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STUDY OF THE BIOLOGICAL ACTIVITY DESCRIPTORS OF THE BARBITURIC ACID DERIVATIVES

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Abstract: Barbituric acid derivatives have been pharmacologically significant compounds for decades. The central nervous system effects are conditioned by the presence of the pyrimidine-trione ring and the nature of the substituent in position 5. Lipophilicity as one of the key molecular descriptors of biological activity for selected barbituric acid derivatives was determined experimentally, using reversed-phase thin layer chromatography (RP TLC18 F_{254s}), in two solvent systems. The influence of the substituent's nature and the effects of applied organic modifiers on the chromatographic behavior of the tested derivatives were examined. For the studied derivatives the values of the partition coefficient (log*P*) as a standard measure of lipophilicity and effective concentration (EC_{50}) as a measure of acute toxicity for different test organisms were calculated applying the appropriate software packages. Dependence between the chromatographic parameters as assumed measures of lipophilicity and the software-derived biological activity parameters of the studied barbituric acid derivatives were studied by linear regression analysis.

Keywords: barbituric acid derivatives, lipophilicity, toxicity.

1. INTRODUCTION

After discovery in 1864, barbiturates first entered clinical practice in 1904, altering access to neurological and psychiatric disorders [1, 2]. The first barbituric acid derivative used as an antiepileptic drug, phenobarbitone, was discovered in 1912 [3]. In the following decades, barbiturate derivatives were widely used in the treatment of insomnia and anxiety, but were replaced by safer benzodiazepine drugs due to easy availability, frequent abuse, dependence and overdose that ended in fatal outcome for patients [4]. In addition, many studies have shown their anti-inflammatory, antioxidant, antimicrobial and antitumor effects [5-10]. The presence of the pyrimidine-trione ring and the nature of the substituent on C-5 determine the type of biological activity of the barbiturate derivative. Therefore, before the synthesis of the new derivative qualitative and quantitative dependencies between its structure, properties and activity need to be determined [11]. The mathematical model that enables the establishment of these dependencies in modern science the QSAR (Quantitative Structure-Activity Relationship) model [12]. The molecular descriptor most commonly used as an indicator of the potential biological activity of a compound is lipophilicity [13].

The most commonly used measure of lipophilicity is partition coefficient, log *P*, which represents the ratio of equilibrium concentrations of a substance in two phases of a system consisting of 1-octanol and water [14, 15]. In addition to the partition coefficient, chromatographic parameters, R_M^0, *m*, and C_0, obtained by reversed-phase thin layer chromatography (RPTLC) [16-19] are used as reliable alternative measures of lipophilicity. The contemporary design of biologically active compounds, beside lipophilicity, requires a relevant assessment of the risks of their toxic effects in the environment and the study of the conditions under which they may be manifested.

Chromatographic parameters (R_M^0, *m*, and C_0) of the selected barbituric acid derivatives were determined by applying RPTLC in water-2-propanol and water-acetonitrile mixtures. Also, applying the appropriate software packages for the studied

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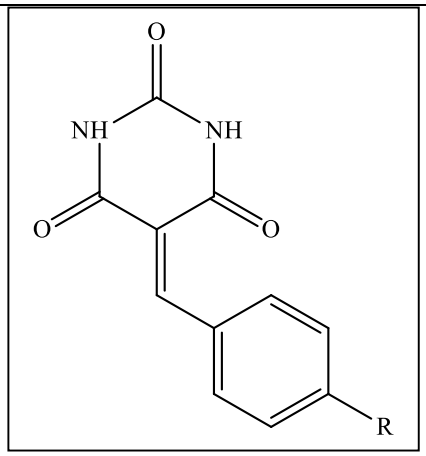
derivatives values of the coefficient, log*P* and effective concentration (EC_{50}) as a measure of acute toxicity for different test organisms were determined. The existence of a relationship between the experimentally obtained lipophilicity parameters (R_M^0, *m*, and C_0) and the mathematically calculated values of the partition coefficient, log*P*, and the toxicity parameters of the studied barbituric acid derivatives was examined by the linear regression analysis.

2. EXPERIMENTAL

Structures of the studied derivatives are shown in Table 1.

