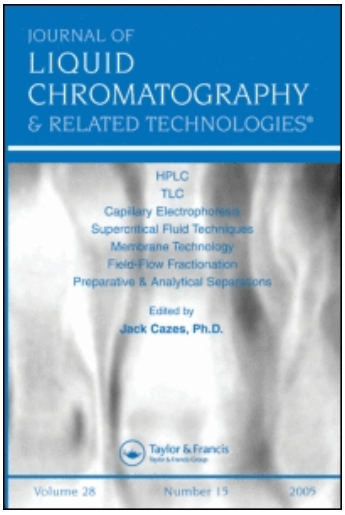

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Lipophilicity of Barbiturates Determined by TLC

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Lipophilicity of Barbiturates Determined by TLC

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ABSTRACT

A series of 13 5,5-disubstituted derivatives of barbituric acid was chromatographed on RP-TLC plates using methanol : water and methanol : buffer mobile phase. A linear relationship was found between R_M values and methanol concentrations in the mobile phase. The retention parameter R_{M0} extrapolated to zero methanol content was related to other lipophilicity parameters such as $\log k_{IAM}$, $\log P$ (calculated), selected biological activity values, and topological indices. Significant correlations were found between these parameters.

Key Words: Lipophilicity; Barbiturates; TLC method; Topological indices.

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INTRODUCTION

Lipophilicity is a molecular property expressing the relative affinity of solutes for an aqueous phase and an organic, water-immiscible solvent. This term is mainly used by medicinal chemists to describe transport processes of a compound in biological systems.[1] Recently, we investigated the retention of several barbituric acid derivatives on immobilized artificial membrane stationary phase and its correlation with biological activity. Good correlation was found between $\log k_{IAM}$ data and such lipophilicity parameters like $\log P$ (experimental and calculated).[2] Also, 13 barbiturates have been separated by reversed-phase thin layer chromatography with mobile phase methanol–water in different volume composition, and we applied the traditional structural descriptors to QSPR and QSAR analysis of these barbiturates.[3] The most accurate prediction of the R_M values of the barbiturates in all the mobile phases investigated, were achieved by use of two-parametric equations employing the dipole moments (or the permittivities) of the mobile phases, and one topological index from among the topological indices ${}^0\chi$, ${}^1\chi$, ${}^0\chi^v$, ${}^1\chi^v$, R, W, A, ${}^1B$, and three parametric equations employing the dipole moments (or the permittivities) of the mobile phases, and two topological indices (I_B and ${}^1\chi$, as well as, I_B and ${}^1\chi^v$), or one electrotopological descriptor (SdssC or SssssC) or Gutman index (M or M^v), and selected partition coefficient.

Since reversed-phase thin-layer chromatography is an alternative method for lipophilicity estimations,[4,5] we were interested in the comparison of other retention parameter R_{M0} for determination of barbiturates lipophilicity and its usefulness in QSAR studies. The results were also compared with those obtained with the use of selected topological indices.

EXPERIMENTAL

Chemicals

5,5-Disubstituted barbituric acid derivatives investigated (Table 1) were commercial samples obtained from different drug manufacturers. The components of mobile phases were obtained from POCh (Gliwice, Poland).

Partition Thin Layer Chromatography

Thin-layer chromatography was performed on TLC aluminium sheets 20×20 cm RP-18 F_{254s} (Merck, Darmstadt, No. 10559). The mixtures of methanol–water (mw) and methanol–Bates–Bower borate buffer solution

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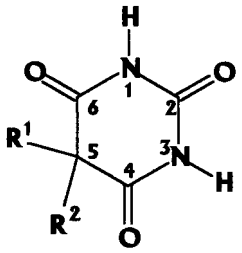
Table 1. Structure and names of the investigated 5,5-disubstituted barbituric acid derivatives.



