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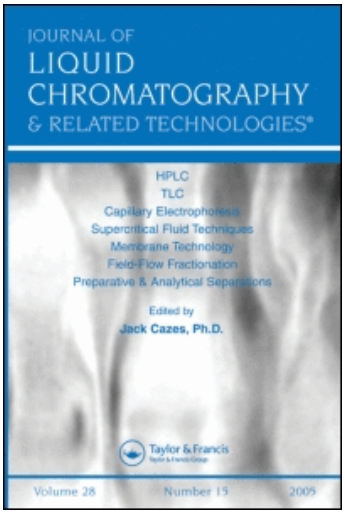

Journal of Liquid Chromatography & Related Technologies

Publication details, including instructions for authors and subscription information:
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Lipophilicity Determination using Both TLC and Calculations

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To cite this Article Kalász, H. , Benkő, B. , Gulyás, Zs. and Tekes, K.(2009) 'Lipophilicity Determination using Both TLC and Calculations', Journal of Liquid Chromatography & Related Technologies, 32: 9, 1342 — 1358
To link to this Article: DOI: 10.1080/10826070902854466
URL: http://dx.doi.org/10.1080/10826070902854466

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Journal of Liquid Chromatography & Related Technologies®, 32: 1342–1358, 2009
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ISSN: 1082-6076 print/1520-572X online
DOI: 10.1080/10826070902854466

Lipophilicity Determination using Both TLC and Calculations

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Abstract: Lipophilicity of four different groups of organic compounds was both measured and calculated. Measurements were done using reversed-phase thin-layer chromatography and lipophilicity was considered as the $R_{M,0}$ values of their R_M versus the percentage of the organic modifier. Calculation was performed using a recent version of the Pallas program of CompuDrug, Inc.

Between $R_{M,0}$ and logP, a surprising deviation was found in case of cyasterone having an extra ring. Other ecdysteroids gave a well arranged group determining a straight line.

RP-TLC-measured lipophilicity values of about 30 phenylalkyl compounds also showed good correlation with those of the calculated logP values. Deviations were found in the case of J-508 (having an indol ring instead of a phenyl ring). Positive differences were found in cases of para-halogen substituted compounds, where the calculated values were higher than those predicted by the corresponding straight line of the experimentally found $R_{M,0}$ versus calculated logP.

$R_{M,0}$ values versus calculated logP series of dermorphine derivatives were also gathered in a cluster. The consequence of consistent substitution gave a larger impetus to lipophilicity experimentally than by calculation.

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Experimental determination of $R_{M,0}$ values of pyridinium aldoximes was not possible using a reversed-phase stationary phase. Calculated hydrophilicity did not correlate with logP.

Keywords: Lipophilicity, Pallas program, Reversed-phased chromatography, Thin-layer chromatography

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INTRODUCTION

Lipophilicity plays a crucial role in the fate of xenobiotics in the body. Lipophilic/hydrophilic character essentially influences the processes of absorption, distribution, metabolism, and excretion, with special emphasis on penetration of xenobiotics through the blood-brain-barrier, blood-placenta-barrier, and the blood-testis-barrier. Only lipophilic compounds have unlimited access to the brain; other, hydrophilic substances, have only limited penetration,[1] if any. Even this limited penetration is due to carriers such as special transporters of endogenous compounds.

The lipophilic character of any drug may essentially influence their drug-receptor interactions, as was stated in the classical works of Overton,[2,3] Meyer,[4,5] Baum,[6] Ferguson,[7] Collander,[8,9] Zahradnik,[10] and Hemker.[11]

Hansch et al.[12,13] introduced the concept of measurable lipophilicity thereby opening the way for the determination and calculation of numerical values. For a long time, the shaken flask procedure was considered the standard reliable reference procedure for logP, i.e., the octanol/water water partition coefficient. However, the shaken flask procedure was a time- and substance-consuming method, and logP was affected by the purity and stability of substances. Concentration dependence of mass balance[14] posed a further problem.

