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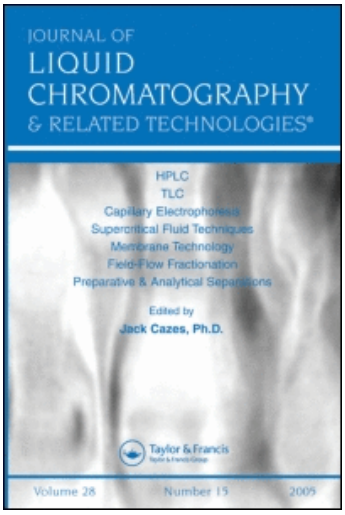


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# HPLC Study Off Some Biologically Active Quinazolines

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# HPLC STUDY OF SOME BIOLOGICALLY ACTIVE QUINAZOLINES

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## ABSTRACT

Experimental log $\overline{k}$ ($R_M$) values were determined for a series of pharmacologically active quinazolines. Statistically significant linear relationships were found between log k' and log P, log $\overline{k}$ and Hansch's parameter. The retention indices (RI) of these compounds were measured, and a statistically significant linear relationship was also found between log P and RI. The resolution factors and selectivity were determined for some pairs of the tested compounds. The relationship between the structure and $\Delta$ log $\overline{k}$ was interpreted. The best linear relationship was found at 60% methanol and 40% water for $C_{18}$ and $C_8$ columns.

## INTRODUCTION

High-performance liquid chromatography (HPLC) has proved to be a valuable technique for the pharmaceutical chemist. It plays important roles in pharmaceutical analysis and in drug research and develepment. As far as the application of HPLC for research purposes is concerned, study of the relationship between retention



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and other physical and chromatographic parameters has received the main emphasis (1,2). Experiments have been carried out to verify the existence of a linear correlation between the HPLC capacity factor and the chemical structure or structure-coherent physical properties for a given type of potencial drug compund (3-5). The main purpose of the present study is to seek such relationships between HPLC data (log $\bar{k}$) and log P and $\pi$ parameter for newly synthetized quinazoline derivatives (Table 1).

The selectivity and efficiency of some chromatographic systems (with stationary-phase $C_8$ and $C_{18}$ columns) have also been studied.

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## EXPERIMENTAL

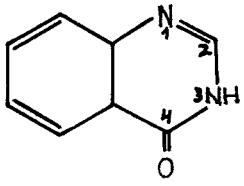
Materials: All the model substances were synthetized in our laboratory (6): Their identification and quality control were achieved by melting point determination and chromatography.

All chemicals and solvents were of analytical grade (Merck) and were used without further purification.

Apparatus, chromatography: The HPLC apparatus was a LIQUOCHROM Model 2010 (LABOR MIM, Budapest, Hungary). A variable-wavelength detector was used, and the column effluent was monitored at different wavelengths between 270 and 330 nm.

Table 1

Structure of model substances




| No. | $C_2$ | $C_3$ |
|---|---|---|
| 1 | H | H |
| 2 | $CH_3$ | H |
| 3 | H | $CH_3$ |
| 4 | $CH_3$ | $CH_3$ |
| 5 | $CH_3$ | $C_2H_5$ |
| 6 | $CH_3$ | $C_3H_7$ |
| 7 | $CH_3$ | $C_4H_9$ |
| 8 | $C_2H_5$ | $CH_3$ |
| 9 | $C_2H_5$ | $C_2H_5$ |
| 10 | $C_2H_5$ | $C_3H_7$ |
| 11 | $C_2H_5$ | $C_4H_9$ |

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The reversed-phase $C_{18}$ and $C_8$ columns were 250 mm x 4.6 mm, prepacked with materials with a particle size of 5 um (Beckman).

25 ul of sample solutions (0.1 mg/ml in methanol) was injected. Mobile phase: methanol-water mixtures containing 80%, 70%, 60% methanol.

The flow rate was 0.7 m l/min.

All experiments were run at room temperature i.e. 25 °C.

