewed by Dearden and Bresnen (1988). Our data support their opinions.

First of all log P determinations are made in dilute solutions, while solubility data are obtained in saturated ones. The activity coefficient of the solute is closer to unity for log P determinations than for solubility measurements, i.e. at high concentrations, lower (in most of the cases) than the theoretical value. The partition coefficient value is the ratio of activities and not the concentrations in two solvents. Our opinion is that this may be one cause of a deviation of log P_{exp} from log SR, in good agreement with the considerations of Yalkowsky and Pinal (1993) and Pinsuvan et al. (1995). The other factor is the miscibility of the two phases, for example the solubility of psoralen is increased in mutually saturated solvents (Said et al., 1996). Solubility data refer to pure solvents, and partitioning data characterize the distribution between two mutually saturated solvents. The result is that solubility ratios differ from partitioning data in several cases.

Two facts must be mentioned. The first is a very well-known one: both the experimental measurement of the partition coefficient and the determination of solubilities in two solvents are very time consuming and usually labor intensive methods. The second is that the experimental error can be appreciable and the computations may increase the effect of this on the result, therefore the calculated log P may be biased. The experimental error in log P determinations is usually ± 0.05 units, and that of solubility determination can be seen in Tables 2 and 4. The differences in Table 3 exceed the experimental errors of both methods, therefore these are considered as significant ones.

Partition coefficients can be used well to calculate water solubilities with Eq. (1) only for those compounds where the differences between log P_{exp} and log SR values are small (Yalkowsky et al., 1988). It cannot be done at the N-bridgehead compounds investigated, because the parameters markedly differ from the theoretical ($c_1 = -1$, $c_2 = -0.01$, $c_3 = 0.8$) ones. Eq. (1) is used to calculate water solubilities (log S_w) with determined log P_{exp} and melting point data (mp) of Table 3:

Table 3
Experimental log P values, computed solubility ratios and melting point data of imidazoquinazolones

Ring-system: **A**		log P			Melting point
Serial number	R-	Determined (log P_{exp})[a]	Computed (log SR)	Difference (log P_{exp} − log SR)	(°C)
1	Methyl-	0.85	−0.40	1.25	113
2	Ethyl-	1.02	1.05	−0.03	108
3	Hydroxyethyl-	0.46	0.27	0.19	133
4	*n*-Propyl-	1.40	1.74	−0.34	117
5	*n*-Butyl-	1.60	2.23	−0.63	58
6	Phenylethyl-	1.80	3.11	−1.31	110
7	Phenylmethyl-	1.69	3.38	−1.69	98

[a] Data from Hankó-Novák et al., 1983.

$$\log S_w = -3.27 \times \log P_{exp} - 0.03 \times (mp - 25) + 4.37, \quad (3)$$

$n = 7$; $r = 0.88$; $F_{2,4} = 243{,}1$

Calculation using Eq. (1) of solubility ratios (log SR) gives a very good fit of data and the parameters are close to the theoretical values:

$$\log S_w = -1.18 \times \log SR - 0.02 \times (mp - 25) + 1.40 \quad (4)$$

$n = 7$; $r = 0.99$; $F_{2,4} = 243{,}1$

Eq. (3) is not significant, but Eq. (4) is at a confidence level of 99%. The main difference between data used for calculations with Eq. (3) and Eq. (4) is the mutual solubility of both phases in each other in Eq. (3). This led us to the conclusion, that deviations between experimental (log P_{exp}) partitioning data and calculated solubility ratios (log SR) are caused primarily by the difference of two solvent systems (saturated with each other and pure). The calculations of solubility ratios are done with solubility data measured in saturated solutions, where the activities differ form the ideal value. The log SR data give better estimates for aqueous solubility (Eq. (4)) than experimentally determined partitioning data (Eq. (3)), which confirm our conclusion.

3.2. Solubility data of pyridoquinazolones in water and 1-octanol

Twelve derivatives of pyridoquinazolones were investigated and seven of these are soluble in water, which are alkyl homologs or the aromatic benzene ring is attached to the ring-system through a methylene group (11–14,19–22). Only one of the three compounds where the aromatic ring is attached directly to the heterocyclic ring has measurable solubility (*p*-methoxyphenyl derivative, 16). The absorbance values of other aromatic derivatives are at the limit of determination, therefore the magnitude (an approximate upper limit) of solubility can only be determined for these (14–15,17–18,22).

Solubility data, confidence intervals at the 95% probability level (in mol/dm^3) and number of measurements (n) are summarized in Table 4. The solubilities are given according to the corresponding confidence intervals, but trends can be followed more easily in Fig. 4.

Aqueous solubilities of alkyl homologs are of the same magnitude and vary somewhat in the order: methyl > ethyl < propyl (11 > 12 < 13). The differences are much less than those of imidazoquinazolones (see Table 2) and have the same trend for both ring-systems (**B**, compounds 11–13 and **C**, compounds 19–21). The single measurable aromatic ring containing derivative (16, methoxy-

