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A TLC Study of the lipophilicity of thirty-two acetylcholinesterase inhibitors - 1,2,3,4-tetrahydroacridine and 2,3-dihydro-1H-cyclopenta[b]quinoline derivatives

Research Article

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Abstract: The lipophilicity of thirty-two novel acetylcholinesterase (AChE) inhibitors - 1,2,3,4-tetrahydroacridine and 2,3-dihydro-1H-cyclopenta[b]quinoline derivatives was studied by thin layer chromatography. The analyzed compounds were chromatographed on RP-18, RP-8, RP-2, CN and NH_2 stationary phases with dioxane – citric buffer pH 3.0 binary mobile phases containing different proportions of dioxane. R_M values for pure water were extrapolated from the linear Soczewiński–Wachtmeister equation and six compounds with known literature log *P* values were used as reference calibration data set for computation of experimental log *P* values.

The obtained results were compared with computationally calculated partition coefficients values (AlogPs, AClogP, AlogP, MlogP, KOWWIN, XlogP2, XlogP3) by PCA and significant differences between them were observed.

Keywords: *Lipophilicity • Calculated partition coefficients • AChE inhibitors • Tetrahydroacridine • Cyclopenta[b]quinoline*

1. Introduction

Alzheimer's disease (AD) is the most frequently occurring form of neurodegenerative disease. It is clinically characterized by a progressive memory loss, disorientation, cognitive dysfunction, personality changes and behavioral disturbances and other cognitive impairments [1,2]. Unfortunately, the etiology of AD is not completely known. Pathogenic mechanisms responsible for cognitive decline in AD include the loss of cholinergic neurotransmission, beta-amyloid cascade, oxidative stress, steroid hormone deficiency and increased level of inflammatory mediators [3]. These facts suggest that AD has different backgrounds against which several research strategies have been developed, including cholinergic and noncholinergic approaches. The current therapeutic options as the first line treatment for AD are acetylcholinesterase (AChE) inhibitors, such as tacrine, galanthamine, huperzine A and donepezil which increase neurotransmission at cholinergic synapses in the brain and reduce the cognitive deficit temporarily [4-6].

Lipophilicity is one of the most important physicochemical properties frequently used in QSAR analysis and it is expressed as either a partition coefficient or its decimal logarithm (log *P*). This parameter can be determinated experimentally by various analytical methods (high performance liquid chromatography - HPLC, spectrophotometric, micellar electrokinetic chromatography MEKC, voltametry, titrimetry), however, in the recent years thin layer chromatography was most frequently used [7-13].

In this study we describe the use of thin layer chromatography(TLC)methodtodeterminethelipophilicity

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of 32 novel AChE inhibitors - 1,2,3,4-tetrahydroacridine (THA) and 2,3-dihydro-1H-cyclopenta[b]quinoline (CPQ) derivatives synthethized according to the procedures previously reported by us [14-18]. The relationship between the concentration of the organic modifier in the mobile phase and the chromatographic properties of the investigated compounds as well as the influence of the substituents on the lipophilicity of THA and CPQ were studied on various stationary phases (RP-18, RP-8, RP-2, CN and NH_2). The lipophilicity values, determinated chromatographically on the tested adsorbents, were compared in a multivariate way with theoretically calculated partition coefficients values obtained by computational methods.

2. Experimental procedure

The studied compounds were synthethized according to the previously described procedures and were of adequate purity [15-18]. The chemical structures of these compounds are presented in Table 1. The reference compounds (literature log *P* values are given in parentheses): acetaminophen (0.5), doxepin (2.4), piroxicam (3.1), opipramol (3.8), nefazodone (5.0) and thioridazine (5.9) were supplied by Sigma-Aldrich (Munich, Germany). Dioxane, methanol and citric buffer pH 3.0 of analytical grade purity were obtained from E. Merck (Darmstadt, Germany).

