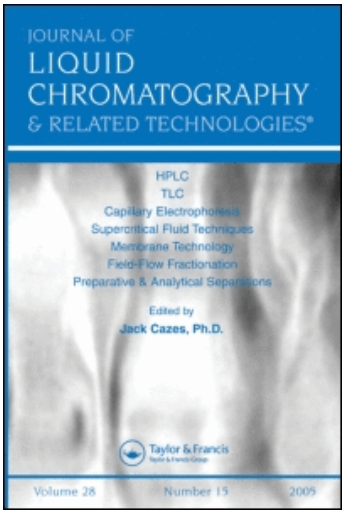

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Lipophilicity Determination of Some ACE Inhibitors by TLC

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Abstract: A simple and reliable reversed-phase TLC method was used to determine the lipophilicity of ACE inhibitors. The TLC silica plates were saturated with paraffin using continuous development with 10% paraffin in hexane for 18 hours. The TLC silica particles covered with the paraffin are used as an inexpensive substituent of the usual RP-18 TLC stationary phase.

Keywords: ACE inhibitors, Lipophilicity calculation, Lipophilicity determination, Reversed-phase TLC

INTRODUCTION

Lipophilicity represents the affinity of a molecule or one part of the molecule to a lipoid environment. Lipophilicity has an eminent role in the determination of the fate of organic compounds in the

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body; lipophilicity may influence their absorption, distribution (protein binding, permeability to cells and to the central nervous system), metabolism and excretion. In general, lipophilic drugs can penetrate better through the cell membranes. Lipophilic drugs can easily reach their receptor; even in the central nervous system, or inside the cell.

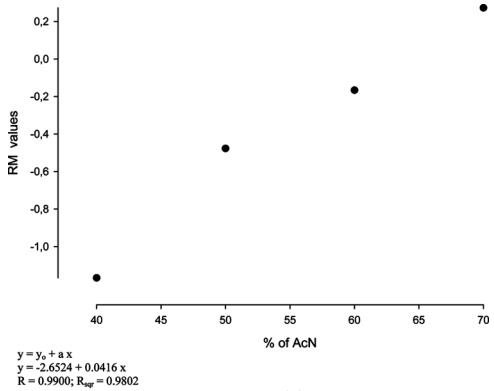
The concept of lipophilicity was introduced by Hansch and Fujita,[1] Leo et al.[2] suggested to determine the octanol-water partition coefficient (P) using a shake-flask method. The logarithmic form of the partition coefficient ($\log P$) has generally been used.

Melander and Horváth[3] started to use reversed-phase high performance liquid chromatography (HPLC) to determine the lipophilicity indices, instead of the more complicated shake flask method. Dependence of a chromatographic characteristic (mainly k') from the amount of organic modifier in the mobile phase was plotted. Its value at 0 percent of organic modifier was calculated (k'_0) as well as the slope of the plots. Melander and Horváth[3] found this type of approximation to be equivalent to the direct measurement of the partition coefficient. Valkó[4] presented an overview of the various methods used for lipophilicity determination, such as the direct analysis of the octanol and water phases, HPLC, biometric chromatography (using immobilized protein stationary phases; immobilized artificial membrane chromatography), providing also an evaluation of the different methods.

Deák et al.[5] investigated the physico-chemical properties of sertraline and other CNS active drugs[6] determining their pK_a and logP values. In this study the logP values of some ACE derivatives have also been determined experimentally.

Biagi et al.[7,8] and Cserháti et al.[9,10] utilized a planar method, that is reversed-phase thin-layer chromatography (RP-TLC), for the determination of lipophilicity. A series of experiments with various ratios of organic modifier (e.g., acetonitrile) determines the R_M values (an equation for R_M calculation is given later, in Experimental), and plots of R_M versus organic modifier concentration gave the $R_{M,0}$ and the slope of the line. Both the $R_{M,0}$ and the value of slope may give information on lipophilicity;[7–10] however, their combination can also be used, as suggested by Pyka and Miszczyk,[11] and also used by Dross el al.[12] Bieganowska et al.,[13] and Odivic et al.[14] RP-TLC was used[14] to determine the lipophilicities of five drugs with ACE inhibitory activity. TLC is an easy and relatively inexpensive technique and has the advantage that several compounds can be analyzed simultaneously.

