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Characterization of potential NMDA and cholecystokinin antagonists II. Lipophilicity studies on 2-methyl-4-oxo-3H-quinazoline-3-alkyl-carboxylic acid derivatives

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Abstract

The lipophilicity of 17 newly synthesized potential NMDA and cholecystokinin antagonist 2-methyl-4-oxo-3H-quinazoline-3-alkyl-carboxylic acid derivatives has been investigated. The apparent partition coefficients of two amphoteric compounds of overlapping protonation (**Q1** and **Q2**) were determined by shake-flask method and converted into true log *P* values using the protonation microconstants. The difference between their lipophilicity expressed with the true partition coefficients was less, than it could be expected from the 2D structures and was explained with conformational preferences and formation of intramolecular interactions. Out of the other 15 monoprotic quinazolone compounds the lipophilicity of ten molecules (**Q8**–**Q17**, experimental set) was determined by TLC method with the help of a calibration set consisting of 12 standard molecules, five quinazolones (**Q3**–**Q7**) and seven pyrido[1,2-a]pyrimidines (**PP1**–**PP7**). In order to justify the suitability of pyrido-pyrimidines as standards for the chromatographic log *P* determination of quinazolones, first **Q3**–**Q7** were examined by TLC and HPLC using **PP1**–**PP7** for calibration. Data showed good agreement of results obtained by shake-flask and two different chromatographic methods indicating the similar chromatographic behavior of the two bicyclic systems and the relevance of **PP1**–**PP7** to extend the calibration set of quinazolones. The obtained log *P* values proved mostly the expected structure–activity relationships. Some findings, however, have revealed specific partition behavior of the compounds providing useful information in the estimation of their pharmacokinetics, and these are discussed in the paper.

Keywords: Quinazolones; Lipophilicity; True partition coefficient; TLC log *P* determination

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1. Introduction

The fate of drug molecules in the body is fundamentally determined by their physico-chemical properties like ionization ability, lipophilicity and conformational characteristics. Information encoded in the lipophilicity of biologically active compounds has gained an important role in the rational drug design during the last nearly three decades.

In medicinal chemistry numerous measured or calculated parameters have been used for the characterization of the lipophilicity but the logarithm of the octanol/water partition coefficient ($\log P$) is still the generally accepted and primarily applied descriptor of the lipophilicity in QSAR studies (Hansch, 1994).

On the basis of earlier results of Yu et al. (1992), Pentassuglia et al. (1996) and Colotta et al. (1997) a series of 2-methyl-4-oxo-3H-quinazoline-3-alkyl-carboxylic acid derivatives was synthesized by us in a project to develop new, potential NMDA and cholecystokinin antagonists and to reveal their structure–activity relationships. The synthesis of the new 35 compounds, the results of the pharmacological screening appear elsewhere (Almási et al., in progress).

In the first part of their physico-chemical characterization the acid/base properties were examined and depicted at the molecular level in terms of protonation macroconstants and at the submolecular level in terms of protonation microconstants (Almási et al., 1999). In the present paper (second part of physico-chemical characterization) the study on the lipophilicity of these molecules was reported. The knowledge of the octanol/water partition coefficient of a compound with potential CNS effects, is necessary to explore the structure–activity relationships, which can serve as a rational base of further developments.

Seventeen quinazolone derivatives (see structures and codes in Fig. 1) have been selected for the lipophilicity investigations. On the basis of their acid/base properties the molecules can be divided into two groups. Amphoteric compounds of overlapping protonation (**Q1** and **Q2**) are listed in the first group, while monoprotic compounds having weak basic character (**Q3**–**Q17**) are classified into the second one. Remarkable differences existing in the ionization of the two classes have to be taken into consideration in the determination of the partition coefficient as well.

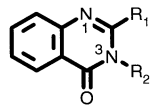
Numerous experimental methods are known for the $\log P$ measurement, out of them the traditional shake-flask technique is the most frequently utilized one. This validated method performed according to GLP rules produces precise and reproducible results (Takács-Novák, 1997), but its shortcomings (time-consuming, lack of automation, problems caused by the impurities of the sample, limitation of measurements in $\log P$ range: $-3-3$, etc.) are also well-known.