TLC was performed on precoated RP-18 F_{254}, RP-8 F_{254}, RP-2 F_{254}, CN F_{254} and NH_2 F_{254} (10×20 cm) plates (E. Merck) in horizontal DSII Chambers (Chromdes, Lublin, Poland) under unsaturated (sandwich) conditions at room temperature and dioxane – citric buffer pH 3.0 mixtures were used as mobile phases. The studied compounds were individually dissolved in methanol (0.1 mg mL^{-1}) and applied to the plates (5 µL) as spots with a Desaga AS-30 applicator. The starting points were 5 mm from the bottom edge of the plates and the development was carried out over 9.0 cm. Five mobile phases were investigated in all the cases and the concentrations of the dioxane in the mobile phases (v/v) were: 50, 60, 65, 70 and 75% (RP-18), 50, 60, 65, 70 and 80% (RP-8), 40, 50, 65, 70 and 75% (RP-2), 35, 40, 50, 60 and 70% (CN) and 60, 65, 70, 75 and 80% (NH_2). After the development the plates were air dried at room temperature (22°C) and examined under a 254 nm UV lamp.

All calculations, data handling, visualization and chemometric analysis were performed using GNU R free open-source software (version 2.15.1).

3. Results and discussion

The lipophilicity of the investigated AChE inhibitors was determinated using five stationary phases: RP-18, RP-8, RP-2, CN and NH_2. We have used six reference compounds, of well-known experimental lipophilicity, chosen to fully cover the expected range of log P values of the studied compounds.

Although methanol is one of the most recommended modifiers for lipophilicity estimation it has also been determined that dioxane gives similar results [19]. In preliminary tests we observed that the use of this organic modifier gives significantly better chromatograms and wider linearity range on all tested adsorbents than methanol. We also found that lowering the pH of the mobile phase improves the shape and symmetry of the spots of the analyzed compounds, and for this reason a binary polar mobile phase: dioxane – citric buffer pH 3.0 was selected for all experiments. Stability and reproducibility of the proposed method was sufficient and the variability of the R_F values was about 0.01 on all stationary phases.

For all the compounds and all chromatographic systems, R_M values were calculated using the Bate-Smith and Westall [20] formula:

$$R_M = \log((1- R_F)/R_F) \quad (1)$$

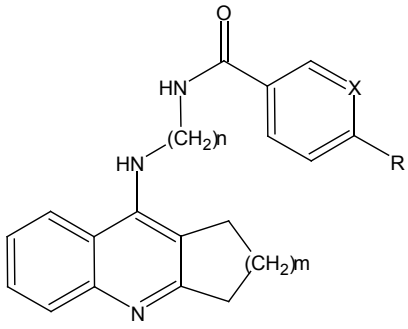
The calculated R_M values were then used for the calculations of R_{M0} values extrapolated to zero percent of dioxane concentration with the Soczewiński–Wachtmeister [21] equation:

$$R_M = R_{M0} + b \cdot C \quad (2)$$

were *C* is the concentration, in volume %, of dioxane in the mobile phase and *b* is the change in R_M caused by the unit of dioxane concentration in the mobile phase and is related to the specific hydrophobic surface area of the compounds.

In order to achieve high accuracy of the lipophilicity estimation, as well as the standardization of the obtained results enabling the appropriate comparison of the determined log *P* values on the different adsorbents, a set of reference compounds was used as a calibration dataset. The six reference compounds (with well-known experimental lipophilicity taken from the *Clarke's* almanac [22]) were analyzed under the same chromatographic conditions as the investigated AChE inhibitors. The estimated R_{M0} values (Table 2) were plotted against the literature log *P* values and the

Table 1. Chemical structures of the investigated compounds.



