Evaluation of ACE inhibitors lipophilicity using *in silico* and chromatographically obtained hydrophobicity parameters

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Abstract

The aim of this study was to compare different calculation methods to determine the lipophilicity, expressed as log *P* value, of seven ACE inhibitors (enalapril, quinapril, fosinopril, lisinopril, cilazapril, ramipril and benazepril) with significantly different structures. Experimentally determined *n*-octanol/water partition coefficients, log $P_{O/W}$ values, were obtained from relevant literature. The correlations between all collected log *P* values were studied and the best agreement between calculated log *P* and experimentally determined log $P_{O/W}$ values was observed for KOWWINlog *P* or Milog *P* values (r = 0.999 or r = 0.974, respectively). The correlations between all collected log *P* values and chromatographically (reversed-phase thin-layer chromatography) obtained hydrophobicity parameters, R_M^0 and C_0, were established. Good correlations (r > 0.90) were obtained in the majority of relationships. The KOWWINlog *P* was established as the most suitable hydrophobicity parameter of the investigated group of ACE inhibitors with r = 0.981 for correlation with R_M^0 and r = = 0.977 for correlation with C_0 parameters (water–methanol mobile phase). Using multiple linear regressions, it was established that application of two selected log *P*, calculated by different mathematical approaches, led to very good correlation due to the benefits of both calculation methods. The good relationships indicate that the computed log *P*, with careful selection of method calculation, can be useful in ACE inhibitors lipophilicity evaluation, as a high-throughput screening technique.

Keywords: Lipophilicity, ACE inhibitors, hydrophobicity parameters, reversed-phase thin-layer chromatography, computed log *P*.

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Lipophilicity is one of the most significant properties of biologically active substances that attract considerable interest in medicinal chemistry, pharmacokinetics and environmental science. Due to hydrophobic interactions of the drugs with biological targets, penetration across biological membranes during drug transport, as well as toxic aspects of drug action, lipophilicity is of great importance in drug research [1]. Lipophilicity influences drugs absorption, distribution, binding to plasma proteins and elimination [2,3]. Lipophilicity is characterized by the *n*-octanol/water partition coefficient (log $P_{O/W}$), and the traditional technique for experimental determination of molecule lipophilicity, *i.e.*, its log *P* value, is the so-called shake flask method [4]. Chromatographic techniques, such as thin-layer chromatography (TLC) [5,6], as well as high-performance liquid chromatography (HPLC) [7] and ultra-high performance liquid chromatography (UHPLC) [8,9], are known as well-established methods for evaluation of lipophilicity. Those methods can yield a significant amount of quantitatively comparable, precise and reproducible retention data for large sets of structurally different compounds, which can be correlated with their physicochemical and biological properties. Alternatively, *in silico* hydrophobicity parameters, calculated log *P* values, are generally accepted as a measure of a drug's lipophilicity [10]. Recently, calculated log *P* values have been used in lipophilicity evaluations of several newly synthesized *s*-triazine derivatives of pesticides and different bile acids [11,12]. Also, the acidity, lipophilicity, solubility or absorption of antihypertensive drugs have been theoretically considered by the use of computer programs based on their molecular structure [13,14].

Angiotensin – converting enzyme (ACE) inhibitors, represent an important group of drugs widely used in the treatment of hypertension, congestive heart failure and renal failure, especially in patients with diabetes mellitus and/or proteinuria, and today they are the most commonly prescribed antihypertensive drugs [15].

ACE inhibitors can be subclassified into three groups based on the differences in chemical structure: those

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with a sulfhydryl group (represented by captopril), those with a carboxyl group (represented by enalapril) and those with a phosphinic acid group (represented by fosinopril) [16] or according literature [15] sulfhydryl-containing inhibitors, dicarboxylate-containing inhibitors and phosphonate-containing inhibitors. The majority of ACE inhibitors are prodrugs and, following administration, they undergo ester's hydrolysis into di-acid active metabolites, with the exception of lisinopril, which is already in di-acid form. In biological materials, plasma, serum or urine, ACE inhibitors can be found as their metabolites just several hours after administration [15].