High-performance liquid chromatography was applied to determine lipophilicity by Nahum and Horváth.[15] Retention characteristics of a given compound were approximated to a 0% organic modifier, and this parameter was accepted as a mirror of the lipophilicity of the sample compound. Valkó et al. determined lipophilicity by various reverse-phase and other HPLC columns and evaluated its possible relationship to molecular behaviour.[16]

Thin-layer chromatography had various advantages over the column techniques. The introduction of R_M values by Boyce and Milborrow[17] made it possible to apply TLC for lipophilicity determination by using a liquid paraffin impregnated silica gel matrix. Biagi et al.[14,18,19] widely used reversed phase thin-layer chromatography for the experimental determination of lipophilicity.

This paper gives an account of how the data of reversed-phase thin-layer chromatography can be completed using computer-based (*in silico*) calculations.

EXPERIMENTAL

Lipophilicity determination was performed using the planar chromatographic techniques in our earlier publications. Chromatographic results were obtained using TLC silica gel impregnated with liquid paraffin when migrations of various ecdysteroids[20] and phenylalkylamines[21] were determined. Data of R_M values on dermorphine related oligopeptides were extracted from the report of Biagi et al.,[14] and their experiments were done on Silica gel G layers impregnated with Silicone DC 200 (350cS). Hydrophilicity indices were determined for pyridinium aldoximes as they did not show any migration on paraffin-coated silica layers.[22] JATE compounds were supplied by Chinoin Chemical Works, Budapest (present name is Chinoin-Sanofi Ltd. Budapest, Hungary), and K-compounds were kindly given by Dr. Kamil Kuca (University of Defence, Hradec Kralove. Czech Republik), while ecdysteroids were isolated by Prof. Dr. Mária Báthori (Department of Pharmacognosy, University of Szeged, Hungary). Details on isolation and the most important physico-chemical characteristics of ecdysteroids were detailed in her earlier publications.[23,24,25]

Calculation of logP and total polar surface area (TPSA) values were done using the Prolog Program of Pallas software of CompuDrug International, Inc. (Sedona, AZ, USA).[26,27]

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RESULTS

Lipophilicities of various drugs and drug candidates were determined using both thin-layer chromatography and *in silico* (computer assisted calculation) methods.

$R_{M,0}$ and logP values of ecdysteroids show a wide variety. Cyasterone showed an extremely high experimental $R_{M,0}$ value as a consequence of its extra ring at the end of the side chain. Positive deviation in $R_{M,0}$ value was shown in the case of 2-deoxy compounds, indicating their more powerful experimental influence than expected by calculation. The number of hydroxyl groups on the steroid structure was determined both experimentally and by calculation (Table 1 and Figure 1).

Phenylalkylamines were subjected to reversed-phase TLC using RP-TLC plates. Determined $R_{M,0}$ values mirrored well the distributional characteristics of the compounds (Table 2). The experimentally determined values showed similarities to those of the calculated ones; however, experimental $R_{M,0}$ versus calculated logP of JATE-508 gave an odd location (Figure 2a) as J-508 has an indol ring instead of a phenolic one. Deviation from the straight line was found in another few cases only, caused by the essential structural differences between these compounds

Table 1. Total polar surface area, chemical structure, determined $R_{M,0}$ (R_M values were determined, then approximated to $R_{M,0}$) and calculated logPs of certain selected ecdysteroids

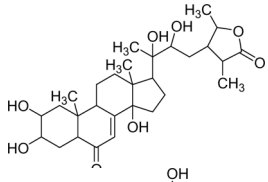
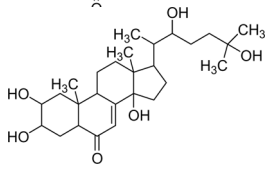
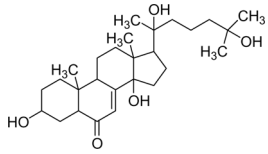
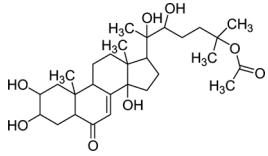
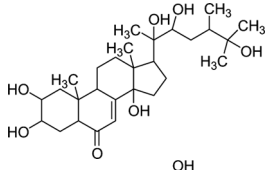
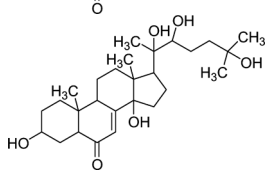
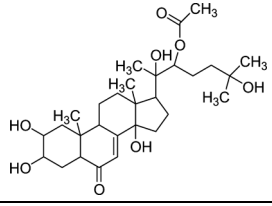
Compound	TPSA (Å^2)	Chemical structure	$R_{M,0}$ (det. calc. 0%)	logP (calc.)
Cyasterone	144.52		6.77	1.38
22-Deoxy-20-hydroxyecdysone	118.22		2.35	2.14
2-Deoxyecdysone	97.99		2.10	3.29
Vitocosterone E	144.52		1.97	2.29
Makisterone A	138.45		1.77	2.01
2-Deoxy-20-hydroxyecdysone	118.22		1.74	2.40
20-Hydroxyecdysone-22-acetate	144.52		1.45	2.29