Table 1 Structures of the studied barbituric acid derivatives

Compound	*R*
1.	H
2.	OC_2H_5
3.	OCH_3
4.	CH_3
5.	F
6.	Br
7.	Cl
8.	OH
9.	NO_2
10.	$CH(CH_3)_2$
11.	CN



At the beginning of the chromatographic examination, solutions of the test compounds were made in ethanol (J.T. Backer, Deventer, The Netherlands), at the concentration of 2mgcm^{-3}. RPTLC C18/ UV254s, (Macherey – Nagel, Germany) which were used as the stationary phase carrier. After applying about 0.2 µl of the prepared solutions on the stationary phase, the plates were developed in mixtures: water-2-propanol (J.T. Backer, Deventer, The Netherlands) and water-acetonitrile (J.T. Backer, Deventer, The Netherlands). The volume ratio of organic modifier was varied in the range φ = 0.36-0.52. The chromatograms were developed in about 15 minutes at room temperature with a one-dimensional ascending technique, without first saturating the atmosphere of the chromatographic tub with vapor modifiers. The identification of the developed compounds was performed under UV light of wavelength λ = 254 nm, with dark spots appearing on the fluorescent medium. Three chromatograms were developed for each modifier, and then the average R_f values were calculated. Based on these, R_M values were calculated [20]. Dependences of the obtained R_M values on the volume fraction of organic modifier, φ, as the intercept gave the chromatographic retention constant R_M^0, while the slope represented the value of the parameter *m* [21] (equation 1):

$$R_M = R_M^0 + m\varphi \quad (1)$$

Based on the obtained parameters, the hydrophobicity parameter, C_0 [22] (equation 2) was calculated:

$$C_0 = - R_M^0/m \quad (2)$$

The experimental results were processed using the Origin 6.1 computer program, while the Molinspiration, SimulationPlus, and PreADMET software packages were used for calculating the coefficients, log*P*, and selected toxicity parameters [23-25].

3. RESULTS AND DISCUSSION

3.1. Experimental and software determination of the lipophilicity of barbituric acid derivatives

The values of chromatographic parameters R_M^0, *m* and C_0 of examined barbituric acid derivatives are presented in Table 2.

Table 2. Values of chromatographic parameters of studied derivatives in applied modifiers

–*R*	2-propanol				acetonitrile			
	R_M^0	*m*	r	C_0	R_M^0	*m*	r	C_0
–H	1.350	-3.465	0.998	0.390	0.985	-1.970	0.996	0.500
$–OC_2H_5$	1.586	-3.789	0.999	0.418	1.224	-2.280	0.998	0.537
$–OCH_3$	1.397	-3.510	0.999	0.398	1.106	-2.111	0.997	0.524
$–CH_3$	1.656	-3.907	0.997	0.424	1.331	-2.357	0.999	0.565
–F	1.438	-3.635	0.998	0.396	1.085	-2.085	0.996	0.520
–Br	1.843	-4.156	0.998	0.443	1.505	-2.503	0.997	0.601
–Cl	1.739	-4.054	0.999	0.429	1.413	-2.440	0.998	0.579
–OH	0.909	-2.705	0.999	0.336	0.654	-1.622	0.999	0.403
$–NO_2$	1.065	-2.920	0.999	0.365	0.810	-1.735	0.996	0.467
$–CH(CH_3)_2$	1.931	-4.278	0.997	0.451	1.593	-2.594	0.998	0.614
–CN	1.001	-2.803	0.999	0.357	0.737	-1.685	0.999	0.437

Based on the high values of the regression coefficient, r, shown in Table 2, it can be concluded that the linear R_M-φ dependence is valid in the selected field of experimental work. Given that the chromatographic retention constant, R_M^0, reflects the retention behavior of a compound in pure water (φ= 0) and depends only on its chemical structure and not on the organic modifier applied, it was expected that for the same compound in different modifiers to have the same value. However, the data in Table 2 show that the obtained R_M^0 values for the same compound in the applied organic modifiers differ from each other, what is often registered during experimental work [26].

Also R_M^0 values of studied derivatives differ in the same organic modifier. This can be interpreted as a consequence of the nature of substituent present in the para position on the benzene ring on the retention behavior of the molecule, i.e. its ability to form interactions with the mobile and stationary phase. In both applied modifiers, it is evident that the barbituric acid derivatives with halogen and nonpolar substituents have higher R_M^0 values than the unsubstituted molecule in the series: –F < $–CH_3$< –Cl < –Br < $–CH(CH_3)_2$. Logically, lower R_M^0 values relative to the unsubstituted derivative were expected for derivatives with polar substituents, but derivatives with the $–OCH_3$ and $–OC_2H_5$ group showed deviation. It was assumed that, unlike other derivatives with polar substituents (–OH, $–NO_2$ and –CN), these derivatives do not have such a pronounced possibility of achieving polar interactions with the mobile phase. In both organic modifiers, the highest value of the chromatographic retention constant, R_M^0, was obtained for the derivative with $–CH(CH_3)_2$ as the substituent, and the lowest for the derivative with the most polar –OH group.