Equations used

a: For retention indices (7):

$$I = 100 \frac{\log k_D - \log k_N}{\log k_{N+1} - \log k_N} + 100\,N \qquad \ldots 1$$

where

$k_D$ = the capacity factor of the drug;

$k_N$ = the capacity factor for 2-ketoalkane eluting just before the test compound;

$k_{N+1}$ = the capacity factor for 2-ketoalkane eluting just after the test compound.

b: For Hansch's parameter:

$$\pi = \log P_X - \log P_H \qquad \ldots 2$$

$\pi$ = Hansch's parameter;

$P_X$ = the partition coefficient of a substututed compound;

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Table 2

The log k and log P values of qzinazoline compounds

| No | $C_{18}$ column | | | $C_8$ column | | | log P |
|---|---|---|---|---|---|---|---|
| | Methanol-water % | | | Methanol-water % | | | |
| | 80:20 | 70:30 | 60:40 | 80:20 | 70:30 | 60:40 | |
| 1 | -0.553 | -0.398 | -0.2518 | -0.7533 | -0.5314 | -0.3853 | 0.9121 |
| 2 | -0.5229 | -0.2518 | -0.1427 | -0.8325 | -0.3853 | -0.2527 | 1.1008 |
| 3 | -0.3873 | -0.237 | -0.1249 | -0.7533 | -0.4175 | -0.2762 | 0.924 |
| 4 | -0.319 | -0.1612 | -0.032 | -0.6863 | -0.2762 | -0.1512 | 1.1115 |
| 5 | -0.2366 | -0.066 | 0.155 | -0.4900 | -0.1512 | 0.0595 | 1.5759 |
| 6. | -0.066 | -0.127 | 0.384 | -0.3273 | -0.0843 | 0.2678 | 2.0648 |
| 7. | 0.0531 | 0.323 | 0.6395 | -0.1512 | 0.2009 | 0.5216 | 2.5722 |
| 8. | -0.1427 | 0.0354 | 0.2380 | -0.45229 | -0.05435 | 0.1119 | 1.6369 |
| 9. | -0.04095 | 0.2069 | 0.439 | -0,2762 | 0.1119 | 0.3318 | 2.1361 |
| 10. | 0.111 | 0.373 | 0.668 | -0.1512 | 0.2609 | 0.5548 | 2.5560 |
| 11. | 0.2695 | 0.5961 | 0.925 | 0.0483 | 0.4597 | 0.7907 | 3.0206 |

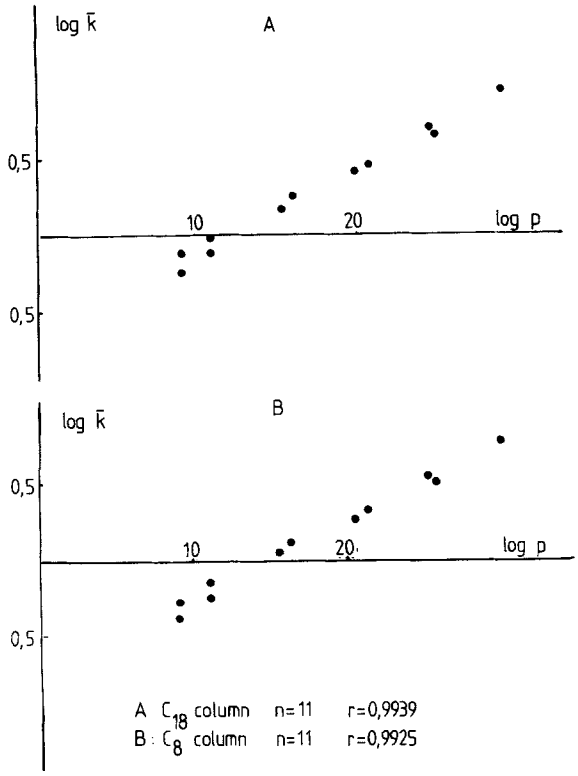


Figure 1. Correlation between log k values and log P values.

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$P_H$ = the partition coefficient of the corresponding unsubstituted compound.