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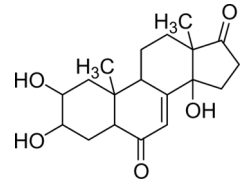
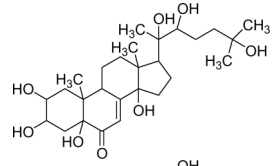
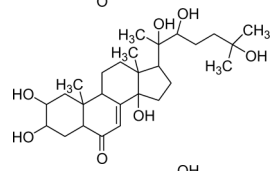
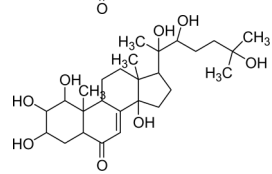
Table 1. Continued

Compound	TPSA (Å^2)	Chemical structure	$R_{M,0}$ (det. calc. 0%)	logP (calc.)
Rubrosterone	94.83		0.80	0.96
Polypodine B	158.68		0.70	1.48
20-Hydroxyecdysone	138.45		0.65	1.92
Integristerone	158.68		0.44	1.52

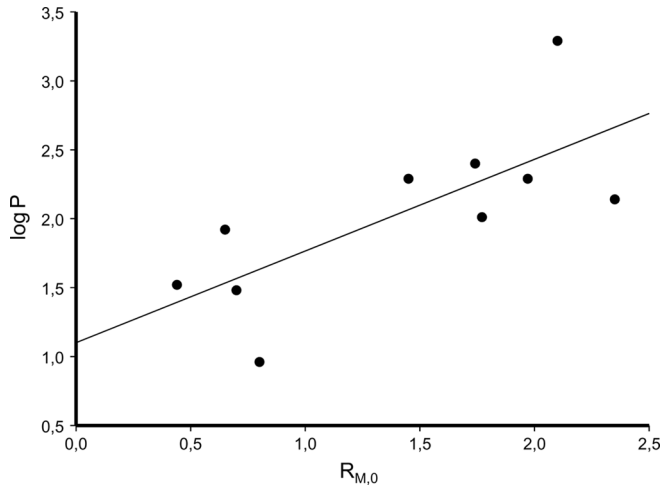


Figure 1. $R_{M,0}$ versus logP relationships of ecdysteroids (without giving the data point for cyasterone).

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Table 2. Total polar surface area, chemical structure, determined $R_{M,0}$ (R_M values were determined, then approximated to $R_{M,0}$) and calculated logPs of some phenylalkylamines

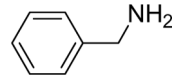
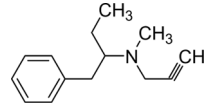
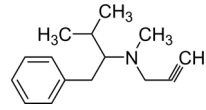
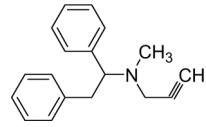
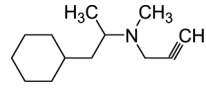
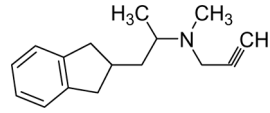
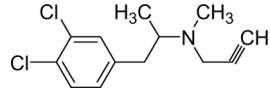
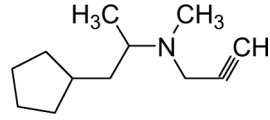
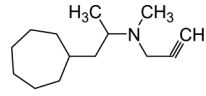
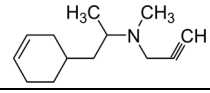
Compound	TPSA (Å^2)	Chemical structure	$R_{M,0}$ (det. calc. 0%)	logP (calc.)
Benzylamine	26.02		1.089	0.56
JATE-501	3.24		3.215	3.29
JATE-502	3.24		3.400	3.56
JATE-504	3.24		3.400	3.86
JATE-505	3.24		3.140	3.89
JATE-508	3.24		1.914	6.07
JATE-510	3.24		2.461	4.25
JATE-511	3.24		2.761	3.49
JATE-513	3.24		3.675	4.39
JATE-514	3.24		2.804	3.67