The value of the chromatographic parameter, *m*, is influenced by the size of the solution, the species, the number of functional groups in the molecule, the specific hydrophobic surface, also, as well as by the organic modifier applied [27]. It can be seen from Table 2 that the slope value, *m*, follows the same trend of changes as the segment value, R_M^0, in both modifiers for all the derivatives tested. Therefore, it was assumed that both chromatographic parameters depend on the same physico-chemical properties. In order to confirm this assumption, the chromatographic retention constant R_M^0 and slope, *m*, are correlated by the linear regression analysis. The equations of the obtained linear dependences and their regression coefficients are shown in Table 3.

Table 3. R_M^0-m equation for studied derivatives in used modifiers

modifier	equation	r
2-propanol	R_M^0 = -0.626-0.780*m*	0.997
acetonitrile	R_M^0 = -0.920-0.824*m*	0.997

High values of the regression coefficients indicate the validity of the established R_M^0- *m* dependencies.

Also, by comparing the values of parameter C_0, it can be seen that they follow the same trend of change as the chromatographic parameters R_M^0 and *m*, which is in line with expectations.

The lipophilicity of barbituric acid derivatives, except experimentally, was also determined computationally. The software values of the partition coefficient, log*P*, as a standard measure of lipophilicity, for the examined barbituric acid derivatives are shown in Table 4.

Table 4. log P values of the studied barbituric acid derivatives

–*R*	logP_{cd}	Clog*P*	milog*P*	Mlog*P*	Mollog*P*
–H	0.58	0.79	0.29	0.82	1.38
$–OC_2H_5$	0.79	1.24	0.73	0.87	1.94
$–OCH_3$	0.45	0.71	0.35	0.60	1.47
$–CH_3$	1.06	1.29	0.74	1.11	1.78
–F	0.73	0.94	0.46	1.23	1.65
–Br	1.40	1.66	1.10	1.51	2.23
–Cl	1.13	1.51	0.97	1.37	2.09
–OH	0.19	0.12	-0.19	0.32	1.12
$–NO_2$	0.76	0.54	0.25	0.91	1.05
$–CH(CH_3)_2$	1.81	2.22	1.80	1.64	2.49
–CN	0.61	0.22	0.05	0.52	1.30

The data presented in Table 4 show that the values of the log*P* coefficient, as a standard measure of lipophilicity for the same compound, differ from each other, which is the consequence of the different approach of calculating this coefficient. However, regardless of the calculation method, the highest log*P* values were obtained for the derivative with $–CH(CH_3)_2$ and the lowest for the derivative with the –OH group as a substituent. The results obtained are consistent with those obtained during chromatographic examinations.

3.2. Correlation of the computational and experimental lipophilicity parameters of barbituric acid derivative

With the idea of possible application of the chromatographic parameters R_M^0, *m* and C_0, as reliable alternative measures of lipophilicity of the studied barbituric acid derivatives, their correlations with the software obtained partition coefficient, log*P*, by linear regression analysis were performed. Figure 1, Figure 2 and Figure 3 show the dependence of the chromatographic parameters R_M^0, *m* and C_0 determined in 2-propanol on the logP_{cd} coefficient, respectively.

Figure 1, Figure 2 and Figure 3 show that derivatives with polar group as substituent (–OH, $–NO_2$ and –CN) deviated from the established linear dependence. This behavior was observed in acetonitrile, also. The correlation matrix obtained as a result of linear regression for R_M^0- log*P*, *m*- log*P* and C_0- log*P* is given in Table 5.