Compound no.	C5 substituents of barbituric acid	Drug name
1	5,5-diethyl	Barbital
2	5-ethyl-5-(1-methylbutyl)	Pentobarbital
3	5-ethyl-5-*n*-pentyl	
4	5-ethyl-5-*n*-octyl	
5	5-ethyl-5-sec-butyl	Butabarbital
6	5-ethyl-5-isopentyl	Amobarbital
7	5-ethyl-5-(4,4-dimethylhexyl)	
8	5-ethyl-5-(3-methylcyclohexyl)	
9	5-ethyl-5-phenyl	Phenobarbital
10	5-allyl-5-isopropyl	Aprobarbital
11	5-allyl5-isobutyl	Butalbital
12	5-allyl-5-sec-butyl	Talbutal
13	5-allyl-5-(2-cyclopentenyl)	Cyclopal

(pH = 8,35, mb) were used as the mobile phases. The methanol content was varied by 5% volume from 40% to 100%.

The ethanol solutions (1%, w/v) of the investigated compounds were applied on the start line with a Hamilton syringe (10 μL). The chromatograms were developed on 12 cm distance at 21 ± 1°C. After development and drying, the spots were visualized with the UV light (254 nm). The chromatograms were run in duplicates. The R_F values were the mean values that were used for calculation of R_M parameters according to the expression:

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

The R_M values were extrapolated to the zero methanol concentration (R_{M0}) using the expression:[6,7]

$$R_M = R_{M0} + bC \quad (2)$$

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where C is the concentration of methanol (in %, v/v) in the mobile phase and b is the change in R_M value due to the 1% increase of methanol content in the mobile phase (associated with the specific hydrophobic surface area).

The relationship between R_{M0} values and slope b was given by the equation:[6,7]

$$R_{M0} = A + Bb \tag{3}$$

The lipophilicity of the investigated compounds, expressed by partition coefficient ($\log P$) was also calculated theoretically ($\log P_c$) using the Prolog V. 5.1 program.[8] The parameters R_{M0} and b were correlated with these values according to the expressions:

$$R_{M0} = A_1 + B_1 \log P_c \tag{4}$$

and

$$\log P_c = A_2 + B_2 b \tag{5}$$

Using the relationship $A_3 + B_3 \log P$ and the values of A_1, B_1, and R_{M0}, the partition coefficient $\mathrm{clog}\, P$ was calculated as

$$\mathrm{clog}\, P = \frac{R_{M0} - A_1}{B_1} \tag{6}$$

Calculations were done using the computer programs Origin 5.0 and Statistica PL 6.0.

RESULTS AND DISCUSSION

Parameters of linear correlations between R_M values of barbiturates and methanol content in the mobile phase methanol : water and methanol : bufer according to Eq. (2) are listed in Tables 2 and 3, respectively. Correlation coefficients for the methanol : water system are slightly better than those for the methanol : buffer mobile phase.

The parameters of lipophilicity are between 0.920–3.566 and 1.141–4.063 for the methanol : water and methanol : buffer system, respectively. In both systems, the same compounds have the highest (compound 7) and the lowest (compound 1) lipophilicity parameters but for some compounds (compounds 3,6; 4,12; and 5,9) the sequence is changed in both systems.

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Table 2. Parameters of linear correlation between R_M values of barbiturates and methanol content in the mobile phase methanol : water acc. to Eq. (2).

Compound no.	R_{M0}	b	n	Correlation coefficient, r	Standard error, s	F-test value
1	0.920 (±0.056)	0.018 (±0.001)	12	−0.991	0.075	540
2	1.957 (±0.058)	0.026 (±0.001)	12	−0.996	0.046	1,122
3	1.984 (±0.041)	0.026 (±0.001)	10	−0.998	0.024	2,555
4	3.514 (±0.085)	0.041 (±0.001)	8	−0.998	0.035	1,411
5	1.661 (±0.046)	0.024 (±0.001)	12	−0.997	0.037	1,526
6	2.118 (±0.030)	0.029 (±0.000)	11	−0.999	0.022	4,600
7	3.566 (±0.118)	0.043 (±0.002)	8	−0.996	0.049	812
8	2.537 (±0.064)	0.032 (±0.001)	10	−0.997	0.040	1,364
9	1.564 (±0.061)	0.024 (±0.001)	12	−0.994	0.049	910
10	1.476 (±0.056)	0.023 (±0.001)	12	−0.995	0.045	942
11	1.783 (±0.048)	0.026 (±0.001)	13	−0.996	0.045	1,490
12	1.739 (±0.036)	0.024 (±0.000)	12	−0.998	0.029	2,551
13	1.764 (±0.045)	0.024 (±0.001)	12	−0.997	0.036	1,618