According to the available literature, a number of authors have investigated the relationship between lipophilicity and ACE inhibitors pharmacological activity, duration of action and absorption [17–19]. In our previous chromatographic studies, the lipophilicity of several ACE inhibitors was examined under different conditions, reversed-phase (RP) as well as normal-phase (NP) TLC [20–22]. RP-TLC [20], performed on RP-18 silica gel plates with different binary solvent systems, was established as a suitable method in ACE inhibitors lipophilicity evaluation. Continuing this research, in the present study, correlations between calculated hydrophobicity parameters (different log *P* values) and chromatographically obtained R_M^0 and C_0 values, as reliable measures of lipophilicity, were examined by simple and multiple linear regression (MLR) analysis. The aim of this work was to establish applicability of *in silico* hydrophobicity parameters, computed log *P* values, in ACE inhibitors lipophilicity evaluation.

EXPERIMENTAL

The selected ACE inhibitors were investigated:

1. Enalapril maleate (Krka Research and Development Division; Novo Mesto, Slovenia).
2. Quinapril hydrochloride (Hemofarm Stada Pharmaceutical Industry; Vršac, Serbia).
3. Fosinopril sodium (Bristol-Mayers Squibb Pharmaceutical Research Institute, Princeton, NJ, USA).
4. Lisinopril dihydrate (Belupo Pharmaceutical Cosmetic Quality Control Department, Zagreb, Croatia).
5. Cilazapril monohydrate (Roche Pharmaceuticals, Paris, France).
6. Ramipril (Hemofarm Stada Pharmaceutical Industry; Vršac, Serbia).
7. Benazepril hydrochloride (EP Reference Standard, Strasbourg, France).

The TLC examination of ACE inhibitors lipophilicity was performed by RP-TLC, as previously reported [20], with additional experiments under the same conditions including ramipril and benazepril in this study.

The Microsoft Excel 2003 and Origin 7.0 PRO (Origin Lab Corporation, USA) were used to perform the statistical analysis of the regression. The different ACE inhibitors log *P* values were calculated using software packages: Molinspiration Depiction Software, Molinspiration Cheminformatics (Milog*P*) [23], Virtual Computational Chemistry Laboratory (Alog*Ps,* AClog*P,* AB/ /log*P,* Alog*P,* Mlog*P,* KOWWINlog*P,* XLOG*P*2*,* XLOG*P*3) [24] and CS Chem Office, version 7.0 (Clog*P*) [25]. Experimentally determined log $P_{O/W}$ values of examined ACE inhibitors were obtained from Clarke's Analysis of Drugs and Poisons [26].

RESULTS AND DISCUSSION

In this research, seven ACE inhibitors (Figure 1) were studied in order to evaluate correlation between their calculated and chromatographically obtained hydrophobicity parameters. The systematic investigation of ACE inhibitors was carried out using the previously described RP-TLC method [20] with the addition of two ACE inhibitors: ramipril and benazepril. The ramipril and benazepril log *P* values were in-between the highest and the lowest log *P* of two drugs (fosinopril and lisinopril, respectively).

Using obtained R_F values, the parameters R_M were calculated for each solute in each mobile phase according to the Bate–Smith and Westall equation [27]:

$$R_M = \log\left(\frac{1}{R_F} - 1\right) \quad (1)$$

The retention behavior of investigated substances was presented as the relationship between R_M values and content of organic modifier in mobile phase, *C*, by the linear equation:

$$R_M = R_M^0 + mC \quad (2)$$

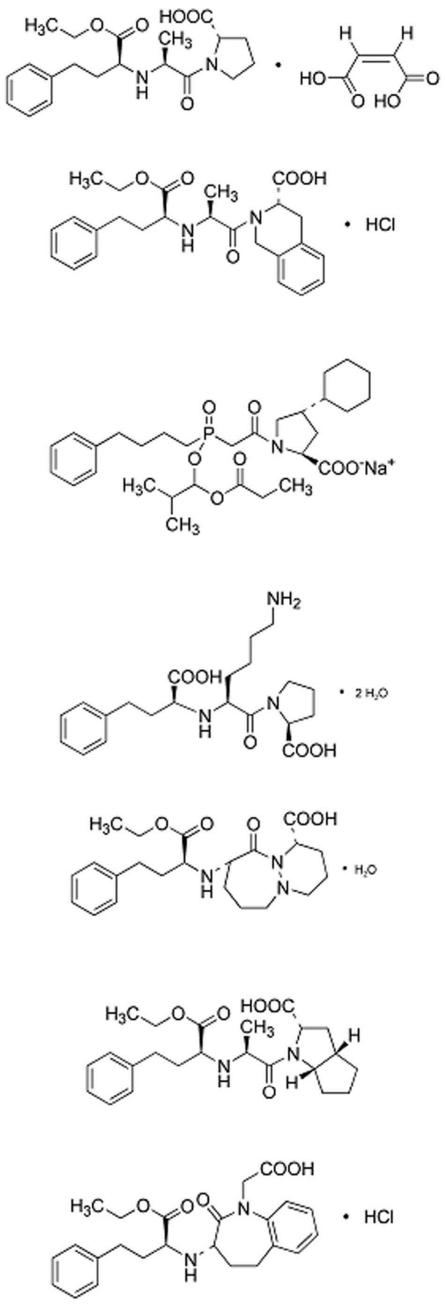
The value of the intercept, R_M^0, represents the lipophilicity of the examined substance while the value of the slope, *m*, corresponds to the specific hydrophobic surface area of the substance in contact with the stationary phase. Another hydrophobicity parameter, C_0, was calculated by the relationship between R_M^0 and *m* values:

$$C_0 = -R_M^0 / m \quad (3)$$

Parameter C_0 represents the volume fraction of the organic modifier in mobile phase for $R_M = 0$ [5,6].

The hydrophobicity parameters, R_M^0 and C_0, obtained in RP-TLC using three mobile phases (water-methanol, water-acetone, and water-ethanol) [20] are presented in Table 1.

The different log *P* values, as lipophilicity descriptors of seven investigated ACE inhibitors were calculated using different software packages [23–25]. The all collected log *P* values of examined ACE inhibitors: cal-



1. enalapril maleate, (S)-1-[N-[1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-proline maleate

2. quinapril hydrochloride, [3S-[2[R*(R*)],3R*]]-2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl] amino]-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid hydrochloride

3. fosinopril sodium, (4S)-4-Cyclohexyl-1-[[(R)-[(1S)-2-methyl-1-(1-oxopropoxy)-propoxy](4-phenylbutyl)phosphinyl]acetyl]-L-proline, sodium salt

4. lisinopril dihydrate, (S)-1-[N^2-(1-carboxy-3-phenylpropyl)-L-lysyl]-L-proline dihydrate

5. cilazapril monohydrate, [1S-[1α,9α(R*)]]-9-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]octahydro-10-oxo-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid monohydrate

6. ramipril, (2S,3aS,6aS)-1-[(2S)-2-[[(1S)-1-(Ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]octahydrocyclopenta[b]pyrrole-2-carboxylic acid

7. benazepril hydrochloride, (3*S*)-3-[[1-(Ethoxycarbonyl)-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepine-1-acetic acid hydrochloride

Figure 1. The chemical structures of the investigated ACE inhibitors.

Table 1. The hydrophobicity parameters (R_M^0 and C_0) of investigated ACE inhibitors

Compound	Water–methanol		Water–acetone		Water–ethanol	
	R_M^0	C_0	R_M^0	C_0	R_M^0	C_0
1	1.895±0.084	0.596	0.866±0.030	0.426	0.902±0.053	0.377
2	2.492±0.113	0.673	1.265±0.022	0.559	1.969±0.170	0.514
3	4.045±0.506	0.802	1.854±0.043	1.018	2.877±0.281	0.807
4	0.671±0.120	0.429	0.129±0.047	0.124	0.484±0.148	0.253
5	2.401±0.131	0.655	1.138±0.028	0.552	1.858±0.144	0.503
6	2.450±0.103	0.660	1.190±0.041	0.470	1.940±0.095	0.504
7	2.530±0.112	0.670	1.210±0.042	0.530	1.951±0.103	0.510

culated log *P* values as well as experimentally obtained log$P_{O/W}$ [26] are presented in Table 2.

The methods used for log *P* calculation can be classified as substructure-based or property-based methods [10].

There are two groups of substructure-based methods: fragmental and atom-based. The fragmental-based methods cut molecules into different fragments with application of correction factors. Summing all fragment contributions gives the final log *P*. Several log *P* values (KOWWINlog*P*, Clog*P*, Milog*P*, etc) can be calculated using fragmental methods. The atom-based methods (Alog*P*, Xlog*P*2, Xlog*P*3, etc.) cut down molecules to the single atoms and commonly do not apply corrections [10].

The property-based methods employ the description of the entire molecules and include: empirical, methods based on molecule's 3D-structure or methods based on topological descriptors (Alog *P*s) [10].