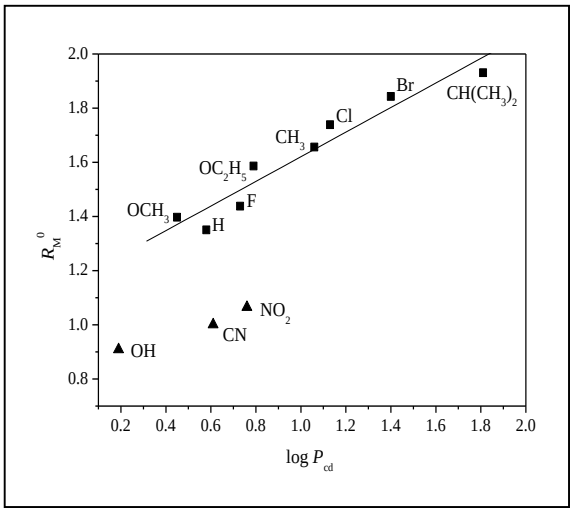


Figure 1. R_M^0- logP_{cd} in 2-propanol

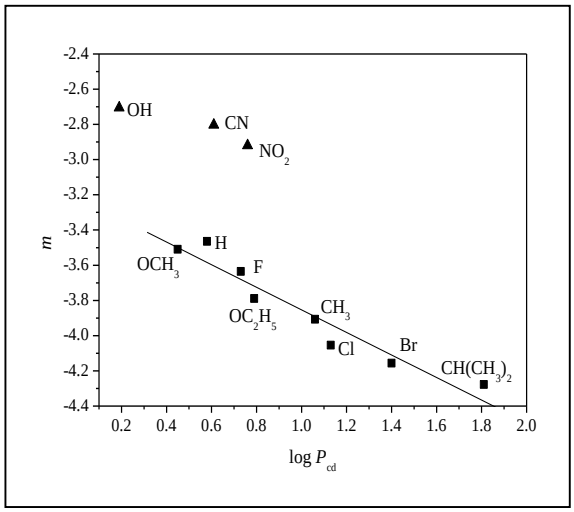


Figure. 2 m- logP_{cd} in 2-propanol

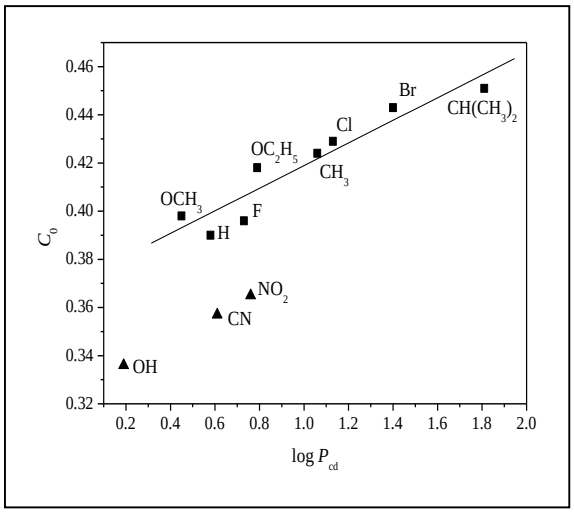


Figure 3. C_0- logP_{cd} in 2-propanol

Table 5. Correlation matrix for R_M^0- log P, m- log P and C_0- log$P$

log$P$	*r*					
	2-propanol			acetonitrile		
	R_M^0	*m*	C_0	R_M^0	*m*	C_0
logP_{cd}	0.963	0.963	0.945	0.946	0.923	0.948
Clog$P$	0.971	0.967	0.958	0.952	0.942	0.941
milog$P$	0.947	0.939	0.937	0.936	0.922	0.926
Mlog$P$	0.857	0.885	0.803	0.828	0.796	0.842
Mollog$P$	0.972	0.971	0.962	0.955	0.956	0.940

The results presented in Table 5 show that the better dependence of all the calculated coefficients of the tested barbituric acid derivatives was obtained in correlation with the chromatographic parameters, R_M^0, *m* and C_0, determined in 2-propanol. Among the partition coefficients, Mollog$P$ showed the best agreement with the values R_M^0, *m* and C_0, and the weakest was noted for Mlog$P$. Also, it is noticeable that among the chromatographic parameters, the best agreement with all the partition coefficients was shown with the chromatographic retention constant R_M^0.

The high values of the regression coefficient r, confirm that the chromatographic parameters, R_M^0, *m* and C_0 determined by reversed-phase thin layer chromatography can be reliably applied as alternative measures of lipophilicity of the studied barbituric acid derivatives.

3.3. Correlation of chromatographic parameters R_M^0, *m* and C_0 with parameters of toxicity

In order to evaluate the possible toxicity of barbituric acid derivatives, using the software, qualitative data about their mutagenic and carcinogenic properties were obtained (Table 6).

Table 6. Mutagenicity and carcinogenicity of the studied derivatives

–*R*	Ames test	Carinogenicity (mouses)	Carinogenicity (rats)
–H	mutagen	+	+
$-OC_2H_5$	mutagen	+	-
$-OCH_3$	mutagen	+	+
$-CH_3$	mutagen	+	+
–F	mutagen	+	-
–Br	mutagen	+	+
–Cl	mutagen	+	+
–OH	mutagen	+	+
$-NO_2$	mutagen	+	+
$-CH(CH_3)_2$	mutagen	+	+
–CN	mutagen	+	+

Based on the data presented in Table 6, it can be seen that, theoretically, all studied barbituric acid derivatives have mutagenic properties (positive Ames test) and that most of them are potentially carcinogenic. Also, the values of the effective concentration of the tested barbituric acid derivatives EC_{50} mgkg^{-1} as a measure of acute toxicity were calculated for the following test organisms: Algae, Daphnia, Medaka, and Minnow (Table 7).