The linear relationship was found for R_{M0} and b values with correlation coefficients −0.993 and −0.995 for methanol : water and methanol : buffer systems, respectively:

$$R_{M0(mw)} = -105.871(\pm 3.673)b - 0.888(\pm 0.105)$$
$$n = 13 \;\; r = -0.993 \;\; s = 0.091 \;\; F = 831 \;\; p < 0.0001 \quad (7)$$
$$R_{M0(mb)} = -104.258(\pm 3.0430)b - 0.864(\pm 0.095)$$
$$n = 13 \;\; r = -0.995 \;\; s = 0.082 \;\; F = 1174 \;\; p < 0.0001 \quad (8)$$

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Table 3. Parameters of linear correlation between R_M values of barbiturates and methanol content in the mobile phase methanol : buffer acc. to Eq. (2).

Compound no.	R_{M0}	b	n	Correlation coefficient, r	Standard error, s	F-test value
1	1.141 (±0.059)	0.020 (±0.001)	12	−0.991	0.051	561
2	2.279 (±0.103)	0.030 (±0.001)	10	−0.992	0.063	476
3	2.443 (±0.082)	0.032 (±0.001)	11	−0.994	0.063	774
4	3.707 (±0.126)	0.043 (±0.002)	8	−0.996	0.052	713
5	1.725 (±0.059)	0.023 (±0.001)	11	−0.995	0.041	912
6	2.394 (±0.091)	0.031 (±0.001)	11	−0.993	0.070	598
7	4.063 (±0.192)	0.048 (±0.002)	8	−0.992	0.080	376
8	2.738 (±0.058)	0.034 (±0.001)	11	−0.997	0.044	1,747
9	1.754 (±0.050)	0.026 (±0.001)	12	−0.996	0.043	1,320
10	1.636 (±0.051)	0.024 (±0.001)	12	−0.995	0.044	1,096
11	2.031 (±0.083)	0.028 (±0.001)	12	−0.991	0.071	548
12	2.018 (±0.064)	0.028 (±0.001)	12	−0.994	0.055	897
13	2.015 (±0.063)	0.028 (±0.001)	12	−0.995	0.054	965

These results prove that the investigated barbiturates may be considered as compounds belonging to the same group under the circumstances used.

The $\log P_c$ values calculated by Prolog P V.5.1 program are presented in Table 4.

The sequence of the lipophilicity increase is close to that obtained with R_{M0} values. The respective correlations between $\log P_c$ values and R_{M0} and b values are given by the equations:

$$R_{M0(mw)} = 0.751(\pm 0.099) + 0.865(\pm 0.058) \log P_c$$
$$n = 13 \;\; r = 0.976 \;\; s = 0.173 \;\; F = 221 \;\; p < 0.0001 \qquad (9)$$

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Table 4. Theoretically calculated values of $\log P_c$, $\operatorname{clog} P$ and their differences.

Compound no.	$\log P_c$	$\operatorname{clog} P$ calculated acc. to Eq. (6)		$\Delta(\log P_c - \operatorname{clog} P)$	
		Methanol : water	Methanol : buffer	Methanol : water	Methanol : buffer
1	0.27	0.195	0.236	0.075	0.034
2	1.58	1.393	1.469	0.187	0.111
3	1.80	1.425	1.647	0.375	0.153
4	3.33	3.193	3.016	0.137	0.314
5	1.07	1.052	0.869	0.018	0.201
6	1.58	1.579	1.594	0.001	−0.014
7	2.92	3.253	3.402	−0.333	−0.482
8	1.92	2.065	1.966	−0.145	−0.046
9	0.91	0.940	0.900	−0.030	0.010
10	0.72	0.837	0.772	−0.117	−0.052
11	1.23	1.192	1.200	0.038	0.030
12	1.23	1.141	1.186	0.089	0.044
13	0.88	1.170	1.183	−0.290	−0.303

$$\log P_c = -1.699(\pm 0.291) - 115.349(\pm 10.224)b$$
$$n = 13 \;\; r = -0.959 \;\; s = 0.253 \;\; F = 127 \;\; p < 0.0001 \qquad (10)$$