The recently developed pH-metric $\log P$ determination method (Avdeef, 1992, 1993) has a lot of advantages. This method can be applied, when the examined compound contains at least one ionizable functional group within the well-measurable pH range and its water-solubility reaches the minimum 0.8–1 mM concentration. The limited water-solubility and/or the low pK_a values of the majority of the compounds hindered the usage of the potentiometric $\log P$ determination.

The limitations of the above mentioned techniques have turned attention to alternative approaches of $\log P$ measurement namely towards the chromatographic methods. The chromatographic $\log P$ determination is based on the linear relationship between the chromatographic retention ($\log k'$ for HPLC and R_M for TLC) and the octanol/water partition coefficient ($\log P$). This relationship exists when the separation mechanism in the chromatographic system is the partition of the sample between the mobile and the stationary phases. Thus for $\log P$ determination the reversed phase (RP) chromatography is used generally (van de Waterbeemd et al., 1996).

RP-HPLC undoubtedly has been more widely used than TLC, but lots of precedents for the application of RP-TLC technique for $\log P$ measurement can be found in the literature as well. Representative reports are by Bird and Marshall (1971), Hulshoff and Perrin (1977), Tsantili-Kakoulidou and Antoniadou-Vyza (1989), Biagi et al. (1990), de Voogt et al., (1990), Darwish et al. (1994), Panderi et al. (1997), etc.

4-oxo-3H-quinazolines



I. Amphoteric derivatives (Q1, Q2)

Q1: R_1= -Me, R_2= -CH_2-COOH

Q2: R_1= -Me, R_2= -CH_2-CH_2-COOH

II. Monoprotic derivatives (Q3-Q17)

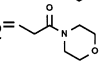
a) calibration set in TLC (Q3-Q7)

Q3: R_1= -Me, R_2= -CH_2-COOMe

Q4: R_1= -Me, R_2= -CH_2-CO-NH-CH_2-COOMe

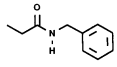
Q5: R_1= -Me, R_2= -CH_2-CO-NEt_2

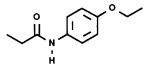
Q6: R_1= -Me, R_2= 

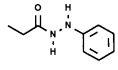
Q7: R_1= -Me, R_2= 

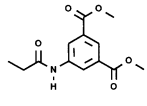
b) experimental set in TLC (Q8-Q17)

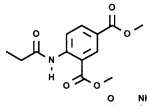
Q8: R_1= -COOEt, R_2= -H

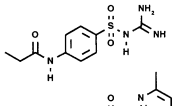
Q9: R_1= -Me, R_2= 

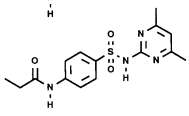
Q10: R_1= -Me, R_2= 

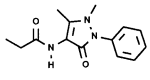
Q11: R_1= -Me, R_2= 

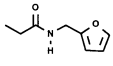
Q12: R_1= -Me, R_2= 

Q13: R_1= -Me, R_2= 

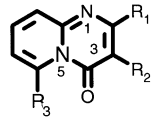
Q14: R_1= -Me, R_2= 

Q15: R_1= -Me, R_2= 

Q16: R_1= -Me, R_2= 

Q17: R_1= -Me, R_2= 

Pyrido[1,2-a]pyrimidines



calibration set in TLC and HPLC (PP1-PP7)

PP1: R_1= -H, R_2= -H, R_3= -H

PP2: R_1= -Me, R_2= -H, R_3= -H

PP3: R_1= -H, R_2= -H, R_3= -Me

PP4: R_1= -Me, R_2= -Me, R_3= -H

PP5: R_1= -Me, R_2= -Et, R_3= -H

PP6: R_1= -H, R_2= -Et, R_3= -Me

PP7: R_1= -Me, R_2= -Et, R_3= -Me

Fig. 1. Structure of model compounds.

In the present study the log *P* values of the newly synthesized 2-methyl-4-oxo-3H-quinazoline-3-alkyl-carboxylic acid derivatives were determined partly by shake-flask and partly by TLC methods.

The aim of this work is: (1) the characterization of lipophilicity of these molecules under development (**Q1**–**Q17**); (2) to explore the relationships between the chemical structure and the lipophilicity at the given type of the molecules; (3) to reveal that actually how wide lipophilicity range can be achieved by the substitution of the central quinazolone ring system at position 3 and which molecules have log *P* value around 2 being optimal to the expectable CNS effects, so what are the possible tendencies of further synthetic developments. An additional purpose is to call attention to some practical view-points of application of TLC for log *P* determination.