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Table 2. Continued

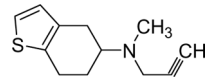
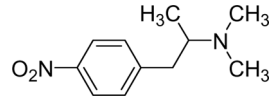
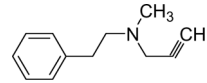
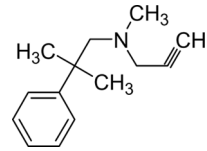
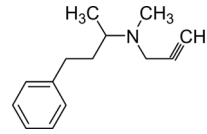
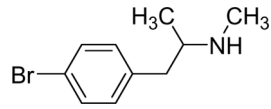
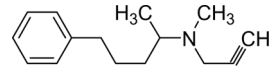
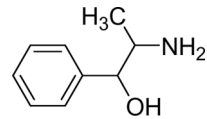
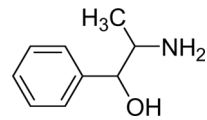
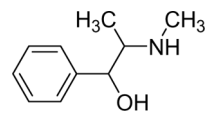
Compound	TPSA (Å^2)	Chemical structure	$R_{M,0}$ (det. calc. 0%)	logP (calc.)
JATE-515	3.24		2.253	2.26
TZ-81/2	49.06		2.308	2.46
TZ-650	3.24		2.119	2.40
TZ-996	3.24		2.404	3.08
TZ-1062/c	3.24		2.445	3.29
V-111	12.03		3.109	2.97
U-1520	3.24		2.857	3.76
nor-Pseudoephedrine	46.25		1.145	0.54
nor-Ephedrine	46.25		1.128	0.54
Ephedrine	32.26		1.529	1.01

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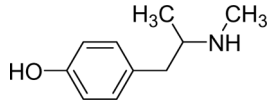
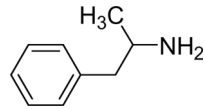
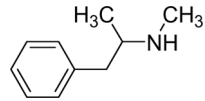
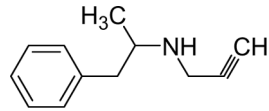
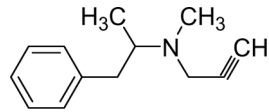
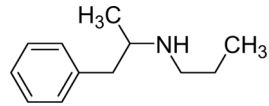
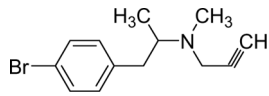
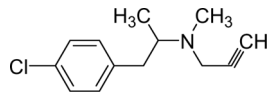
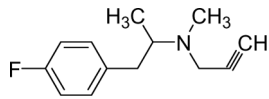
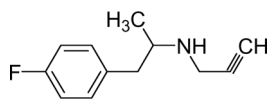
Table 2. Continued

Compound	TPSA (Å^2)	Chemical structure	$R_{M,0}$ (det. calc. 0%)	logP (calc.)
p-Hydroxy-methamphetamine	46.25		0.727	0.27
Amphetamine	26.02		2.106	1.55
Methamphetamine	12.03		1.599	2.10
nor-Deprenyl	12.03		1.594	2.45
Deprenyl	3.24		1.417	2.85
Propylamphetamine	12.03		2.330	3.11
p-Br-deprenyl	3.24		2.694	3.59
p-Cl-deprenyl	3.24		2.519	3.55
p-F-deprenyl	3.24		1.886	3.04
p-F-nordeprenyl	12.03		1.639	2.63

(*Continued*)