for methanol : water mobile phase, and:

$$R_{M0(mb)} = 0.923(\pm 0.114) + 0.923(\pm 0.067) \log P_c$$
$$n = 13 \;\; r = 0.972 \;\; s = 0.198 \;\; F = 191 \;\; p < 0.0001 \qquad (11)$$
$$\log P_c = -1.706(\pm 0.309) - 105.372(\pm 9{,}876)b$$
$$n = 13 \;\; r = -0.955 \;\; s = 0.266 \;\; F = 114 \;\; p < 0.0001 \qquad (12)$$

for methanol : buffer mobile phase.

It was affirmed that strong correlation exists between $\log P_c$ and b values, as well as, between R_{M0} and b values.

In earlier investigations,[3] we calculated selected traditional topological indices based on connectivity: Randic ($^0\chi$, $^1\chi$, $^2\chi$, $^0\chi^v$, $^1\chi^v$, $^2\chi^v$), Gutman (M, M^v), Pyka (χ^v_{012}, $\mathbf{A_{012}}^v$), on distance matrix: Rouvray (R), Wiener (W), Balaban (I_B), and Pyka (A, ^0B, ^1B, C, D), as well as, the sums of electro-topological states: SdO, SdssC, $SsCH_3$, SssNH, and SssssC in the molecules of barbituric acid derivatives investigated in this work.

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Table 5. Comparison of linear correlations ($Y = A + BX$) between some biological properties of barbiturates and different lipophilicity parameters determined and taken from the literature.

Compound no.	Y	X	A	B	Correlation coefficient, r
1–3,6,9–11	$\log 1/c$[a]	$R_{M0(mw)}$	0.216 (±0.265)	1.269 (±0.153)	0.965
		$R_{M0(mb)}$	0.179 (±0.194)	1.114 (±0.097)	0.982
		$\log k_{IAM}$[2]	1.855 (±0.085)	1.288 (±0.158)	0.964
		$\log P$[9]	0.814 (±0.176)	0.988 (±0.108)	0.972
		$\log P_c$[2]	1.248 (±0.109)	0.958 (±0.086)	0.980
		^1B	6.984 (±0.693)	−11.088 (±1.652)	−0.949
1,2,6,9–11	$\log 1/c$[b]	$R_{M0(mw)}$	−0.023 (±0.211)	1.551 (±0.126)	0.987
		$R_{M0(mb)}$	−0.124 (±0.294)	1.409 (±0.153)	0.977
		$\log k_{IAM}$[2]	1.983 (±0.083)	1.653 (±0.172)	0.979
		$\log P$[9]	0.638 (±0.244)	1.283 (±0.159)	0.971
		$\log P_c$[2]	1.210 (±0.200)	1.243 (±0.174)	0.963
		χ^v_{012}	−3.356 (±0.592)	1.025 (±0.103)	0.981
1,2,5,6,9–12	$\log 1/c$[c]	$R_{M0(mw)}$	2.474 (±0.238)	0.649 (±0.142)	0.835
		$R_{M0(mb)}$	2.391 (±0.251)	0.617 (±0.133)	0.840
		$\log k_{IAM}$[2]	3.290 (±0.063)	0.760 (±0.132)	0.887
		$\log P$[9]	2.672 (±0.174)	0.593 (±0.115)	0.864
		$\log P_c$[2]	2.923 (±0.126)	0.587 (±0.112)	0.868
		$^o\chi^v$	−0.566 (±0.648)	0.331 (±0.070)	0.888

[a]c is concentration causing 50% inhibition of division of Arbacia egg cells at pH 8.[9]
[b]Data for barbiturate inhibition of rat brain oxygen consumption.[9]
[c]c is a molar concentration of barbiturate causing hypnosis (compiled in and cited after[10]).