2. Materials and methods

2.1. Materials

Compounds **Q1** and **Q2** were prepared by the method of Errede and McBrady (1978). The synthesis of **Q3**–**Q17** were carried out according to Almási et al. (in progress). The method of Hermecz and Mészáros (1983) was used for the synthesis of compounds **PP1**–**PP7**.

Purification of the molecules was completed by both crystallization and RP-TLC.

n-Octanol was of HPLC grade (Aldrich) and methanol was of spectroscopic grade (Fluka). Britton-Robinson buffer (acetic, phosphoric and boric acids, each at 0.04 and 0.2 M sodium hydroxide) was used for the pH range 2.8–7.4. All other reagents were of analytical grade.

2.2. Methods

2.2.1. Purification of compounds *Q3*–*Q7*

The purification of compounds **Q3**–**Q7** was completed by RP-TLC (Silica gel 60 F_{254} silanized pre-coated, layer thickness = 0.25 mm, 20 × 20 cm plates, Art. 5747 Merck, MeOH:H_2O = 55:45 was used as the mobile phase). Before applying the spots, the plates had been washed in methanol, dried and they were heated on 160°C for 1 h. The compounds were dissolved in methanol (4 mg/ml) and 1200 μl of each solution was spotted onto the plate at 18 cm length in stripe by an automatic spotting machine (Camag Linomat IV, Muttenz, Switzerland). The plates were developed in TLC glass tank (Desaga, Heidelberg, Germany) at room temperature. After development, the plates were dried, and the stripes were detected with a dual wavelength flying spot scanning densitometer (Shimadzu, CS-9301PC). On the basis of UV spectra detected by the densitometer the main spot was identified. This main spot was scraped off and eluted by methanol filtering through microcrystalled cellulose layer (1 cm thickness). In the last step the methanol was evaporated under N_2 gas and the pure sample was obtained. Two plates per compound produced enough quantity of samples (4.0–6.0 mg).

2.2.2. Determination of log P values by shake-flask method

The partition coefficients of **Q1**–**Q7** and **PP1**–**PP7** were measured using the shake-flask technique according to GLP rules (Takács-Novák, 1997) at 25.0 ± 0.1°C temperature. The organic and aqueous phases were mutually saturated. The compounds were dissolved in aqueous buffer solution (stock solution: 7–10 mg/100 ml) and aliquots of the stock solution were equilibrated with octanol for 1 h in a shaking thermostat (Lauda, M20S). In the case of **Q1** and **Q2** pH values of the aqueous phase corresponded to the isoelectric points of these compounds. The pH value of the aqueous phase at compounds **Q3**–**Q7** was set to 7.4. The phase ratio (V_w/V_o) was 10:1 or 10:2. The samples were centrifuged at 730 × *g* for phase separation and the concentration decrease of the solute was determined in the aqueous phase by UV spectrophotometry (Hewlett-Packard 8452A, UV-Vis spectrophotometer) at the λ_{max} of each compound. Measurements of the pH were performed by PHM3 Radiometer Reference pH Meter. Each log *P* value is an average of 12 parallel measurements, the standard deviation being indicated in the Tables 1 and 2.

Table 1
Partition coefficients of amphoteric quinazolone derivatives determined by shake-flask method at the isoelectric point

Code	Isoelectric point	log P_{app}	log P[a]
Q1	2.80	0.08 ± 0.01	0.86
Q2	3.20	0.64 ± 0.04	0.97

[a] True partition coefficient of the neutral microspecies calculated by equation in the text.

2.2.3. Determination of log P values by TLC method

The compounds were dissolved in methanol (**PP1**–**PP7**: 10 mg/ml, **Q3**–**Q17**: 1 mg/ml). Two μl of **PP1**–**PP7** and 10 μl of **Q3**–**Q17** solutions were spotted onto the plate. The preparation of the layer and the applied chromatographic system was identical as described above at the purification method of **Q3**–**Q7**. After developments the plates were dried and the spots were detected either under UV lamp or with densitometer. Eight parallel TLC determinations were carried out and five plates were evaluated by densitometry, three visually.