Most antihypertensive drugs lower blood pressure by decreasing peripheral resistance via various mechanisms. Vasodilatation induced by angiotensin-converting enzyme inhibitors (ACE inhibitors) occurs through the combined effects of diminished levels of angiotensin II



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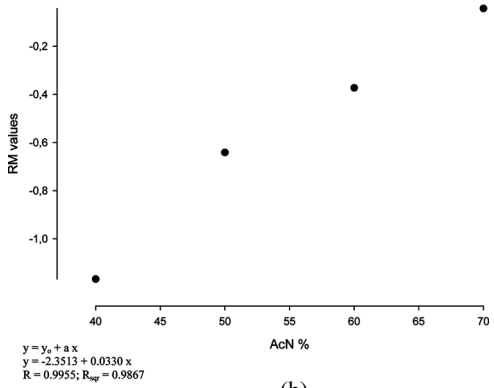

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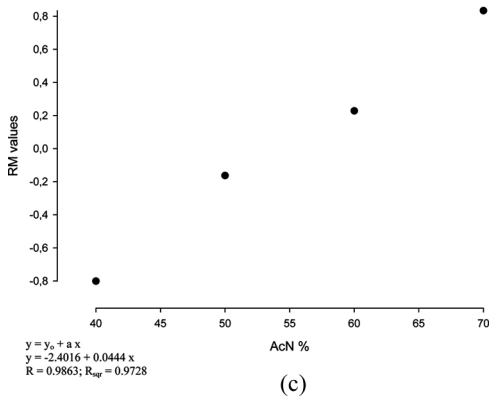
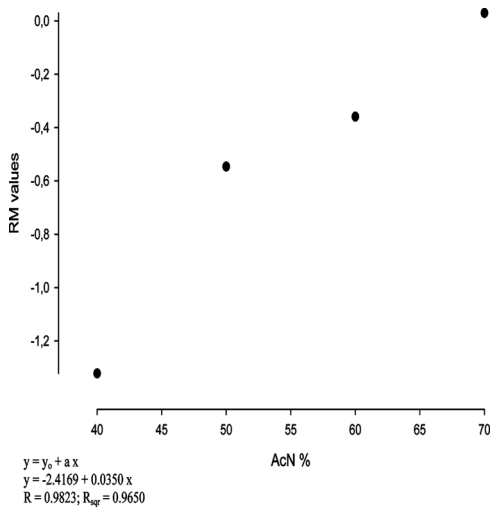


(c)

Figure 1. R_M values versus the acetonitrile content of five selected ACE inhibitors; determined on the paraffin oil coated TLC silica plates. (a) captopril; (b) delapril; (c) enalapril; (d) lisinopril; and (e) moexipril.



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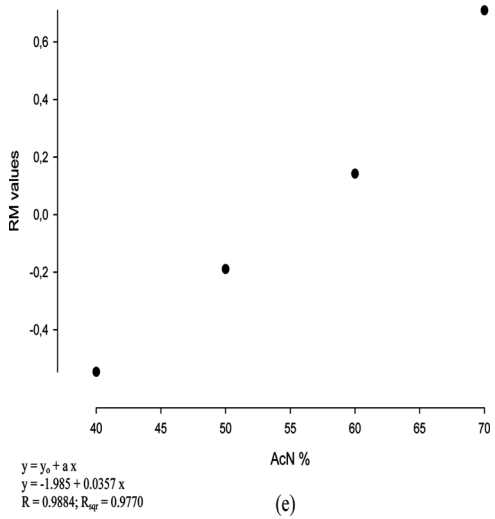


(e)

Figure 1. Continued

and effect of increased bradykinin. ACE inhibitors are the first line drugs in heart failure and high blood pressure. These drugs block the ACE that cleaves angiotensin I to form the potent vasoconstrictor angiotensin II. ACE inhibitor drugs also diminish the rate of bradykinin inactivation. Presently, over 20 such drugs are clinically available; representatives of this group are captopril, delapril, enalapril, lisinopril

and moexipril. With the exception of captopril and lisinopril, they are actually pro-drugs; the ethyl-ester part in their molecule (Table 2) is hydrolyzed in the liver, resulting the actual active drug.[15,16] The name of the ACE inhibitory drugs always ends in –pril, while the name of the active drug formed in the body is indicated by the ending –prilat.[15,16]

The lipophilicity of the drugs is an important characteristic, and the present paper suggests the use of a fast and economical method for its determination.