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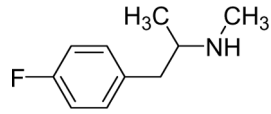
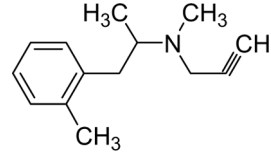
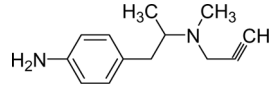
Table 2. Continued

Compound	TPSA (Å^2)	Chemical structure	$R_{M,0}$ (det. calc. 0%)	logP (calc.)
p-F-methamphetamine	12.03		2.240	2.24
o-Methyldeprenyl	3.24		2.353	3.13
p-Amino-deprenyl	29.26		1.046	2.16

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(Figure 2b). A group of some p-halogenated phenolic compounds showed a deviation from $R_{M,0}$ versus logP straight line.

Dermorphine related oligopeptides were also subjected to reversed-phase TLC. Their $R_{M,0}$, total polar surface area and chemical structures are given in Table 3. All of them gave regular RP-TLC behaviour, and the comparison of their experimentally determined and *in silico* calculated values did not deviate from the straight line (Figure 3).

$R_{M,0}$ of pyridinium aldoximes could not be directly determined. None of the standard compounds migrated along the reversed-phase surface, nor on RP-TLC silica of Merck, and on paraffin-impregnated TLC silica. As reversed-phase plates serve for the determination of lipophilicity, we focused our effort on the determination of the "reversed-reversed" characteristic, that is, hydrophilicity. Straight phase chromatography was done on naked silica, and the experimental determination resulted in hydrophilicity (Table 4). These hydrophilicity versus lipophilicity values indicated opposite trends (Figure 4, negative slope) as in the other reversed-phase $R_{M,0}$ versus logP lines, where positive slopes were obtained.

DISCUSSION

Lipophilicity of any organic compounds may be determined using a wide variety of methods. The overwhelming majority of these methods offered useful information; however, they are not able to handle charged compounds, such as quaternary amines.