No	Compound	X	R	n	m
1	6-hydrazino-N-[2-(1,2,3,4-tetrahydroacridin-9-ylamino)ethyl]nicotinamide	N	$NHNH_2$	2	2
2	6-hydrazino-N-[3-(1,2,3,4-tetrahydroacridin-9-ylamino)propyl]nicotinamide	N	$NHNH_2$	3	2
3	6-hydrazino-N-[4-(1,2,3,4-tetrahydroacridin-9-ylamino)butyl]nicotinamide	N	$NHNH_2$	4	2
4	6-hydrazino-N-[5-(1,2,3,4-tetrahydroacridin-9-ylamino)pentyl]nicotinamide	N	$NHNH_2$	5	2
5	6-hydrazino-N-[6-(1,2,3,4-tetrahydroacridin-9-ylamino)hexyl]nicotinamide	N	$NHNH_2$	6	2
6	6-hydrazino-N-[7-(1,2,3,4-tetrahydroacridin-9-ylamino)heptyl]nicotinamide	N	$NHNH_2$	7	2
7	6-hydrazino-N-[8-(1,2,3,4-tetrahydroacridin-9-ylamino)octyl]nicotinamide	N	$NHNH_2$	8	2
8	6-hydrazino-N-[9-(1,2,3,4-tetrahydroacridin-9-ylamino)nonyl]nicotinamide	N	$NHNH_2$	9	2
9	6-hydrazino-N-[2-(2,3-dihydro-1H-cyclopenta[b]quinolin-9-ylamino)ethyl]nicotinamide	N	$NHNH_2$	2	1
10	6-hydrazino-N-[3-(2,3-dihydro-1H-cyclopenta[b]quinolin-9-ylamino)propyl]nicotinamide	N	$NHNH_2$	3	1
11	6-hydrazino-N-[4-(2,3-dihydro-1H-cyclopenta[b]quinolin-9-ylamino)butyl]nicotinamide	N	$NHNH_2$	4	1
12	6-hydrazino-N-[5-(2,3-dihydro-1H-cyclopenta[b]quinolin-9-ylamino)pentyl]nicotinamide	N	$NHNH_2$	5	1
13	6-hydrazino-N-[6-(2,3-dihydro-1H-cyclopenta[b]quinolin-9-ylamino)hexyl]nicotinamide	N	$NHNH_2$	6	1
14	6-hydrazino-N-[7-(2,3-dihydro-1H-cyclopenta[b]quinolin-9-ylamino)heptyl]nicotinamide	N	$NHNH_2$	7	1
15	6-hydrazino-N-[8-(2,3-dihydro-1H-cyclopenta[b]quinolin-9-ylamino)octyl]nicotinamide	N	$NHNH_2$	8	1
16	6-hydrazino-N-[9-(2,3-dihydro-1H-cyclopenta[b]quinolin-9-ylamino)nonyl]nicotinamide	N	$NHNH_2$	9	1
17	4-fluoro-N-[2-(1,2,3,4-tetrahydroacridin-9-ylamino)ethyl]-benzamide	C	F	2	2
18	4-fluoro-N-[3-(1,2,3,4-tetrahydroacridin-9-ylamino)propyl]-benzamide	C	F	3	2
19	4-fluoro-N-[4-(1,2,3,4-tetrahydroacridin-9-ylamino)butyl]-benzamide	C	F	4	2
20	4-fluoro-N-[5-(1,2,3,4-tetrahydroacridin-9-ylamino)pentyl]-benzamide	C	F	5	2
21	4-fluoro-N-[6-(1,2,3,4-tetrahydroacridin-9-ylamino)hexyl]-benzamide	C	F	6	2
22	4-fluoro-N-[7-(1,2,3,4-tetrahydroacridin-9-ylamino)heptyl]-benzamide	C	F	7	2
23	4-fluoro-N-[8-(1,2,3,4-tetrahydroacridin-9-ylamino)octyl]-benzamide	C	F	8	2
24	4-fluoro-N-[9-(1,2,3,4-tetrahydroacridin-9-ylamino)nonyl]-benzamide	C	F	9	2
25	N-[2-(2,3-dihydro-1H-cyklopenta[b]quinolin-9-ylamino)ethyl]-4-fluorobenzamide	C	F	2	1
26	N-[3-(2,3-dihydro-1H-cyklopenta[b]quinolin-9-ylamino)propyl]-4-fluorobenzamide	C	F	3	1
27	N-[4-(2,3-dihydro-1H-cyklopenta[b]quinolin-9-ylamino)butyl]-4-fluorobenzamide	C	F	4	1
28	N-[5-(2,3-dihydro-1H-cyklopenta[b]quinolin-9-ylamino)penthyl]-4-fluorobenzamide	C	F	5	1
29	N-[6-(2,3-dihydro-1H-cyklopenta[b]quinolin-9-ylamino)hexyl]-4-fluorobenzamide	C	F	6	1
30	N-[7-(2,3-dihydro-1H-cyklopenta[b]quinolin-9-ylamino)heptyl]-4-fluorobenzamide	C	F	7	1
31	N-[8-(2,3-dihydro-1H-cyklopenta[b]quinolin-9-ylamino)octyl]-4-fluorobenzamide	C	F	8	1
32	N-[9-(2,3-dihydro-1H-cyklopenta[b]quinolin-9-ylamino)nonyl]-4-fluorobenzamide	C	F	9	1