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In this work, we affirmed that the $R_{M0(mw)}$ and $R_{M0(mb)}$ values were best correlated with topological indices based on an adjacency matrix ${}^0\chi$, ${}^1\chi$, χ_{012}, ${}^0\chi^v$, ${}^1\chi^v$, and χ^v_{012}, as well as, distance matrix R, W, A, ${}^1B$, and D ($r \geq 0.96$). For example:

$$R_{M0} = -3.941(\pm 0.305) + 0.608(\pm 0.031) \times {}^0\chi^v$$
$$n = 13 \;\; r = 0.9862 \;\; s = 0.131 \;\; F = 391 \;\; p < 0.0001 \quad (13)$$
$$R_{M0(mb)} = -4.068(\pm 0.388) + 0{,}647(\pm 0.039) \times {}^0\chi^v$$
$$n = 13 \;\; r = 0{,}9805 \;\; s = 0{,}167 \;\; F = 273 \;\; p < 0.0001 \quad (14)$$

where ${}^0\chi^v$ is Randic index of 0-order.[3]

Table 5 summarizes the comparisons of correlations obtained using our data with other parameters of lipophilicity and, also, with selected biological properties of the investigated barbiturates.

The results presented confirm conclusions of other authors about the possibility of correlations of chromatographic parameters of barbiturates with their lipophilicity and biological activity.[2,11–18] On the other hand, various topological indices were also well correlated with their retention parameters, lipophilicity, and biological activity.[12,19–24] Recently, excellent reviews on advances on the role of topological indices in drug discovery research[25] and application of topological indices in TLC[26] also appeared.

The R_{M0} values obtained by RP-TLC and selected topological indices (${}^1B$, χ^v_{012}, ${}^0\chi^v$) are compatible with other lipophilicity parameters and, sometimes, are better correlated with biological activity of barbiturates than $\log k_{IAM}$ data or $\log P$ determined or theoretically calculated [cf. Table 5, Eqs. (16) and (21)]. Such results are probably due to rather high structural homogeneity of the investigated set of compounds, and correlations are more meaningful. It was demonstrated that such type of correlations are valid only when dealing with series of strictly congeneric compounds.[21,27]

REFERENCES

1. Pliška, V.; Testa, B.; Van de Waterbeemd, H. Lipophilicity: the empirical tool and the fundamental objective. An introduction. In *Lipophilicity in Drug Action and Toxicology*; Pliska, V., Testa, B., Van de Waterbeemd, H., Eds.; VCH: Weinheim, 1996; 1–6.
2. Kepczyńska, B.; Bojarski, J.; Haber, P.; Kaliszan, R. Retention of barbituric acid derivatives on immobilized artificial membrane stationary phase and its correlations with biological activity. Biomed. Chromatogr. **2000**, *14*, 256–260.

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

3. Pyka, A.; Kepczyńska, E.; Bojarski, J. Application of selected traditional structural descriptors to QSPR and QSAR analysis of barbiturates. Indian J. Chem. A **2003**, *42A*, 1405–1413.
4. Mannhold, R.; Dross, K.; Sonntag, Ch. Estimation of lipophilicity by reversed-phase thin-layer chromatography. In *Lipophilicity in Drug Action and Toxicology*; Pliska, V., Testa, B., Van de Waterbeemd, H., Eds.; VCH: Weinheim, 1996; 141–156.
5. Dross, K.; Rekker, R.F.; de Vries, G.; Mannhold, R. The lipophilic behaviour of organic compounds: 3. The search for interconnections between reversed-phase chromatographic data and $\log P_{oct}$ values. Quant. Struct. -Act. Relat. **1999**, *18*, 549–557.
6. Cserháti, T.; Oros, G. Determination of hydrophobicity parameters of antibiotics by reversed-phase chromatography. The effect of support. Biomed. Chromatogr. **1996**, *10*, 117–121.
7. Cserháti, T.; Forgács, E.; Hajós, G. Determination of the lipophilicity of fused-ring nitrogen heterocycles by reversed-phase thin-layer chromatography. The effect of pH. J. Planar Chromatogr.-Modem TLC **1998**, *11*, 64–69.
8. Compudrug Chemistry, Budapest, Hungary.
9. Hansch, C.; Anderson, S.M. The structure-activity relationship in barbiturates and its similarity to that in other narcotics. J. Med. Chem. **1967**, *10*, 745–753.
10. Hansch, C.; Steward, A.S.; Anderson, S.M.; Bentley, D. The parabolic dependence of drug action upon lipophilic character as revealed by a study of hypnotics. J. Med. Chem. **1968**, *11*, 1–11.
11. Plá-Delfina, J.M.; Moreno, J.; Durn, J.; del Pozo, A. Calculation of the gastric absorption rate constants of 5-substituted barbiturates through the Rm values or substituent ΔRm constants in reversed-phase partition chromatography. J. Pharmacokin. Biopharmaceut. **1975**, *3*, 115–141.
12. Wells, M.J.M.; Clark, C.R.; Patterson, R.M. Correlation of reversed-phase capacity factors for barbiturates with biological activities, partition coefficients, and molecular connectivity indices. J. Chromatogr. Sci. **1981**, *19*, 573–581.
13. Cserháti, T.; Bojarski, J.; Fenyvesi, E.; Szejtli, J. Reversed-phase thin-layer chromatography of barbiturates in the presence of soluble β-cyclodextrin polymer. J. Chromatogr. **1986**, *351*, 356–362.
14. Forgács, E.; Cserháti, T. Retention behaviour of some barbituric acid derivatives on a polyethylene-coated silica column. J. Chromatogr. B **1994**, *656*, 233–238.
15. Jandera, P.; Fischer, J.; Effenberger, H. Characterisation of retention in micellar high-performance liquid chromatography and in micellar electrokinetic chromatography using lipophilicity and polarity indices. J. Chromatogr. A **1998**, *807*, 57–70.