Table 2
Partition coefficients of monoprotic quinazolone and pyrido-pyrimidine derivatives determined by shake-flask, TLC and HPLC methods

Molecules	log $P_{shake\text{-}flask}$	log P_{TLC}	log P_{HPLC}
Quinazolones			
Q3	1.46 ± 0.03	1.48	1.57
Q4	0.40 ± 0.05	0.32	0.44
Q5	1.07 ± 0.01	1.08	1.14
Q6	1.27 ± 0.01	1.31	1.42
Q7	0.36 ± 0.01	0.36	0.45
Pyrido-pyrimidines			
PP1	0.21 ± 0.01	–	–
PP2	0.60 ± 0.01	–	–
PP3	0.76 ± 0.01	–	–
PP4	1.14 ± 0.04	–	–
PP5	1.58 ± 0.01	–	–
PP6	1.84 ± 0.01	–	–
PP7	2.08 ± 0.01	–	–

2.2.4. Determination of log P values by RP-HPLC method

For the determination of log P values of compounds **Q3**–**Q7** RP-HPLC was also applied. The system consisted of a pump (Isco Model 2350), an injection valve (10 μl, Isco Model 2350) a UV detector (Isco V^4) operated at 270 nm and an integrator (HP 3396 Series II.). The column (Ultrasphere, Beckman) was 4×250 mm and contained a 5 μm wide pore bonded C_8 packing. MeOH:H_2O = 50:50 was used as mobile phase with 1 ml/min flow velocity. The compounds were dissolved in methanol (**Q3**–**Q7**: 0.34 mg/ml, **PP1**–**PP7**: 0.1 mg/ml) and 10 μl was injected from each of the solutions.

2.2.5. Theoretical and statistical calculations

Compounds **Q1** and **Q2** were subsequently optimized with the molecular mechanical MM+ method and then the semiempirical AM1 method using the PC SPARTAN 1.0 molecular modeling software package. The STATISTICA 5.0 mathematical and statistical software package was used for required mathematical calculations for log P determination.

3. Results and discussion

The lipophilicity of examined quinazolone derivatives is characterized here with the true partition coefficient which relates to the same (nonionized, monomer) molecular form of the partitioning solute in both phases. Due to the marked difference in the acid/base properties of the compounds, the experimental determination of log P_{app} and the calculation of the true log P value was carried out by different ways in group I and II of quinazolones (see Fig. 1) and the results are discussed below separately.

3.1. The amphoteric 2-methyl-4-oxo-3H-quinazoline-3-alkyl-carboxylic acid derivatives (*Q1* and *Q2*)

Compounds **Q1** and **Q2** are amphoteric molecules of overlapping protonation and they exist in aqueous solution in forms of four mi-

crospecies (anion, zwitterion, neutral, cation). Thus, the measured partition coefficient at the given pH of the aqueous phase (at isoelectric point in this case) is the apparent partition coefficient or distribution coefficient ($\log P_{app}$ or $\log D$). The relationship between the apparent and the true partition coefficient of amphoteric compounds with overlapping protonation was defined by Takács-Novák et al. (1992, 1995). The exclusive partitioning of the neutral microspecies into the organic phase was proved experimentally using spectroscopic methods (Takács-Novák et al., 1995) and was supported by theoretical calculations as well (Nagy and Takács-Novák, 1997). The mathematical relationship derived for the calculation of the true partition coefficient using the protonation microconstants is the following:

$$\log P = \log P_{app} + \log\left(1 + \frac{1}{k^{C}[H^{+}]} + \frac{k_{C}^{N}}{k_{N}^{C}} + k_{N}^{C}[H^{+}]\right) \quad (1)$$

The $\log P_{app}$ values of **Q1** and **Q2** were determined by shake-flask method at pH of their isoelectric point and then the log P of the neutral microspecies was calculated according to equation above. The applied protonation microconstants (k^{C}, k_{N}^{C}, k_{C}^{N}) were determined and published earlier (Almási et al., 1999). The lipophilicity data are listed in Table 1.