Table 2. The R_{M0} values and correlation coefficients obtained for reference compounds.

Compound	RP-18		RP-8		RP-2		CN		NH_2	
	R_{M0}	r	R_{M0}	r	R_{M0}	r	R_{M0}	r	R_{M0}	r
Acetaminophen	-0.327	-0.8199	-0.298	-0.7701	-0.295	-0.9062	0.103	-0.9567	1.009	-0.8139
Doxepin	0.875	-0.8173	1.390	-0.9752	1.293	-0.9976	0.971	-0.9490	-3.513	0.7018
Piroxicam	1.946	-0.9864	1.781	-0.9040	1.729	-0.9760	1.082	-0.9494	-3.262	0.9895
Opipramol	1.938	-0.8957	1.974	-0.9939	1.719	-0.9830	1.100	-0.9555	-3.832	0.9568
Nefazodone	1.660	-0.9474	1.965	-0.9861	2.300	-0.9907	1.991	-0.9384	-4.353	0.8938
Thiridazine	2.610	-0.9699	2.397	-0.9521	2.683	-0.9853	1.975	-0.9327	-5.071	0.9119

obtained linear regression equations: $y = 0.4884x - 0.2340$ (r = 0.9058) for RP-18, $y = 0.4557x - 0.0369$ (r = 0.9161) for RP-8, $y = 0.5229x - 0.2321$ (r = 0.9686) for RP-2, $y = 0.3580x - 0.0310$ (r = 0.9716) for CN and $y = -1.0112x + 0.3183$ (r = 0.9047) for NH_2 plates were used for the calculation of the experimental log *P* values of the analyzed compounds.

As shown in Table 3 the relationships between R_M values and the concentration of dioxane in the mobile phase produced sufficient linearity for all the chromatographic systems ($r > 0.79$). The best linearity was observed for the RP-8 and RP-2 stationary phases and the average correlation coefficients were 0.9880 and 0.9676 respectively. It was also observed that the relative lipophilicity (R_{M0}) was different (lower in most cases) than the estimated experimental log *P* when using the reference compounds as a calibration method. This fact confirmed the legitimacy of the determination of lipophilicity of the investigated compounds by the TLC method using a standardization procedure.

It should be pointed out that the comparison of the obtained experimental log *P* values with the theoretical values of partition coefficients (AlogPs, AClogP, AlogP, MlogP, KOWWIN, XlogP2, XlogP3) calculated with the use of the Virtual Computational Laboratory website (www.vcclab.org) shows also noticeable differences (Table 4).