EXPERIMENTAL

Materials

HPLC grade acetonitrile, methanol, and analytical grade hexane, and ammonium hydroxide were purchased from Merck (Darmstadt, Germany). Water was double distilled and deionized. Paraffin oil (Pharmacopeia Hungarica VIII. quality, was purchased from a local pharmacy: Högyes Endre Pharmacy, Üllői út 39–43, Budapest, Hungary). ACE inhibitory drugs (captopril, delapril, enalapril, lisinopril, and moexipril) were generously provided by the manufacturers.

Chromatography

Thin-layer chromatography was performed on 20 cm × 20 cm plates with 0.2 mm layer of uncoated silica gel 60 F_{254}; and on 20 × 20 cm plates of reversed-phase silica RP-18 F_{254}.; the plates were purchased from Merck (Darmstadt, Germany). The uncoated silica gel 60 F_{254} plates were impregnated with paraffin by continuous development with 10% paraffin oil in *n*-hexane for 18 hours. Next, the plates were dried and used within 48 hours following impregnation. The sample solution aliquots (10 μL from 5 mg mL solutions) were spotted 3 cm from the bottom edge of the plates, and the TLC plates were developed in Desaga (Heidelberg, Germany) all glass TLC chambers with glass lids, without any special chamber saturation. The development of the LC plates was terminated when the mobile phase front was 2 cm from the top of plates.

After development, the spots were observed under the UV light of the Desaga lamp at $\lambda = 254$ nm. The R_F and R_M values were calculated according to the relationship:

$$R_F = \frac{\text{Distance of spot from origin}}{\text{Distance of mobile phase front from origin}}$$

$$R_M = \log\left[(1/R_F) - 1\right]$$

The mobile phases used are listed in Table 1.

Table 1. The composition of mobile phases used. Numbers refer the volumetric ratio of the organic modifier, water and ammonium hydroxide

Mobile phase	Acetonitrile	Water	Ammonium hydroxide
No. 1.	40	59	1
No. 2.	50	49	1
No. 3.	60	39	1
No. 4.	70	29	1

Experimental logP Determination

The traditional shake-flask method was used to measure the octanol/water logP values of delapril ($\log P = 1.92 \pm 0.05$; $n = 4$) and moexipril ($\log P = 1.06 \pm 0.02$; $n = 4$). Dual phase potentiometric titration was applied for the measurement of captopril ($\log P = -0.27 \pm 0.01$; $n = 3$). The experimental conditions were identical, as published previously.[5]

Calculations

The logP values of the compounds listed in Table 2 were calculated using various computer programs. One of them was the PrologP module of Pallas 3413 software (CompuDrug Inc., Sedona, AZ, USA); the recent one is the newest version of the software series we have used for years.[17–19]

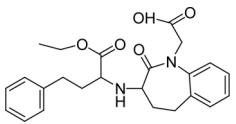
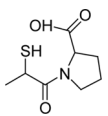
The logP values of some derivatives were calculated by Atom Fragment Contribution method using Kowwin v.1.51 software (Syracuse Research Corporation, Syracuse, NY, USA).[20] A unique option of this logP prediction program is the "Experimental Value Adjusted" (EVA) calculation approach. Taken the experimentally measured logP value of moexipril, the lipophilicities of other three compounds were calculated by EVA option.

RESULTS

Figure 1 demonstrates that the R_M values of the five selected ACE inhibitors follow a linear relationship against the acetonitrile content of the mobile phase.

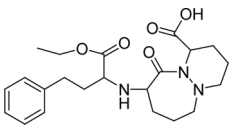
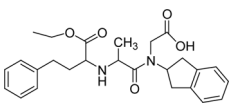
Table 2 lists the logP values of 12 drugs with ACE inhibitory activity, determined using various methods, indicating their lipophilicities. Different methods never give the same value; however, their comparison indicates which drugs are more (or less) lipophilic relative to the others.