The obtained EC_{50} values indicate that the highest toxicity among the studied derivatives for all the test organisms has the compound with $-CH(CH_3)_2$

group, and the least in average derivatives with –OCH_3 and –OH as substituents. All tested derivatives are the most toxic to *Algae* species.

The dependence between the experimentally determined lipophilicity (R_M^0, m and C_0) of the studied barbituric acid derivatives and the values of their toxicity parameters (EC_{50}) for different test organisms were examined using the linear regression analysis. Table 8 shows the correlation matrix of the obtained dependencies.

Table 7. Software calculated values of EC_{50} of studied derivatives for the selected test organisms

–*R*	*Algae*	*Daphnia*	*Medaka*	*Minnow*
–H	0.207	0.497	0.344	0.324
$–OC_2H_5$	0.114	0.364	0.194	0.222
$–OCH_3$	0.163	0.501	0.356	0.367
$–CH_3$	0.127	0.321	0.148	0.177
–F	0.163	0.419	0.247	0.155
–Br	0.097	0.183	0.058	0.086
–Cl	0.127	0.321	0.148	0.177
–OH	0.168	0.540	0.415	0.332
$–NO_2$	0.205	0.496	0.357	0.206
$–CH(CH_3)_2$	0.072	0.181	0.050	0.065
–CN	0.200	0.420	0.267	0.244

Table 8. Correlation matrix obtained for chromatographic parameters- EC_{50} values relationships

EC_{50}	r					
	2-propanol			acetonitrile		
	R_M^0	*m*	C_0	R_M^0	*m*	C_0
Algae	0.932	0.918	0.946	0.931	0.948	0.910
Daphnia	0.977	0.975	0.969	0.958	0.948	0.957
Medaka	0.968	0.974	0.956	0.946	0.946	0.938
Minnow	0.852	0.875	0.813	0.815	0.802	0.817

The high values of the regression coefficient r, given in Table 8, confirm that the chromatographic parameters R_M^0, m and C_0 can be successfully used to evaluate the ecotoxicity and, therefore, to predict the biological activity of the studied barbituric acid derivatives.

4. CONCLUSION

Lipophilicity, as one of the most important molecular descriptors of the biological activity of a compound, for selected barbituric acid derivatives was determined using RPTLC in the presence of two organic modifiers and by relevant software packages. It was found that the retention behavior of the studied derivatives is more dependent on the nature of the substituent and to a lesser extent dependent on the applied organic modifier. The polarity of the substituent has dominant effect on the lipophilicity of the tested derivatives. A linear dependence was established between the chromatographic parameters (R_M^0, m and C_0) of the test derivatives and their software values of the partition coefficient, log*P*, as a standard measure of lipophilicity, as well as toxicological parameters. All the obtained results indicate that the chromatographic parameters R_M^0, m and C_0 obtained by RPTLC method can be accurately and reliably applied as alternative molecular descriptors of the biological activity of the studied barbituric acid derivatives.

5. ACKNOWLEDGEMENTS

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ПРОУЧАВАЊЕ ДЕСКРИПТОРА БИОЛОШКЕ АКТИВНОСТИ
ДЕРИВАТА БАРБИТУРНЕ КИСЕЛИНЕ

Сажетак: Деривати барбитурне киселине деценијама представљају фармаколошки значајна једињења. Ефекат који испољавају у централном нервном систему условљен им је присуством пиримидин-трионског прстена и природом супституента у положају 5. Липофилност као један од кључних молекулских дескриптора биолошке активности је за одабране деривате барбитурне киселине одређена експериментално, применом танкослојне хроматографије на обрнутим фазама (RP TLC18 F_{254s}), у два система растварача. Испитиван је утицај природе супституента и примењених органских модификатора на хроматографско понашање проучаваних деривата. Применом одговарајућих софтверских пакета за проучаване деривате барбитурне киселине су израчунате вредности подеоног коефицијента (log*P*) као стандардног мерила липофилности и ефективне концентрације (EC_{50}) као мерила акутне токсичности за различите тест организме. Методом линеарне регресије испитана је зависност између хроматографских параметара као претпостављених мерила липофилности и софтверски добијених параметара биолошке активности проучаваних деривата барбитурне киселине.

Кључне речи: деривати барбитурне киселине, липофилност, токсичност.

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