The multivariate comparison of the experimentally obtained values and the coefficients calculated by computational methods (for a correlation matrix see Table 5) was done by Principal Component Analysis (PCA, Fig. 1). This technique is a very efficient way of multivariate data analysis. It is based on finding the linear combinations of the retention values (called principal components), which represent the main trends in the data analysis in context of overall explained evariance. Since these trends are separated and are also not intercorrelated, this technique is very efficient in visualization of multidimensional data in lower-dimensional space, especially as a 2D plot. Additionally,

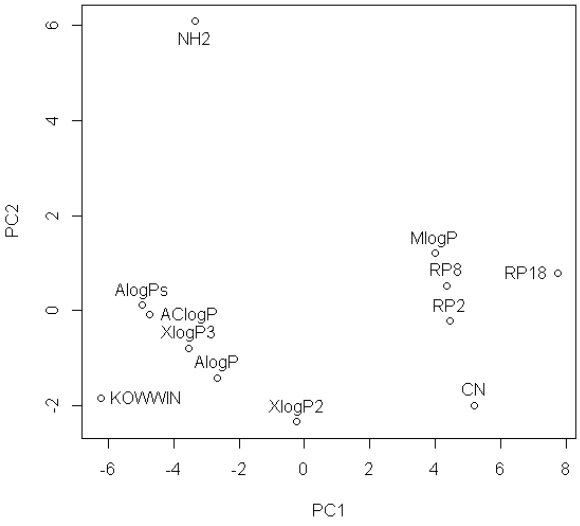


Figure 1. Comparison of the experimental log P values with the computationally calculated coefficients by PCA.

the analysis of the contributions of the particular retention values (TLC systems) to the principal components (called loadings) allows to interpret the main trends of the retention, also in the context of lipophilicity. The unfamiliar readers are referred to [23], where they can find full description of the method with typical chemical applications.

In the current study the PC1 explained 78.35% of the total variance and the first two PC explained 95.04% of the variance. The PCA analysis of the obtained results (Fig. 1) confirmed no significant differences especially between the experimental log *P* values obtained on the RP-8 and RP-2 stationary phases (to a small degree also on the RP-18 and CN stationary phases) and the one calculated coefficient (MlogP). The other algorithms, as well as the chromatographic method using the NH_2 stationary phase, differ appreciably from the above group of methods. Although the low retention of the analyzed compounds on the NH_2 plates makes this method different from the other used adsorbents, these results are more similar to the results obtained

Table 3. R_{M0} (intercept), r (correlation coefficient) and experimental log P values for the investigated AChE inhibitors.