## RESULTS AND DISCUSSION

The log $\bar{k}$ values of the 11 compounds are shown in Table 2. The differences in $\bar{k}$ values due to the different hydrophobicities of the stationary phases may be observed. A good linear relationship was found between

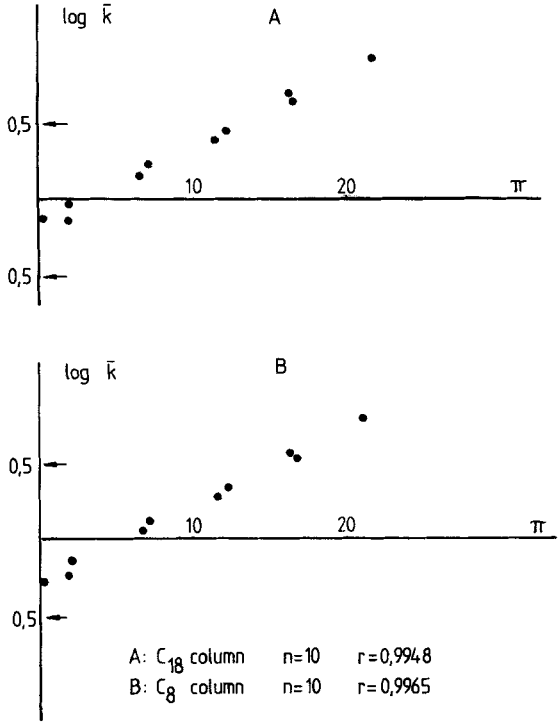


Figure 2. Correlation between log k values and Hansch's π parameter.

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log $\bar{k}$ (at 60% methanol and 40% water) and log P (see Fig. 1); analogous correlations were obtained for $C_{18}$ and $C_8$ columns (Table 2 and Fig. 1). This also holds for Hansch's parameter ($\pi$) calculated according to Eq. (2) (see Fig. 2).

The effect of hydrophobic properties can be seen in Table 3 where $R_s$ is reported for 16 pairs of test compounds. The selectivity is shown in Fig. 3.

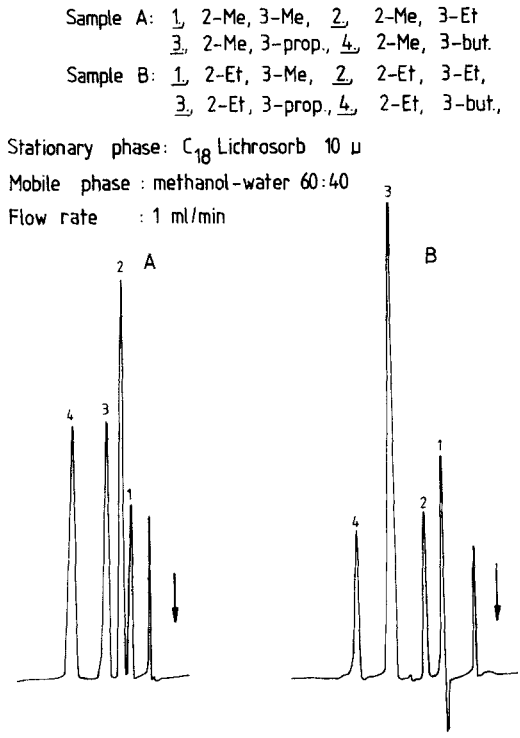


Figure 3. Separation of quinazoline homologues.

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It may be seen that the separation is much better for a $C_8$ than for a $C_{18}$ column. Table 3 also gives the selectivity (relative retention): the results were nearly the same for the $C_{18}$ column and the $C_8$ column. The effect of hydrophobic properties can also be seen in Table 4, where $\underline{N}$ and $\underline{H}$ were calculated for our tested compounds. The results again indicate the higher efficiency of the $C_8$ column. For the same test compounds,