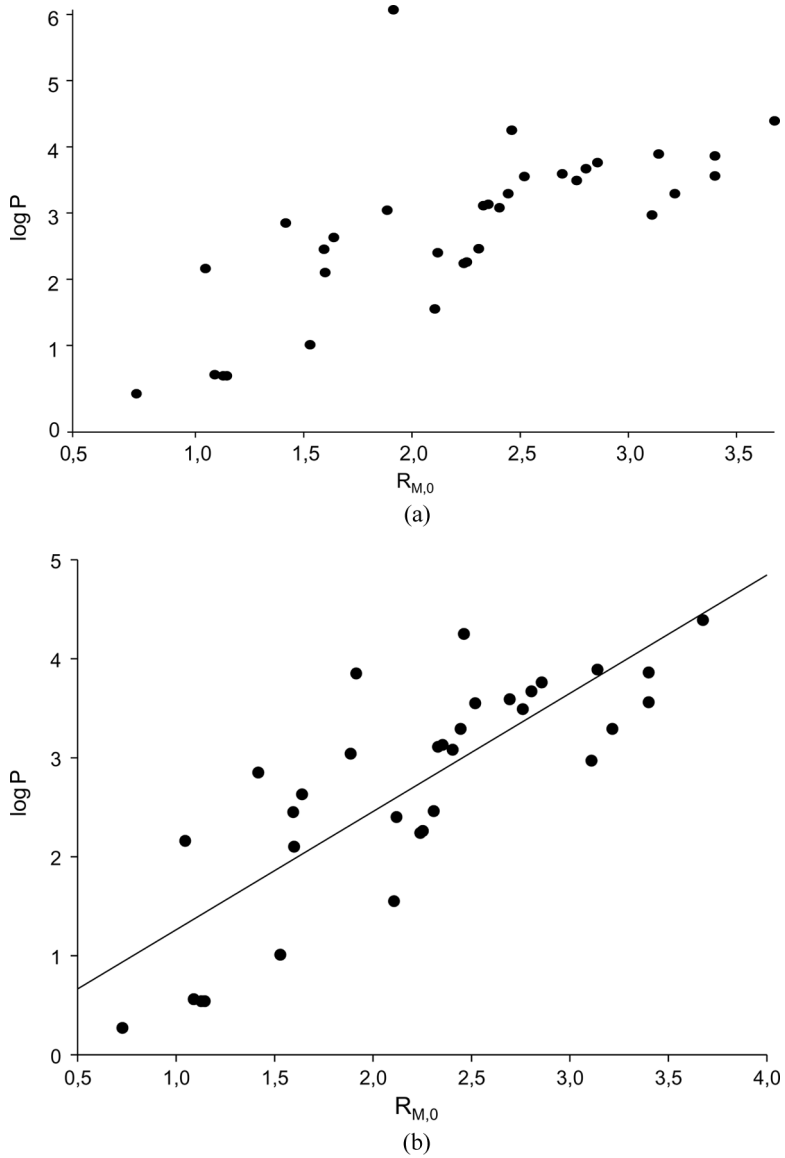

Figure 2. (a) $R_{M,0}$ versus logP relations for phenylalkylamines (with the data for JATE-508), (b) $R_{M,0}$ versus logP relations for phenylalkylamines (without giving the data for JATE-508).

We decided on using thin-layer chromatography for the experimental determination of lipophilicity ($R_{M,0}$). Reversed-phase thin-layer chromatography was used to determine non-polar compounds, and straight-phase

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Table 3. Total polar surface area, chemical structure, determined $R_{M,0}$ (R_M values were determined, then approximated to $R_{M,0}$) and calculated logPs of certain dermorphine derivatives

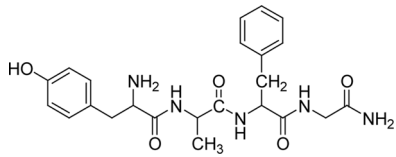
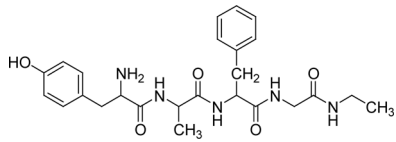
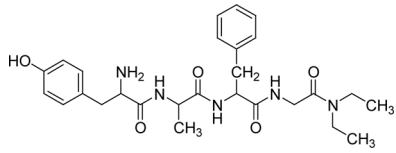
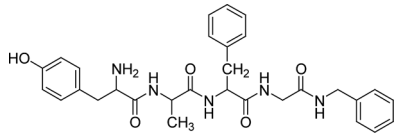
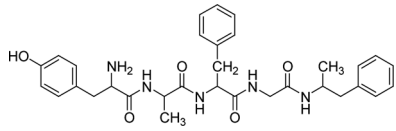
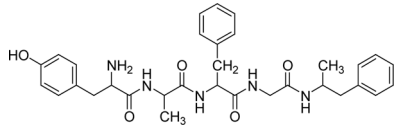
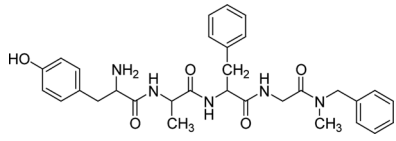
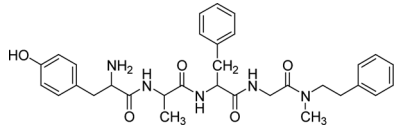
Compound	TPSA (Å^2)	Chemical structure	$R_{M,0}$ (det. calc. 0%)	logP (calc.)
DeM No. 1	176.64		1.22	−0.28
DeM No. 2	162.65		1.38	0.30
DeM No. 3	153.86		1.95	0.86
DeM No. 4	162.65		2.24	1.48
DeM No. 5	162.65		3.09	1.66
DeM No. 6	133.35		3.07	2.22
DeM No. 7	124.76		2.83	1.75
DeM No. 8	153.86		3.00	1.77