Compound	RP-18			RP-8			RP-2			CN			NH_2		
	R_{M0}	r	log P	R_{M0}	r	log P	R_{M0}	r	log P	R_{M0}	r	log P	R_{M0}	r	log P
1	0.743	-0.9592	2.001	1.245	-0.9971	2.812	0.939	-0.9026	2.239	0.679	-0.8926	1.983	-4.350	0.9178	4.616
2	0.958	-0.9597	2.441	1.250	-0.9964	2.824	0.968	-0.9028	2.295	0.704	-0.9194	2.054	-4.596	0.9084	4.860
3	0.796	-0.9317	2.109	1.255	-0.9944	2.836	1.035	-0.9343	2.424	0.646	-0.9026	1.890	-4.569	0.9105	4.833
4	0.838	-0.9549	2.196	1.291	-0.9996	2.913	1.008	-0.9378	2.372	0.714	-0.9507	2.080	-4.471	0.8950	4.736
5	0.949	-0.9652	2.423	1.100	-0.9880	2.494	1.141	-0.9709	2.627	0.677	-0.9401	1.978	-4.465	0.9475	4.730
6	0.905	-0.9569	2.332	1.229	-0.9876	2.778	1.197	-0.9769	2.734	0.900	-0.9403	2.602	-4.722	0.8707	4.984
7	0.779	-0.9553	2.074	1.439	-0.9828	3.238	1.340	-0.8574	3.007	0.876	-0.9005	2.533	-4.684	0.9588	4.947
8	0.887	-0.9557	2.295	1.655	-0.9792	3.712	1.924	-0.9630	4.123	1.384	-0.9600	3.951	-4.508	0.9743	4.772
9	0.754	-0.9295	2.022	0.999	-0.9927	2.272	0.916	-0.9445	2.195	0.596	-0.8843	1.751	-4.717	0.9510	4.979
10	1.062	-0.9561	2.653	1.041	-0.9981	2.365	1.076	-0.9974	2.502	0.644	-0.9703	1.884	-4.561	0.9538	4.825
11	0.804	-0.9318	2.124	0.947	-0.9950	2.160	1.071	-0.9969	2.493	0.654	-0.8460	1.914	-4.702	0.9555	4.965
12	0.948	-0.9540	2.420	0.982	-0.9970	2.235	1.088	-0.9936	2.525	0.633	-0.9223	1.854	-4.677	0.9556	4.940
13	0.748	-0.9030	2.011	1.091	-0.9909	2.475	1.035	-0.9649	2.424	0.686	-0.9265	2.003	-5.136	0.9385	5.394
14	0.819	-0.9020	2.156	1.281	-0.9839	2.892	1.338	-0.9745	3.004	0.785	-0.8748	2.281	-5.059	0.9374	5.317
15	1.080	-0.9457	2.690	1.539	-0.9856	3.459	1.937	-0.9740	4.150	1.030	-0.9054	2.963	-5.138	0.9419	5.395
16	1.299	-0.9577	3.140	1.777	-0.9592	3.982	1.901	-0.9595	4.080	1.060	-0.9319	3.047	-5.846	0.9064	6.095
17	1.540	-0.9235	3.633	1.867	-0.9824	4.178	1.497	-0.9867	3.307	1.044	-0.9406	3.004	-4.455	0.9920	4.721
18	0.902	-0.9569	2.326	1.746	-0.9892	3.912	1.588	-0.9687	3.481	1.060	-0.9048	3.049	-4.415	0.9838	4.681
19	1.183	-0.9031	2.902	1.582	-0.9843	3.552	1.465	-0.9599	3.245	1.148	-0.9514	3.294	-4.373	0.9948	4.639
20	1.315	-0.9029	3.171	1.662	-0.9880	3.729	1.629	-0.9685	3.559	1.450	-0.9820	4.137	-4.286	0.9958	4.553
21	1.500	-0.8963	3.550	1.944	-0.9707	4.348	2.228	-0.9811	4.705	1.622	-0.9801	4.618	-4.642	0.9357	4.905
22	1.814	-0.8987	4.194	2.177	-0.9766	4.858	2.373	-0.9871	4.982	1.724	-0.9153	4.901	-4.627	0.9389	4.891
23	1.955	-0.9156	4.483	2.539	-0.9677	5.654	2.552	-0.9964	5.325	1.961	-0.9751	5.564	-4.690	0.8400	4.953
24	2.164	-0.9166	4.910	2.274	-0.9979	5.071	2.688	-0.9923	5.585	1.955	-0.8024	5.549	-4.466	0.9415	4.731
25	1.501	-0.9114	3.553	1.661	-0.9926	3.727	1.246	-0.9827	2.827	1.031	-0.9737	2.968	-4.515	0.9603	4.780
26	1.454	-0.9133	3.457	1.679	-0.9945	3.766	1.388	-0.9956	3.098	1.123	-0.9503	3.223	-4.401	0.9437	4.666
27	1.206	-0.9272	2.949	1.513	-0.9910	3.400	1.514	-0.9882	3.340	1.365	-0.9457	3.899	-4.366	0.9660	4.632
28	1.249	-0.9250	3.036	1.733	-0.9945	3.885	1.837	-0.9791	3.957	1.565	-0.9170	4.458	-4.573	0.9895	4.837
29	1.344	-0.9025	3.231	1.970	-0.9911	4.405	1.933	-0.9875	4.141	1.755	-0.9048	4.988	-5.519	0.9819	5.772
30	1.620	-0.9142	3.795	1.976	-0.9945	4.417	1.950	-0.9778	4.174	1.944	-0.8975	5.517	-5.306	0.9828	5.562
31	1.836	-0.9150	4.239	1.924	-0.9931	4.304	2.322	-0.9856	4.885	2.047	-0.9169	5.804	-5.380	0.9818	5.635
32	2.173	-0.9164	4.928	2.263	-0.9807	5.046	2.713	-0.9752	5.633	1.997	-0.7959	5.664	-4.987	0.9208	5.246

by the computational method (high negative impact on PC1) and were considered in all the calculation in this study.