These two molecules can be regarded as a homologue of each other with only one methylene group difference between their structures. However, remarkable difference was found in their protonation properties and explained with electronic and conformational differences (Almási et al., 1999). For **Q1**, the major protonation pathway is the anion → zwitterion → cation route, thus at the isoelectric point the zwitterion form predominates relative to the neutral one. Elongation of the aliphatic carboxylic acid side chain in **Q2** has significantly modified the electron density of the ring system (including its basic site N_1 atom) and especially the carboxylate functional group. It has brought about intramolecular interactions (via H-bond formation) that has promoted the anion → neutral species → cation alternative protonation pathway to the predominant one, and the neutral microspecies, the major form being present at the i.e. point.

The 0.56 difference between their $\log P_{app}$ values (Table 1) apparently corresponds to a plus $-CH_2-$ group. Whereas the proportion of the partitioning neutral species (α_N) in the aqueous phase is different for the two molecules (**Q1**: $\alpha_N = 16.35\%$, **Q2**: $\alpha_N = 46.46\%$ at i.e. point pH), only the true partition coefficients can reflect correctly their partition behavior and can serve as a base of comparison of their lipophilicity. However, the difference of two log P values (0.11) less than it can be expected from the simple consideration of the 2D structures.

This finding can also be explained with conformational preferences and formation of intramolecular interactions. Earlier investigations on pyrido[1,2-a]pyrimidines (which have closely related bicyclic ring system and presumable similar solvation properties to 4-oxo-3H-quinazolines) have proved that the 4-carbonyl oxygen is the primary site of hydration in aqueous solution and the N_1 atom has only limited importance (Takács-Novák, 1986). The same solvation sites can be assumed in the ring system of quinazolones of the present work. Any intramolecular interaction on these two polar sites influences the solvation properties of the compounds.

Theoretical calculations on **Q1** and **Q2** supported the formation of intramolecular H-bonds between different functional groups of the two homologous structures (Almási et al., 1999). The more flexible side chain of **Q2** provides favorable H-bond formation between the COOH group and the N_1 atom (COOH…N_1: angle = 162.44°, bond length = 2.27 Å) thus the hydration of the carbonyl group at position 4 is not hindered. In **Q1**, due to the shorter side chain, the 4-carbonyl oxygen is involved in the H-bond formation with COOH group (C_4=O…HOOC: angle = 156.07°, bond length = 2.17 Å) causing a weaker hydration capacity and hereby a more lipophilic behavior than expected.

Table 3
Regression equations used in the chromatographic log P determination method

N^0	$y = ax + b$	a	b	r	s	F	n
	Pyrido-pyrimidines						
1.	$\log P_{\text{shake-flask}} = aR_M + b$	3.77	1.18	0.996	0.03	558	7
2.	$\log P_{\text{shake-flask}} = a \log k' + b$	1.76	0.81	0.999	0.02	1815	7
	Quinazolones + pyrido-pyrimidines						
3.	$\log P_{\text{shake-flask}} = aR_M + b$	3.36	1.00	0.995	0.02	1060	12
4.	$\log P_{\text{shake-flask}} = aR_{M(\text{vis})} + b$	3.40	0.97	0.995	0.02	919	12
5.	$\log P_{\text{shake-flask}} = aR_{M(\text{dens})} + b$	3.40	1.05	0.994	0.02	1018	12

*3.2. The monoprotic 2-methyl-4-oxo-3H-quinazoline-3-alkyl-carboxylic acid derivatives (**Q3**–**Q17**)*

Members of quinazolone II group (see Fig. 1) are monoprotic compounds with weak basic character ($pK_a \sim 2$–3). Under appropriate experimental conditions (pH > 5) the true partition coefficient can be measured directly by shake-flask and indirectly by TLC methods.

The lipophilicity of **Q8**–**Q17** was determined by TLC method with the help of a calibration set consisting of 12 standard molecules, five quinazolones (**Q3**–**Q7**) and seven pyrido-pyrimidines (**PP1**–**PP7**). The latter ones were selected to complete the calibration set for a wider log P range, on the basis of earlier investigations on their lipophilicity and chromatographic behavior (Papp et al., 1982).

The log P values of the standard compounds were measured by shake-flask technique at pH 7.4 and are summarized in Table 2.