The differences between above presented calculation methods led to distinctions between absolute ACE inhibitors log *P* values (Table 2). The relationships between all collected log *P* values were studied. The obtained coefficients are presented in Table 3. Although good agreements were obtained between all collected log *P* values, the best can be observed between experimentally determined log $P_{O/W}$ [26] and three calculated log *P* values: KOWWINlog *P* (r = 0.999), *AC*log *P* (r = 0.994) and *Mi*log *P* values (r = 0.974).

Data in Table 3 shows good agreement (as proposed in literature [28]) with $r > 0.90$ between log *P* values calculated using different methods: fragmental (KOWWINlog *P*) and the atom-based methods (*X*log*P*2, *X*log*P*3). Opposite to these findings, in RP-TLC characterization of ADME data for polyphenols [29], the correlations established between log *P* calculated using different software packages (KOWWINlog *P* and *X*log*P)* were lower (r = 0.75), probably due to significant structure differences between two groups of examined compounds. The satisfactory intercorrelation established for ACE inhibitors log *P* values can indicate that *in silico* log *P* values may be suitable in lipophilicity evaluation of investigated drugs.

The KOWWINlog *P*, which showed the best correlation, was developed by Meylan and Howard as a fragment contribution method [10]. As it is defined, the each non-hydrogen atom in a compound's structure is a core for a fragment, and the exact fragment is determined by the type of the atoms connected to the core. The calculation of the final log *P* starts from the measured log *P* values of compound's structural analogues, which are modified by subtracting and adding fragments and factors to build the examined compound.

In the next stage of the study, hydrophobicity parameters R_M^0 and C_0 were correlated with all collected log *P* values, with the aim to establish the application and reliability of *in silico* parameters in ACE inhibitors lipo-

Table 2. The log P values of investigated ACE inhibitors

Compound	log $P_{O/W}$ [26]	*C*log *P*	*A*log *Ps*	*AC*log *P*	*AB*/log *P*	*Mi*log *P*	*A*log *P*	*M*log *P*	KOWWIN	XLOG*P*2	XLOG*P*3
1	2.45	0.67	0.19	1.52	0.63	0.50	2.46	1.63	2.45	2.11	–0.07
2	3.72	1.91	1.40	2.08	1.11	1.49	3.66	2.48	3.72	3.16	1.24
3	6.61	7.57	4.71	3.05	5.83	4.59	5.44	4.09	6.61	6.31	6.24
4	–1.22	–1.69	–1.23	0.53	–2.00	–2.43	1.78	1.11	–0.94	1.24	–2.86
5	–	1.47	–0.20	0.25	2.51	0.57	2.69	2.14	2.27	2.15	0.55
6	3.32	1.54	0.92	2.07	1.41	2.40	3.31	2.29	3.32	2.89	1.43
7	3.50	2.75	1.14	2.09	–	2.524	3.73	2.54	3.50	3.28	1.26

Table 3. Intercorrelations between different log P values

	log $P_{O/W}$ [26]	*C*log *P*	*A*log *Ps*	*AC*log *P*	*AB*/log *P*	*Mi*log *P*	*A*log *P*	*M*log *P*	KOWWIN	XLOG*P*2	XLOG*P*3
Log $P_{O/W}$ [25]	1	0.9409	0.9445	0.9937	0.9606	0.9742	0.9490	0.9418	0.9997	0.9203	0.9686
*C*log *P*		1	0.9723	0.7835	0.9621	0.9203	0.9712	0.9885	0.9479	0.9825	0.9864
*A*log *Ps*			1	0.8806	0.8840	0.9058	0.9811	0.9715	0.9450	0.9947	0.9729
*AC*log *P*				1	0.6311	0.8570	0.8712	0.7932	0.8512	0.8487	0.8071
AB/log *P*					1	0.9094	0.8963	0.9450	0.9206	0.8990	0.9605
*Mi*log *P*						1	0.9378	0.9268	0.9737	0.8983	0.9477
*A*log *P*							1	0.9875	0.9537	0.9830	0.9678
*M*log *P*								1	0.9492	0.9814	0.9840
KOWWIN									1	0.9280	0.9734
XLOG*P*2										1	0.9724
XLOG*P*2											1

philicity evaluation. Good correlations [28], with $r > 0.90$, were obtained in the majority of relationships (Table 4).