As expected the extension of the aliphatic chain (C_2 - C_9) in the studied AChE inhibitors causes the increase of the lipophilicity of these compounds (Table 3). However, the multivariate comparison of the (only experimental, without computational) lipophilicities of the investigated compounds (PC1 *vs*. PC2 is shown on Fig. 2) showed that the most important factor influencing this parameter is the presence of either a hydrazino or a fluoro substituent. The results of RP18,

Table 4. Theoretical log *P* values obtained by the use of computational methods.

Compound	$AlogP_s$	AClogP	AlogP	MlogP	KOWWIN	XlogP2	XlogP3
1	3.280	3.000	2.700	2.430	2.850	2.140	2.880
2	3.700	3.460	2.760	2.650	3.350	2.490	3.790
3	3.980	3.930	3.340	2.860	3.840	2.850	3.590
4	4.370	4.390	3.800	3.070	4.330	3.210	3.950
5	4.820	4.850	4.260	3.280	4.820	3.570	4.310
6	5.290	5.320	4.710	3.490	5.310	4.140	4.850
7	5.690	5.780	5.170	3.690	5.800	4.710	5.390
8	6.080	6.240	5.630	3.890	6.290	5.280	5.930
9	2.850	2.680	2.240	2.210	2.360	1.570	2.340
10	3.210	3.140	2.310	2.430	2.850	1.930	3.240
11	3.580	3.610	2.890	2.650	3.350	2.280	3.050
12	3.990	4.070	3.340	2.860	3.840	2.640	3.410
13	4.350	4.540	3.800	3.070	4.330	3.000	3.760
14	4.840	5.000	4.260	3.280	4.820	3.570	4.310
15	5.330	5.460	4.710	3.490	5.310	4.140	4.850
16	5.720	5.930	5.170	3.690	5.800	4.710	5.390
17	4.630	4.140	4.410	3.450	4.800	4.070	4.450
18	5.060	4.600	4.470	3.660	5.290	4.430	5.360
19	5.440	5.070	5.050	3.870	5.780	4.780	5.160
20	5.830	5.530	5.510	4.080	6.270	5.140	5.520
21	6.190	5.990	5.960	4.280	6.760	5.500	5.880
22	6.470	6.460	6.420	4.480	7.260	6.070	6.420
23	6.840	6.920	6.880	4.680	7.750	6.640	6.960
24	7.250	7.390	7.330	4.870	8.240	7.210	7.500
25	4.090	3.820	3.950	3.230	4.310	3.500	3.930
26	4.580	4.280	4.010	3.450	4.800	3.860	4.840
27	5.020	4.750	4.590	3.660	5.290	4.210	4.650
28	5.450	5.210	5.050	3.870	5.780	4.570	5.010
29	5.870	5.680	5.510	4.080	6.270	4.930	5.360
30	6.200	6.140	5.960	4.280	6.760	5.500	5.900
31	6.500	6.600	6.420	4.480	7.260	6.070	6.450
32	6.850	7.070	6.880	4.680	7.750	6.640	6.990

RP8, RP2 and CN are quite intercorrelated and they contribute to PC1, increasing its value with increasing R_M values. The retention on NH_2 is not correlated with the rest of the results and it contributes mainly to PC2 – increasing of R_M has a negative impact on its value. Hydrazine derivatives are visibly categorized into one group with a negative impact on the PC1 and PC2 components. Fluoro derivatives, which are characterized by higher lipophilicity, are not grouped but scattered all over the rest of the sector of the graph. In this case PC1 explained 90.11% of the total variance and the first two PC explained 93.81% of the variance. On the other hand the Wilcoxon paired test showed no statistical differences between the lipophilicity of

Table 5. Correlation matrix of experimental and computational lipophilicities of all investigated compounds.