In order to justify the suitability of pyrido-pyrimidines as standards for the chromatographic log P determination of quinazolones, first **Q3**–**Q7** were examined by TLC and HPLC. Their log P values were calculated from the retention data by linear regression (Eqns. (1) and (2) in Table 3) set up using seven pyrido-pyrimidines (**PP1**–**PP7**). Data in Table 2 show good agreement of results obtained by shake-flask and two different chromatographic methods. This fact and the very close correlation between $\log P_{TLC}$ and $\log P_{HPLC}$ of compounds ($r = 0.999$) indicate the similar chromatographic behavior of the two bicyclic systems and the relevance of **PP1**–**PP7** to extend the calibration set of quinazolones.

Thereafter eight TLC measurements were carried out applying the experimental set (**Q8**–**Q17**, log P unknown) and the completed calibration set (**Q3**–**Q7** + **PP1**–**PP7**, log P known) on each plate. Eqn. (3) in Table 3 shows the correlation between the average R_M and the log P values. Three plates were evaluated visually under UV lamp ($R_{M(\text{vis})}$) and five by densitometry ($R_{M(\text{dens})}$). The related linear regression equations ((3)–(5) in Table 3) are highly significant and have almost identical slope, intercept and statistical parameters. All this shows that since the used chromatographic system is optimalized producing symmetrical shape of plots, there is no difference in the evaluation approaches. According to this study, however, densitometry has several advantages over the manual handling (e.g. the identification of spots is based on UV spectra, detection of invisible impurities, determination of spot position with precision of 0.01 mm, data transfer and processing by computer, etc.).

Fig. 2 shows graphically the calibration curve (according to Eqn. (3) in Table 3) served for log P estimation of **Q8**–**Q17**. The confidence limit (dotted lines) is also indicated to visualize the expectable precision of the prediction. The wider log P range can be covered by the standards, the less error can be obtained at low and high values.

The log P values determined by TLC are collected in Table 4. The average standard deviation of $\log P_{TLC}$ values (based on all the eight runs) is ± 0.06 log unit which is practically identical to the generally accepted precision of shake-flask

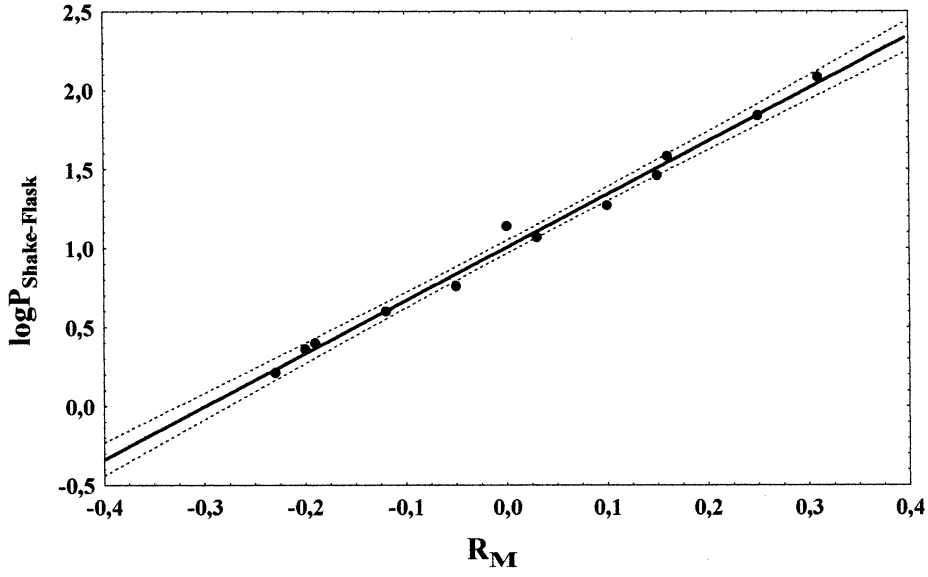


Fig. 2. Linear relationships between log P and R_M values of standards (**Q3**–**Q7** + **PP1**–**PP7**).

method (0.05). The highest uncertainty is obtained at low (± 0.14) and high (± 0.13) log P values, as expected from Fig. 2, as well.

Analyzing the relationship between the chemical structure and lipophilicity, the results prove mostly the expected relations. Some findings, however, have revealed specific partition behavior of 2-methyl-4-oxo-3H-quinazoline-3-alkylcarboxylic acid derivatives providing useful information in estimation of their pharmacokinetics. (1) Within the series, **Q14** containing a sulfaguanidino side chain has the highest polarity.