The best relationships were established between experimentally determined log $P_{O/W}$ values and R_M^0 and C_0 parameters obtained for water–methanol mobile phase. The best relationship between R_M^0 (r = 0.981) or C_0 (r = 0.977) parameters and calculated log P values was established for KOWWINlog P (Figure 2). The KOWWINlog P values previously showed the best relationship with experimentally determined log $P_{O/W}$ (Table 3). The *Mi*log P values showed slightly lower correlation coefficients – corresponding values for water–methanol were 0.958 for R_M^0 and 0.957 for C_0 (Table 4). Although *AC*log P values showed good correlation with experimentally determined log $P_{O/W}$ (Table 3), the lowest r values were obtained, as presented in Table 4 0.756 (R_M^0) and 0.735 (C_0).

Since hydrophobicity parameter C_0 is generally recognized as more reliable measure of a compound's lipophilicity in the RP-TLC, in the final stage of this study, MLR analysis between C_0 values and two diffe-

Table 4. The correlation coefficients, r, between R_M^0 or C_0 values (for all used modifiers) and different log P values

Mobile phase		log $P_{O/W}$ [26]	*C*log *P*	*A*log *Ps*	*AC*log *P*	*AB*/log *P*	*Mi*log *P*	*A*log *P*	*M*log *P*	KOWWIN	XLOG*P*2	XLOG*P*3
Water–methanol	R_M^0	0.9906	0.9681	0.9302	0.7556	0.9746	0.9585	0.9476	0.9707	0.9805	0.9295	0.9852
	C_0	0.9971	0.9211	0.8783	0.7351	0.9471	0.9597	0.9119	0.9301	0.9768	0.8699	0.9497
Water–acetone	R_M^0	0.9964	0.9254	0.8892	0.7478	0.9440	0.9608	0.9216	0.9378	0.9801	0.8802	0.9552
	C_0	0.9676	0.9801	0.9405	0.7145	0.9819	0.9042	0.9372	0.9707	0.9564	0.9428	0.9819
Water–ethanol	R_M^0	0.9403	0.9088	0.8665	0.6964	0.9210	0.9257	0.9278	0.9496	0.9202	0.8771	0.9287
	C_0	0.9578	0.9802	0.9465	0.7379	0.9723	0.9277	0.9618	0.9906	0.9521	0.9557	0.9878

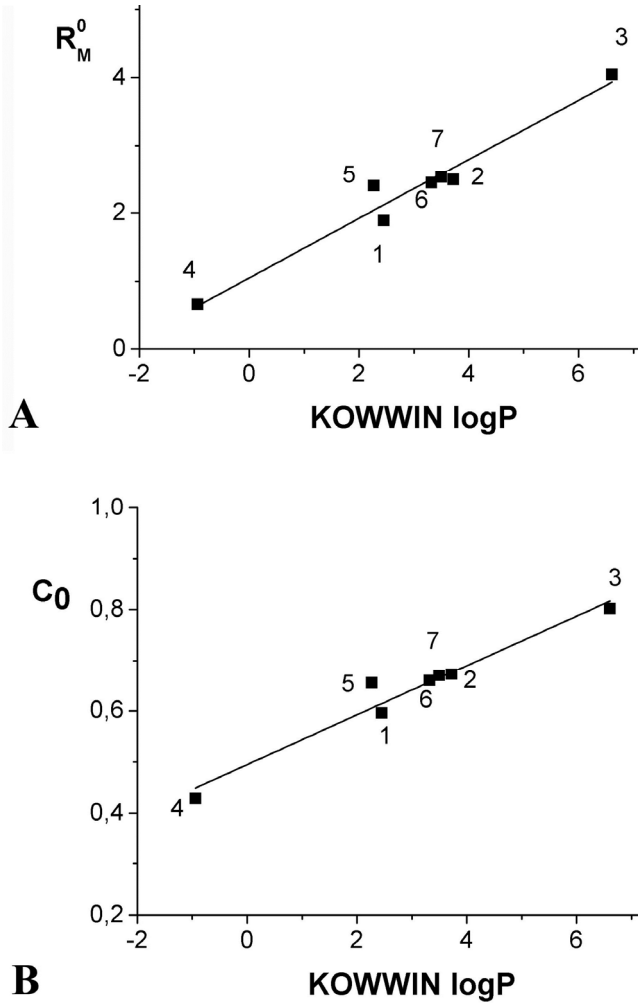


Figure 2. The relationships between KOWWINlog P and R_M^0 (r = 0.981) (A) or C_0 (r = 0.977) (B) parameters obtained in water–methanol mobile phase.

rent calculated log *P* as independent variable was investigated. The application of MLR using two log *P* values as independent variables, calculated by different mathematical approaches, should lead to excellent correlation due to benefits of both calculations methods. More than two log *P* values as independent variables was not appropriate for this study, since the number of investigated compounds was limited to usually prescribed ACE inhibitors.