Table 2. The chemical structures, and calculated log P values of some drugs with ACE inhibitory activity (-pril)

Name	Structure	log P (Prolog P program)[21]	log P (KOWWIN program)[20]		log P from the literature
			EVA	"a priori"	
Benazepril {2-[4-(1-ethoxycarbonyl -3-phenyl-propyl) amino-5-oxo-6-azabicyclo[5.4.0] undeca-7,9,11-trien-6-yl]acetic acid} $C_{24}H_{28}N_2O_5$		3.57	—	—	3.22[22]
Captopril {(2S)-1-[(2S) -2-methyl-3-sulfanyl-propanoyl] pyrrolidine-2 -carboxylic acid}; $C_9H_{15}NO_3S$		0.44	—	0.84	0.34[23] 1.02[24] 0.55[22]

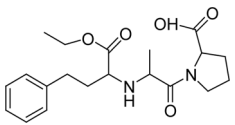
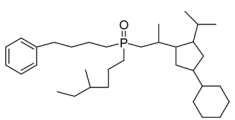
(continued)

Table 2. Continued

Name	Structure	logP (PrologP program)[21]	logP (KOWWIN program)[20]		logP from the literature
			EVA	"a priori"	
Cilazapril {(5*S*,8*S*)-5-{[(1*S*)-1 -ethoxycarbonyl -3-phenyl-propyl] amino} -6-oxo-1,7 -diazabicyclo[5.4.0] undecane-8- carboxylic acid}; $C_{22}H_{33}N_3O_6$		2.03	—	—	—
Delapril {N-(2,3-dihydro-1 H-inden-2-yl) -N-(N-(1- (ethoxycarbonyl) -3-phenylpropyl) alanyl)glycine} $C_{26}H_{32}N_2O_5$		2.68	1.91	4.21	—

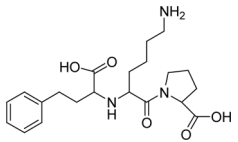
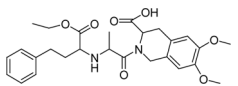
(continued)

Table 2. Continued

Name	Structure	logP (PrologP program)[21]	logP (KOWWIN program)[20]		logP from the literature
			EVA	"a priori"	
Enalapril {1-[2-(1 -ethoxycarbonyl -3-phenylpropyl) -aminopropanoyl] pyrrolidine-2- carboxylic acid} $C_{20}H_{28}N_2O_5$		0.98	0.14	2.45	0.16[26] 0.27[25] 2.27[22]
Fosinopril {4-cyclohexyl -1-[2-[(2-methyl -1-propanoyloxy -propoxy)- (4-phenylbutyl) phosphoryl] -acetyl] -pyrrolidine -2-carboxylic acid]} $C_{30}H_{46}NO_7P$		8.40	—	—	6.61[22]

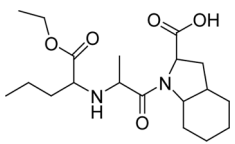
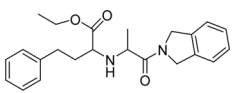
(continued)

Table 2. Continued

Name	Structure	logP (PrologP program)[21]	logP (KOWWIN program)[20]		logP from the literature
			EVA	"a priori"	
Lisinopril {1-[6-amino -2-(1-carboxy -3-phenyl-propyl) amino-hexanoyl] pyrrolidine -2-carboxylic acid dehydrate} $C_{21}H_{31}N_3O_5$		−1.16	−3.24	−0.94	−1.22[22] −1.22[26]
Moexipril {2-[2-[(1 -ethoxycarbonyl -3-phenylpropyl) amino]propanoyl] -6,7-dimethoxy -3,4-dihydro -1H-isoquinoline -3-carboxylic acid} $C_{27}H_{34}N_2O_7$		2.88	—	3.36	3.31[22]

(continued)

Table 2. Continued

Name	Structure	logP (PrologP program)[21]	logP (KOWWIN program)[20]		logP from the literature
			EVA	"a priori"	
Perindopril {1-[2-(1 -ethoxycarbonyl -butylamino) propanoyl] -2,3,3a,4,5,6,7,7a- octahydroindole -2-carboxylic acid} $C_{19}H_{32}N_2O_5$		2.24	—	—	2.63[22]
Quinapril {2-[2-(1 -ethoxycarbonyl -3-phenylpropyl) aminopropanoyl] -1,2,3,4- tetrahydroisoquinoline- 3-carboxylic acid} $C_{25}H_{30}N_2O_5$		3.86	—	—	3.38[22]