Table 3

Resolution- and selectivity factors of some pair of compounds

| Mixture | $C_{18}$ column | | $C_8$ column | |
|---|---|---|---|---|
| | $R_s$ | selectivity $\alpha$ | $R_s$ | selectivity $\alpha$ |
| 1/ 2 | 0.67 | 0.77 | 0.93 | 0.74 |
| 1/ 3 | 0.83 | 0.75 | 1.15 | 0.78 |
| 2/ 3 | 0.128 | 0.96 | 2.04 | 0.95 |
| 2/ 4 | 0.85 | 0.77 | 0.97 | 0.79 |
| 2/ 5 | 2.48 | 0.50 | 3.75 | 0.49 |
| 2/ 6 | 5.02 | 0.30 | 7.58 | 0.30 |
| 2/ 7 | 9.13 | 0.17 | 12.05 | 0.17 |
| 4/ 9 | 5.43 | 0.34 | 6.13 | 0.33 |
| 8/ 9 | 2.9 | 0.63 | 3.45 | 0.60 |
| 8/10 | 6.98 | 0.37 | 9.07 | 0.36 |
| 8/11 | 12.3 | 0.21 | 17.37 | 0.21 |
| 7/11 | 6.55 | 0.52 | 8.88 | 0.54 |
| 6/10 | 4.75 | 0.52 | 7.56 | 0.52 |
| 5/ 9 | 3.8 | 0.52 | 4.45 | 0.53 |
| 8/ 4 | 2.67 | 0.53 | 2.8 | 0.55 |
| 10/11 | 5.93 | 0.55 | 8.28 | 0.58 |

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Table 4

The efficiency data of $C_8$ and $C_{18}$ columns of quinazoline compounds

| No. | $C_{18}$ | | $C_8$ | |
|---|---|---|---|---|
| | N | H | N | H |
| 1 | 1058 | 0,236 | 1888 | 0,132 |
| 2 | 936 | 0,267 | 1984 | 0,126 |
| 3 | 1077 | 0,232 | 1445 | 0,173 |
| 4 | 1002 | 0,249 | 1612 | 0,155 |
| 5 | 1313 | 0,190 | 3869 | 0,065 |
| 6 | 1471 | 0,169 | 5791 | 0,043 |
| 7 | 2325 | 0,107 | 4788 | 0,05 |
| 8 | 1688 | 0,148 | 2334 | 0,107 |
| 9 | 2162 | 0,115 | 2997 | 0,08 |
| 10 | 2687 | 0,093 | 5851 | 0,04 |
| 11 | 3304 | 0,075 | 10068 | 0,025 |

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Table 5

Retention index data of quinazoline compounds in four different systems

| No. | RI | | | |
|---|---|---|---|---|
| | $C_{18}$ | | $C_8$ | |
| | 70% | 60% | 70% | 60% |
| 1 | 382 | 391 | 346 | 355 |
| 2 | 461 | 433 | 457 | 444 |
| 3 | 469 | 440 | 445 | 436 |
| 4 | 506 | 476 | 457 | 477 |
| 5 | 553 | 552 | 565 | 557 |
| 6 | 646 | 642 | 647 | 636 |
| 7 | 737 | 759 | 732 | 727 |
| 8 | 605 | 588 | 614 | 577 |
| 9 | 682 | 687 | 691 | 659 |
| 10 | 760 | 741 | 759 | 712 |
| 11 | 859 | 833 | 855 | 823 |

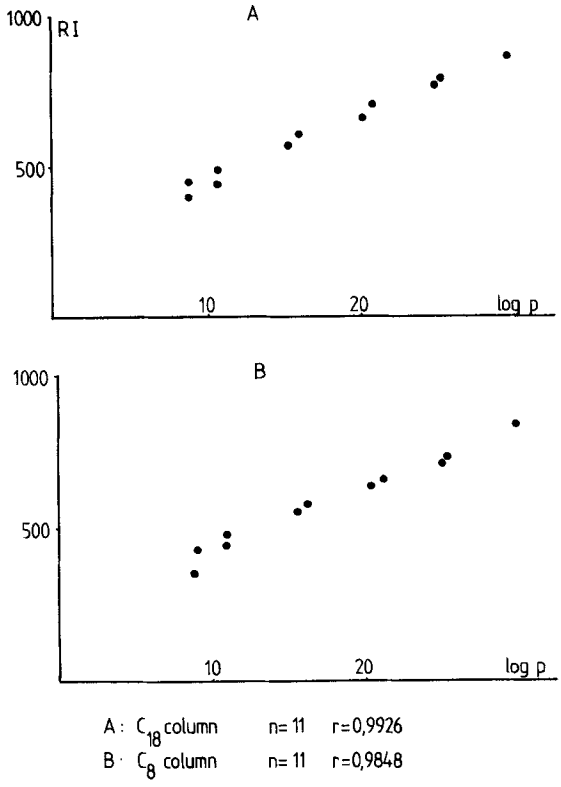


Figure 4. Correlation between RI values and log P values.