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Table 3. Continued

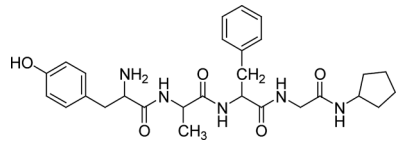
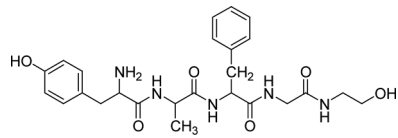
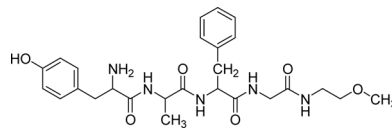
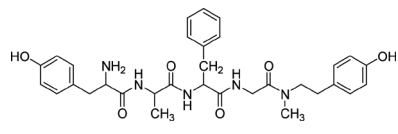
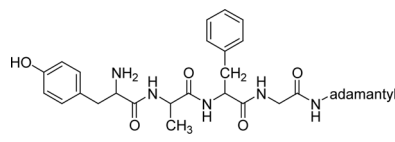
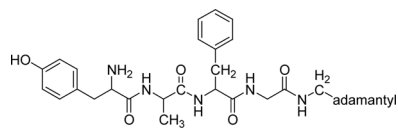
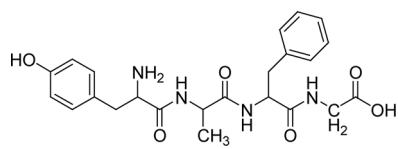
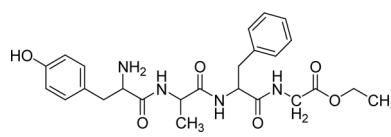
Compound	TPSA (Å^2)	Chemical structure	$R_{M,0}$ (det. calc. 0%)	logP (calc.)
DeM No. 9	162.65		2.30	1.48
DeM No. 10	182.88		1.31	−0.61
DeM No. 11	171.88		1.52	0.02
DeM No. 12	182.88		1.85	1.26
DeM No. 13	162.65		3.73	2.32
DeM No. 14	133.55		4.02	2.42
DeM No. 15	170.85		0.83	0.74
DeM No. 16	159.85		1.41	0.55

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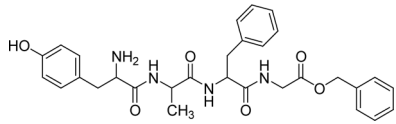
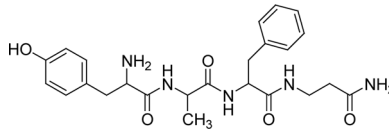
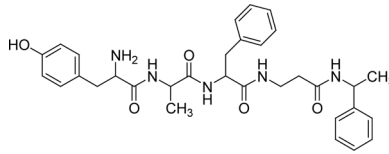
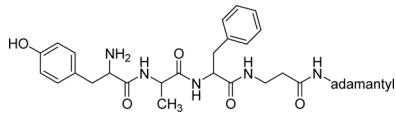
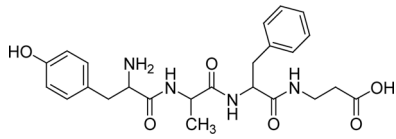
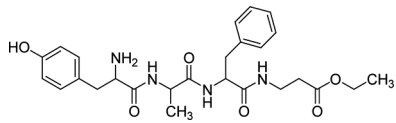
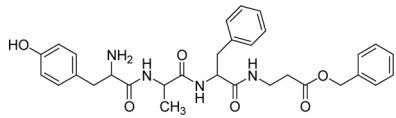
Table 3. Continued

Compound	TPSA (Å^2)	Chemical structure	$R_{M,0}$ (det. calc. 0%)	logP (calc.)
DeM No. 17	159.85		3.13	1.69
DeM No. 18	152.62		1.15	0.10
DeM No. 19	150.62		3.15	2.25
DeM No. 20	162.65		4.06	2.21
DeM No. 21	158.82		0.86	0.10
DeM No. 22	147.82		1.91	1.02
DeM No. 23	147.82		3.09	1.87

thin-layer chromatography was applied when polar organic compounds were determined. Hydrophilicity was determined in this latter case when the compounds did not show any mobility using reversed-phase plates.