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16. Martin-Biosca, Y.; Molero-Monfort, M.; Sagrado, S.; Villanueva-Camañas, R.M.; Medina-Hernández, M.J. Development of predictive retention-activity relationship models of barbiturates by micellar liquid chromatography. Quant. Struct.-Act. Relat. **2000**, *19*, 247–256.
17. Molero-Monfort, M.; Martin-Biosca, Y.; Sagrado, S.; Villanueva-Camañas, R.M.; Medina-Hernández, M.J. Micellar liquid chromatography for prediction of drug transport. J. Chromatogr. A **2000**, *870*, 1–11.
18. Jakab, A.; Schubert, G.; Prodan, M.; Forgacs, E. PCA followed by two-dimensional nonlinear mapping and cluster analysis, versus multilinear regression in QSRR. J. Liq. Chromogr. & Rel. Technol. **2002**, *25*, 1–16.
19. Millership, J.S.; Woolfson, A.D. The relation between molecular connectivity and gas chromatographic retention data. J. Pharm. Pharmacol. **1978**, *30*, 483–485.
20. Bonjean, M.-C.; Luu Duc, C. Connectivité moléculaire: relations dans une Série de Barbituriques. Eur. J. Med. Chem. **1978**, *13*, 73–76.
21. Bojarski, J.; Ekiert, L. Relationship between molecular connectivity indices of barbiturates and chromatographic parameters. Chromatographia **1982**, *15*, 172–176.
22. Ray, S.K.; Basak, S.C.; Raychaudhury, C.; Roy, A.B.; Ghosh, J.J. The utility of information content, structural information content, hydrophobicity and van der Waals volume in the design of barbiturates and tumor inhibitory triazenes. Arzneim.-Forsch. **1983**, *33*, 352–356.
23. Basak, S.C.; Harriss, D.K.; Magnuson, V.R. Comparative study of lipophilicity versus topological molecular descriptors in biological correlations. J. Pharm. Sci. **1984**, *73*, 429–437.
24. Basak, S.C.; Monsrud, L.J.; Rosen, M.E.; Frane, C.M.; Magnuson, V.R. A comparative study of lipophilicity and topological indices in biological correlation. Acta Pharm. Jugosl. **1986**, *36*, 81–95.
25. Estrada, E.; Uriarte, E. Recent advances on the role of topological indices in drug discovery research. Curr. Med. Chem. **2001**, *8*, 1573–1588.
26. Pyka, A. The application of topological indexes in TLC. J. Planar Chromatogr.-Modern TLC **2001**, *14*, 152–159.
27. Biagi, G.L.; Barbaro, A.M.; Sapone, A.; Recanatini, M. Determination of lipophilicity by means of reversed-phase thin-layer chromatography I. Basic aspects and relationship between slope and intercept of TLC equations. J. Chromatogr. A **1994**, *662*, 341–361.

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