Table 4
Equilibrium solubilities of pyridoquinazolones in water and 1-octanol

Ring systems: **B** and **C**		Water solvent			1-Octanol solvent		
Serial number	R-	Solubility (mol/dm^3)	Confidence interval ($\pm$)	*n*	Solubility (mol/dm^3)	Confidence interval ($\pm$)	*n*
Ring-system **B**							
11	Methyl-	0.0048	0.0005	15	0.021	0.001	15
12	Ethyl-	0.0036	0.0003	15	0.0117	0.0001	15
13	*n*-Propyl-	0.00494	0.00006	15	0.058	0.001	10
14	Phenylmethyl-	$\leq$0.00001	—	6	0.0112	0.0002	15
15	Phenyl-	$\leq$0.00001	—	6	0.0059	0.0002	15
16	*p*-Methoxyphenyl-	0.00096	0.00005	15	0.0181	0.0001	15
17	*p*-Ethoxyphenyl-	$\leq$0.00001	—	6	0.0093	0.0002	15
18	*p*-Chlorphenyl-	$\leq$0.00001	—	6	0.0083	0.0002	15
Ring-system **C**							
19	Methyl-	0.0082	0.0005	15	0.0223	0.0006	15
20	Ethyl-	0.0035	0.0001	15	0.0131	0.0004	10
21	*n*-Propyl-	0.00581	0.00002	15	0.0166	0.0006	10
22	Phenylmethyl-	$\leq$0.00001	—	6	0.0139	0.0002	15

phenyl-**B**) dissolves worse than aliphatic homologs (11–13). The difference is an order of magnitude, while the other aromatic ring containing derivatives (14–15,17–18,22) have a solubility value two magnitudes lower . The increase of lipophilicity has a pronounced effect on aqueous solubility like for imidazoquinazolones.

Solubilities in 1-octanol are determined for each compound. The high values compared with water point again to favourable solvation of apolar compounds by octanol. That was observed for the imidazoquinazolones also. A relationship is observed between octanol solubility data and the alkyl derivatives of ring-systems **B** and **C**: methyl > ethyl < propyl (11 > 12 < 13; 19 > 20 < 21). The somewhat higher solubilities of the propyl derivatives indicate that other physical parameters change parallel with the lipophilicity increases that have an effect on solubility too. The phenylmethyl derivatives (14,22) have nearly the same solubilities as the ethyl homologs (12,20). The latter means that an increase in the side chain of a methylene group (methyl $\rightarrow$ ethyl) has almost the same effect on solubility in octanol as substitution of the methyl derivative with a benzene ring (methyl $\rightarrow$ phenylmethyl) for both ring-systems (**B** and **C**). The lipophilicity increase is generally manifested in octanol solubility data. In general the lowest solubility values were observed at those derivatives (15–18) where phenyl group is attached directly to the ring-system (B). The least soluble is the phenyl substituted derivative (15), while the para-substituted aromatic derivatives (16–18) have nearly the same solubilities. The small difference corresponds to the increasing hydrophilicity of substituents, the order having: *p*-chlor- < *p*-ethoxy- < *p*-methoxyphenyl derivative (18 < 16). The difference of lipophilicity affects the solubility in octanol to a much smaller extent than in water. Similarities with the previously investigated imidazoquinazolones and the parallel alteration of solubility data with differences in lipophilicities prove the trend between these two parameters even in the lack of experimental logP values.

3.3. Conclusions

The described procedure is offered for determination of exact solubility data, which are precise enough to obtain high quality data for pharmacopeial and other official regulatory tasks. The

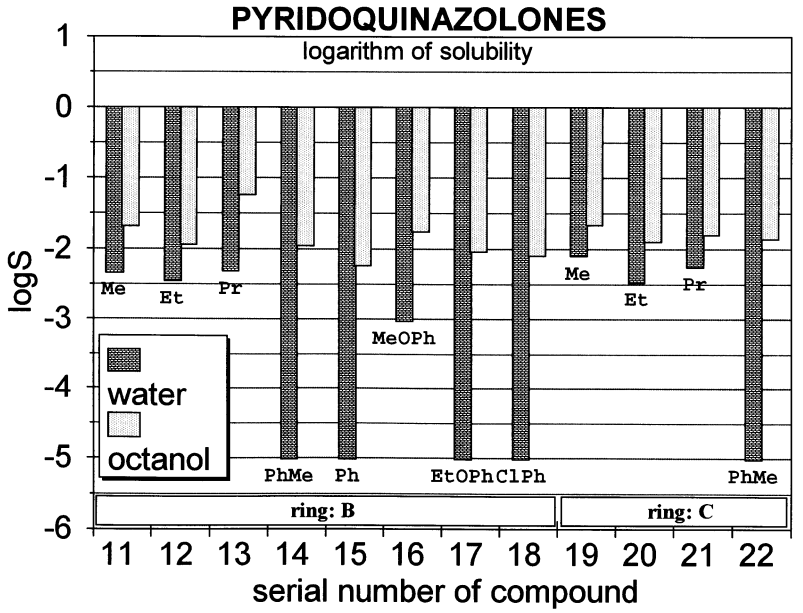


Fig. 4. Solubilities of pyridoquinazolones (mol/dm^3) in logarithmic units.

data determined in water and 1-octanol characterize the hydrophilicity–lipophilicity of a compound well, thus either solubilities or solubility ratios can be used as parameters in drug design. The water solubilities of the examined nitrogen-bridgehead compounds are much more sensitive to alteration of lipophilicity than octanol solubilities. Comparing solubilities and solubility ratios (log SR) with log P values the conclusion is that the calculated solubility ratios follow the tendency of lipophilicity of molecules, but markedly differ from log P values determined by the traditional shake-flask method. Our conclusion is that most of the differences in solubilties can be explained with the change of lipophilicities of these compounds caused by structural modifications of the molecules; only a few derivatives have considerable effects on differences of other physical properties on solubility data.

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