Table 4
Partition coefficients of quinazolone experimental set (compounds **Q8**–**Q17**) determined by TLC method

Code	log $P_{TLC(vis)}$	log $P_{TLC(dens)}$	log P_{TLC}
Q8	0.69 ± 0.04	0.71 ± 0.02	0.64 ± 0.08
Q9	1.79 ± 0.03	1.77 ± 0.01	1.78 ± 0.05
Q10	2.18 ± 0.02	2.20 ± 0.02	2.19 ± 0.05
Q11	1.34 ± 0.02	1.33 ± 0.01	1.34 ± 0.04
Q12	2.92 ± 0.03	3.03 ± 0.03	2.98 ± 0.07
Q13	3.45 ± 0.08	3.60 ± 0.11	3.53 ± 0.13
Q14	0.12 ± 0.11	0.05 ± 0.08	0.09 ± 0.14
Q15	0.66 ± 0.04	0.62 ± 0.03	0.70 ± 0.07
Q16	1.09 ± 0.02	1.05 ± 0.01	1.07 ± 0.04
Q17	1.24 ± 0.01	1.23 ± 0.01	1.24 ± 0.04

Its partition coefficient (log P: 0.09) shows that the molecule dissolves actually in the same extent in aqueous and organic phases, predicting a very poor membrane penetration. (2) Changing this side chain to a heteroaromatic sulfadimethylpyrimidine moiety in **Q15**, the log P increases with 0.61 unit. (3) Substitution of an –NH– group in the side chain of **Q11** with a $-CH_2-$ in **Q9** causes similar log P enhancement: 1.34–1.78. (4) Further significant lipophilicity increase was achieved by introducing a p-OC_2H_5 group to the phenyl ring of **Q10**, or ester functionalities to **Q12** and **Q13**. (5) It is interesting to note, despite **Q12** and **Q13**, that constitutional isomers with log P values which differ with more than 0.5 log unit. The reason for this can be probably searched for in conformational differences as well.

The column-chart in Fig. 3 illustrates the lipophilicity range of quinazolone derivatives under study (**Q1**–**Q17**). More than three orders of magnitude lipophilicity change was provided by enlarging the central quinazolone ring system with different substituents at position 3.

Concerning the projected pharmacological direction (NMDA and cholecystokinin antagonism) the best penetration into CNS can be expected from **Q9** and **Q10** having approximately ideal

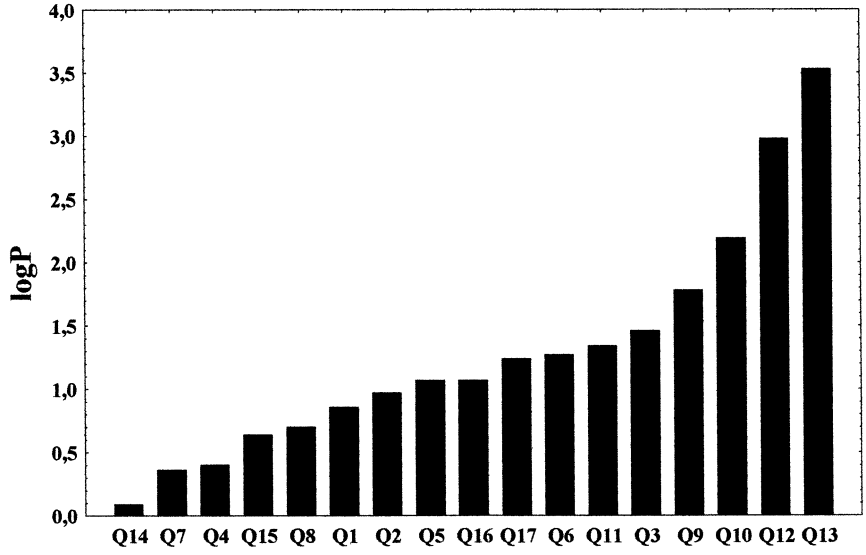


Fig. 3. Lipophilicity of 2-methyl-4-oxo-3H-quinazoline-3-alkyl-carboxylic acid derivatives.

(log $P \sim 2$) lipophilicity. On the basis of structure–property relationships of present study, the further synthetic developments of 2-methyl-4-oxo-3H-quinazoline-3-alkyl-carboxylic acid derivatives are in progress.

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