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retention index (RI) was calculated via Eq. 1 (see Table 5). To some extent there are similarities between the RI values obtained at 60% and 70% methanol for the $C_{18}$ and $C_8$ columns. The RI data obtained at 60% methanol on both $C_{18}$ columns. The RI data obtained at 60% methanol on both $C_{18}$ and $C_8$ columns were correlated with log P (see Fig. 4). The results show that HPLC-RI can be used in the prediction of log P and also in other fields of SAR research.

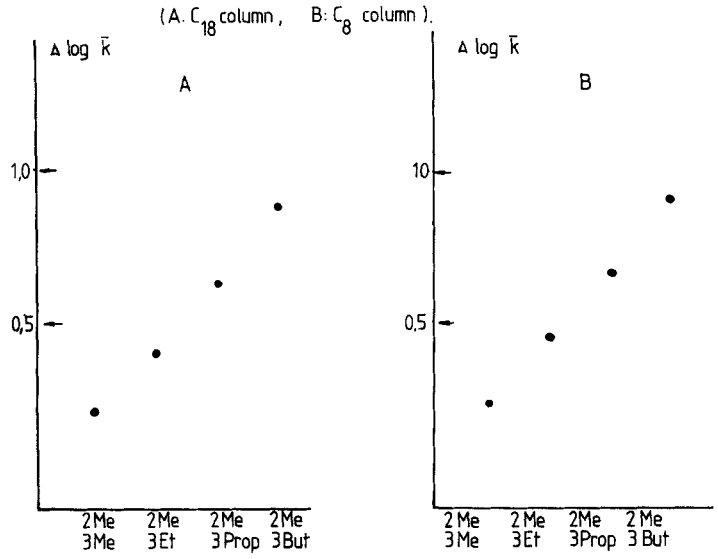


Figure 5. Relationship between log k and structure of some tested compounds.

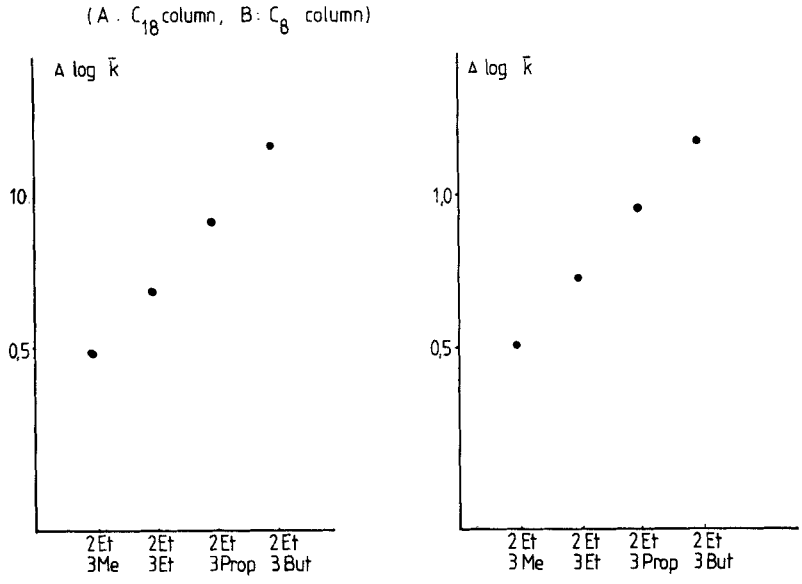


Figure 6. Relationship between log k and structure of some tested compounds.

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Figures 5 and 6 illustrate the linearity between log $\overline{k}$ and the carbon atom number at positions $C_2$ and $C_3$ for the same compounds using $C_{18}$ and $C_8$ columns. The average values for log k are: $\log k_{C_2\text{-}CH_3}$: 0.22 ($C_8$), 0.23 ($C_{18}$), $\log k_{N_3\text{-}CH_3}$: 0.27 ($C_8$), 0.28 ($C_{18}$).

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