According to equations obtained by MLR, the predicted C_0 values of investigated ACE inhibitors could be calculated as:

$$C_0(\text{predict}) = a\log P_1 + b\log P_2 + c \quad (4)$$

Selected log *P* values, KOWWINlog *P*, *Mi*log *P*, *AC*log *P,* were applied in Eq. (4). The *AC*log *P* values were chosen for MLR due to its lowest correlations in simple linear regression (Table 4). In MLR analysis using *AC*log *P* and KOWWINlog *P* as independent variables, $r = 0.994$ with acceptable probability values was obtained, while using *AC*log *P* and *Mi*log *P* resulted in a good *r* value (0.975) but with unacceptable value of probability. Applying variables KOWWINlog *P* and *Mi*log *P*, as log P_1 and log P_2, *r* value of 0.997 was obtained, but with insufficient probability value, indicating that MLR is not adequate for these two log *P* values.

Despite the differences observed in absolute log *P* values, the comparison of the correlations between chromatographically established hydrophobicity parameters, C_0 or R_M^0 values, with different calculated log *P* values led to the conclusion that *in silico* hydrophobicity parameters, with careful selection of the method calculation, can be considered as suitable, simple and easy approach in ACE inhibitors lipophilicity evaluation.

CONCLUSION

Lipophilicity is one of the most important properties of biologically active substances, and defining an appropriate method for rapid, simple and inexpensive determination of lipophilicity is essential for studies of substances biological activity.

The correlations between *in silico* hydrophobicity parameters (calculated log *P* values) and chromatographically (RP-TLC) determined hydrophobicity parameters (R_M^0 and C_0 values) obtained by simple linear regression, indicated that KOWWINlog *P* was the most suitable hydrophobicity parameter for investigated group of ACE inhibitors. Application of two selected log *P* values, calculated by different mathematical approaches in MLR analysis, led to very good correlation due to benefits of both calculation methods.

The good correlations between *in silico* hydrophobicity parameters and those chromatographically obtained validated the calculation of log *P* as a high-throughput screening technique for the evaluation of the selected compounds' lipophilicity.

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IZVOD

PROCENA LIPOFILNOSTI ACE INHIBITORA PRIMENOM *IN SILICO* I HROMATOGRAFSKI DOBIJENIH PARAMETARA HIDROFOBNOSTI

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U radu je analizirana lipofilnost sedam ACE inhibitora (enalapril, kvinapril, fosinopril, lizinopril, cilazapril, ramipril i benazepril) različitih hemijskih struktura. Primenom programskih paketa izračunato je deset različitih deskriptora lipofilnosti, log *P* vrednosti, za ispitivane ACE inhibitore dok su njihovi eksperimentalno određeni *n*-oktanol/voda koeficijenti raspodele (log $P_{O/W}$) preuzeti iz stručne literature. Između izračunatih log *P* vrednosti uočene su značajne razlike zbog razlika u primenjenim metodama izračunavanja. Ispitane su korelacije između svih log *P* vrednosti. Najbolje slaganje je dobijeno između eksperimentalnih log $P_{O/W}$ i izračunatih KOWWINlog *P* (*r* = 0,999) ili *Mi*log *P* vrednosti (*r* = 0,974). Analiziran je odnos između svih log *P* vrednosti i hromatografski određenih parametara hidrofobnosti, R_M^0 i C_0 (reverzno-fazna hromatografija na tankom sloju). Za najveći broj zavisnosti dobijene su dobre korelacije (*r* > 0,90). Najbolja korelacija dobijena je između KOWWINlog *P* i R_M^0 (*r* = 0,981), odnosno C_0 (*r* = 0,977) (voda–metanol mobilna faza). Multiplom linearnom regresionom analizom utvrđeno je da se primenom dve odabrane log *P* vrednosti, koje su izračunate korišćenjem različitih metoda, dobijaju odlične zavisnosti zahvaljujući prednostima primenjenih metoda. Dobijene dobre zavisnosti ukazuju da matematičke metode izračunavanja, kao tehnike za analizu velikog broja rezultata u kratkom vremenskom periodu (eng. *high-throughput screening techniques*), mogu biti od velike koristi u proceni lipofilnosti ACE inhibitora.

Ključne reči: Lipofilnost • ACE inhibitori • Parametri hidrofobnosti • Reverzno-fazna hromatografija na tankom sloju • Izračunate log *P* vrednosti