	AlogPs	AClogP	ALOGP	MLOGP	KOWWIN	XlogP2	XlogP3	RP18	RP8	RP2	NH2	CN
AlogPs		0.987	0.993	0.983	0.995	0.986	0.981	0.73	0.85	0.915	0.273	0.88
AClogP	0.987		0.976	0.95	0.976	0.96	0.959	0.695	0.796	0.901	0.342	0.838
ALOGP	0.993	0.976		0.991	0.997	0.994	0.977	0.78	0.881	0.928	0.245	0.904
MLOGP	0.983	0.95	0.991		0.995	0.993	0.978	0.806	0.901	0.926	0.207	0.927
KOWWIN	0.995	0.976	0.997	0.995		0.995	0.984	0.78	0.879	0.928	0.239	0.907
XlogP2	0.986	0.96	0.994	0.993	0.995		0.99	0.804	0.907	0.935	0.193	0.912
XlogP3	0.981	0.959	0.977	0.978	0.984	0.99		0.785	0.892	0.928	0.198	0.889
RP18	0.73	0.695	0.78	0.806	0.78	0.804	0.785		0.881	0.856	0.155	0.863
RP8	0.85	0.796	0.881	0.901	0.879	0.907	0.892	0.881		0.915	0.178	0.909
RP2	0.915	0.901	0.928	0.926	0.928	0.935	0.928	0.856	0.915		0.298	0.925
NH2	0.273	0.342	0.245	0.207	0.239	0.193	0.198	0.155	0.178	0.298		0.244
CN	0.88	0.838	0.904	0.927	0.907	0.912	0.889	0.863	0.909	0.925	0.244	

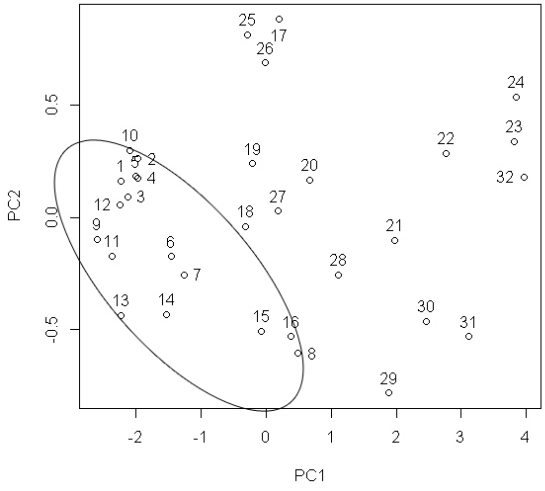


Figure 2. Comparison of lipophilicity of the investigated compounds (experimental log *P* values) by PCA.

THA and CPQ derivatives (V = 1406, p = 0.3058) which may suggest that the biological activity of these compounds is similar to the tacrine AChE inhibitors analogues.

4. Conclusion

Thin layer chromatography method with the use of various stationary phases allows to estimate the experimental lipophilicity of the studied thirty-two acetylcholinesterase inhibitors derivatives of 1,2,3,4-tetrahydroacridine and 2,3-dihydro-1H-cyclopenta[b] quinoline. The best linear correlation between the volume fraction of dioxane and R_M values was obtained on the RP-8 and RP-2 stationary phases. Moreover, the PCA technique shows that the experimental log *P* values obtained on these adsorbents can be compared with a computationally calculated partition coefficient (MlogP). The standardization of the developed TLC method with the use of six reference compounds with well-known experimental lipophilicity significantly improved the estimation of the log *P* values of the investigated compounds.

The obtained results show that there are no significant differences between the lipophilicity of the tested analogues - 1,2,3,4-tetrahydroacridine and 2,3-dihydro-1H-cyclopenta[b]quinoline. The most important factor in this case is the presence of either a hydrazino or a fluoro substituent.

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