The *in silico* method is applied for the calculation of logP based on the functional groups of organic compounds. Several computer based methods are known; however, they are mainly restricted to handle the

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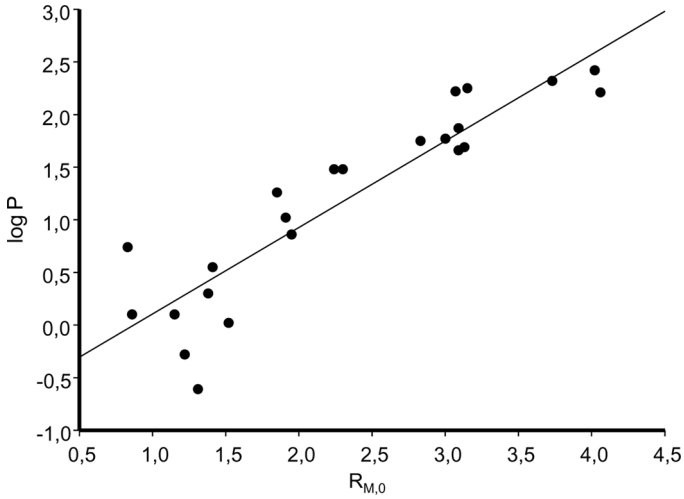

Figure 3. $R_{M,0}$ versus logP relations for dermorphine derivatives.

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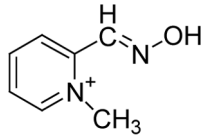
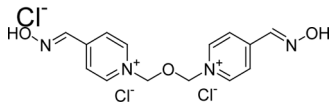
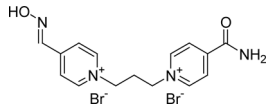
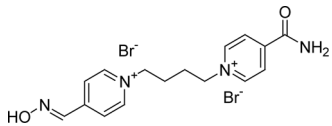
Table 4. Chemical structure, $R_{M,0}$ (R_M values were determined, then approximated to $R_{M,0}$) and calculated logPs of certain selected pyridinium aldoximes

Name	Chemical structure	$R_{M,o}$	logP (combined)
Pralidoxime		0.513	−2.56
Obidoxime		0.953	−2.87
K-27		0.918	−2.84
K-48		1.04	−2.79

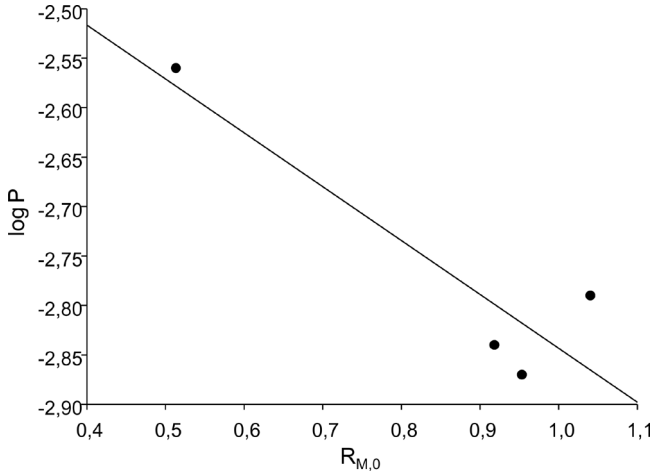


Figure 4. $R_{M,0}$ versus logP relations for pyridinium aldoximes.

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logP of non-ionized organic compounds. Our calculations were done using the Pallas program of CompuDrug Ltd.,[26] which is able to handle all organic molecular fragments and neglects charge. Substitution by halogen is not considered to influence the polar surface, neither in the polar surface area (TPSA) nor in the calculated logP values.[26–28]

CONCLUSIONS

Correlations between the results of experimental determinations (RP-TLC-silica) and computer assisted calculations (*in silico*) indicate acceptability of both methods to such an extent that lipophilicity can be considered to bear definitive biological and pharmacological behaviour. The validity of our conclusions applies to the same group of organic compounds, while other ring systems, odd rings, and quaternary amines alter the results, especially the value of polar surface area. Further experiments and calculations will be needed to establish the hydrophilicity versus logP relationship.

ACKNOWLEDGMENTS

This project was sponsored by the T049492 grant of National Research Fund (OTKA), Budapest, Hungary. Thanks are due to Dr. K. Kuca for supplying the K-compounds, Dr. F. Darvas and CompuDrug International, Inc. for making the use of their softwares possible. Advices of Mr. J. Horváth and Dr. T. Csermely are appreciated.

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Received December 22, 2008
Accepted January 9, 2009
Manuscript 6469E

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