(continued)

Table 2. Continued

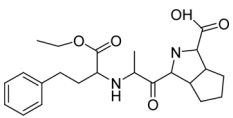
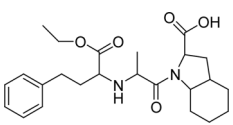
Name	Structure	log P (PrologP program)[21]	log P (KOWWIN program)[20]		logP from the literature
			EVA	"a priori"	
Ramipril {4-[2-(1 -ethoxycarbonyl -3-phenylpropyl) aminopropanoyl] -4-azabicyclo[3.3.0] octane-3- carboxylic acid} $C_{23}H_{32}N_2O_5$		2.83	—	—	3.15[22]
Trandolapril {1-[2-[(1- ethoxycarbonyl -3-phenyl- propyl)amino] propanoyl] -2,3,3a,4,5,6,7,7a -octahydroindole -2-carboxylic acid} $C_{24}H_{34}N_2O_5$		3,46	—	—	3.60[22]

Table 3. Determined lipophilicity values for five drugs with ACE inhibitory activity determined by reversed-phase TLC ($R_{M,0}$, a)

	Lipophilicity indices determined by TLC		
	$R_{M,0}$	a	$R_{squared}$
C	−2.65	0.041	0.97
D	−2.35	0.033	0.99
E	−2.40	0.044	0.95
M	−2.41	0.035	0.94
L	−1.98	0.035	0.96

Table 3 gives $R_{M,0}$ (R_M extrapolated to 0% of organic modifier), a (slope) values that our experiments resulted; and the measured lipophilicity values.

DISCUSSION

There are numerous methods either to calculate or to determine lipophilicity.[21–31] Some of them are based on the additivity of hydrophobic fragmental values, while some other methods consider the relationships between physico-chemical (and electronic) parameters of the compounds and the lipophilicity.

Molnár et al.[21] discussed the way lipophilicity can be modeled and calculated; as they called "neural network based prediction of octanol-water partition coefficients." The appropriate parts/fragments of individual compounds were considered, and their contributions to the (lipophilic) nature were subjected to a non-linear combination. The validity of their calculation method was controlled by the plotting the predicted and observed log P values.[21]

In any case, the lipophilicity is increased by the presence of carbon chains and rings, which make the compound to be hydrophobic. Conversely, lipophilicity is decreased by polarizable, highly polarized, and ionic groups.[21] As mentioned earlier, Biagi et al.[7,8] started to use thin-layer chromatography for the estimation of lipophilicities of drugs and drug candidate organic compounds. They utilized the features of planar chromatography, such as the ease of detection, chromatography of many compounds at the same time, and simplicity of the technique.

There are some virtual controversies in the use of lipophilicity as a basic parameter.

1. The log *P* is not a definitive parameter to define or influence the effect (dose) of the drug, but only indicates the penetration from one body

compartment to another one, such as penetration through the blood-brain, blood-placenta, etc., barriers. Moreover, the metabolism of the drug is generally directed to making less lipophilic (more hydrophilic) metabolites from the parent compound, facilitating, thereby, excretion from the body.

2. Penetration ability through barriers (such as blood-brain barrier) could theoretically be restricted to lipophilic drugs. However, numerous cases are known when highly hydrophilic drugs can penetrate through the blood brain barrier. The lipophilicity of pyridinium aldoximes is so low that it can not even be determined by any one of the established experimental methods. Even so, some of them were found to penetrate through the blood brain barrier of rats, as Sakurada et al.[32] and Lorke at al.[33] published for pralidoxime and K-48, respectively. Considering the highly hydrophilic nature of pyridinium aldoximes, a transporter system had to be postulated. Sakurada et al.[32] were unable to identify such a transporter. They solely found the neural uptake of pralidoxime as being Na^+ dependent.

At the same time, lipophilicity remained an important parameter of any drug or drug candidate. Neither one of the values of lipophilicity (such a log P, R_M, etc.) has an absolute value, but may be used when an individual compound is to be characterized. The position of either log P or R_M is valuable in the scale given by their homologues. It gives a relationship to other compounds with similar chemical structures.

Impregnation of the plain silica stationary phase gives an inexpensive way of lipophilicity determination. These results are reliable and will facilitate further experiments to determine lipophilicity.

ACKNOWLEDGMENT

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