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ANALYSIS

A COMPARISON OF THEORETICAL METHODS OF CALCULATION OF PARTITION COEFFICIENTS FOR SELECTED DRUGS

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Abstract: Hundred ninety three drugs of different pharmacological activity were studied. Lipophilicity of a drug is one of the parameters, which influence its biological activity. The *n*-octanol-water partition coefficients were calculated for these compounds by use of different theoretical procedures (Alog*P*s, IAlog*P*, miLogP, Clog*P*, logP_{Kowwin}, and xlog*P*). Particular theoretical partition coefficients were compared with experimental *n*-octanol-water partition coefficients (logP_{exp}) for all studied drugs. It was shown that experimental partition coefficients correlate the best with theoretical partition coefficients calculated by use of logP_{Kowwin} and AlogPs methods. It was shown that it exists the possibility of the prediction of experimental *n*-octanol-water partition coefficients on the basis of logP_{Kowwin}, AlogPs, and ClogP for fifteen drugs (adrenalin, clobazam, 5,5-dimethylbarbituric acid, ethyl nicotinate, fluphenazine, ibuprofen, methyllorazepam, pimozide, prednisolone, promethazine, spironolactone, surital, theophylline, triamterene, and trimethoprim).

Keywords: Drug, lipophilicity, theoretical partition coefficient, experimental logP, QSAR

Lipophilicity of a substance, including drugs, is one of the parameters, which influence its biological activity (1-9). The *n*-octanol-water partition coefficients, usually expressed as logP values, are used as a measure of lipophilicity. LogP values can be computed or determined experimentally. LogP can be determined experimentally by a classical method of measuring partition of organic compounds between a non polar phase and water (10). The importance of the use of partition coefficients in quantitative structure activity relationships (QSAR) is well established for prediction of biological or pharmacological activity of compounds (11-20). Hansch et al. initiated the study of QSAR in 1962, with a publication on plant growth regulation in which bioactivity was successfully coupled with lipophilicities and electronic character of the phenyl substituents (10,21). QSAR play a crucial role in designing new drugs. The possibility to predict drugs biological properties due to their lipophilicity allows the optimization of new drugs structure designs. Measurement of partition coefficients is not as easy as one would expect from their simple definition. The measurement of partition coefficients by equilibration methods is frequently difficult, or even impossible, due to the impurity or instability of compounds, by a strong preference of the compounds for one of the two phases of the system, or by the formation of stable emulsions after shaking. The compatibility of experimental and theoretical approaches to determination of lipophilicity of organic compounds, including drugs, remains a focus of scientific interest (10,11,18).

The aim of this work was the comparison of the experimental *n*-octanol-water partition coefficients with theoretical partition coefficients calculated by use of different theoretical procedures for 193 drugs with different pharmacological activity.

EXPERIMENTAL

The *n*-octanol-water partition coefficients were calculated for the hundred ninety three drugs by use of different theoretical procedures (22-28). Numerical values of the partition coefficients were obtained using the following methods:

AlogPs – this method, for the assessment of *n*-octanol-water partition coefficient, was developed on the basis of neutral network ensemble analysis of 12908 organic compounds. The atom and bond-type E-state indices, the number of hydrogen and non-hydrogen atoms were considered in calculations. A first selection of indices was performed by multiple linear regression analysis, and 75 input parameters were selected. Some of the parameters combined several atom-type or bond-type indices with similar physicochemical properties (23,25).

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IAlogP – this method bases on the set of 238 MolconnZ molecular indices generated from 13000 organic structures with accurately measured logP values. Interactive Analysis, using neutral networks technology to derive a set of 10 fold cross-validated networks, developed the IAlogP predictor (22,23).

ClogP – this method estimates interaction parameters for new fragments; ClogP bases on estimation of these interactions on the well-accepted principles defined by Hammett, so not only is ClogP the most accurate calculation available. but it produces results that are based on established chemical interactions, unlike other programs which are based solely on statistics (23,26)

logP$_{Kowwin}$ – this is an atom-fragment contribution method for *n*-octanol-water logP calculation. This method logP$_{Kowwin}$ bases on data for 13058 organic compounds, for which accurate experimental partition coefficients logP are published (23,27).

xlogP – this is an atom-additive method for n-octanol-water logP calculation. XlogP method includes correction factors to account for some intramolecular interactions; 1831 organic compounds were analyzed by multivariate regression to derive the parameters. After including these correction factors, the final logP is described as:

$$\log P = \sum_i a_i A_i + \sum_j b_j B_j \qquad [1]$$

where a_i and b_j are regression coefficients, A_i is the number of occurrences of the ith atom type, and B_j is the number of occurrences of the jth correction factor identified by this program (23,28)

MILOGP – method for logP prediction developed at Molinspiration (miLogP 2.2) is based on group contributions. These have been obtained by fitting calculated logP with experimental logP for a training set of more than twelve thousand, mostly drug-like molecules (24).

RESULTS AND DISCUSSION

Hundred ninety three drugs with different pharmacological activity were studied. The theoret-

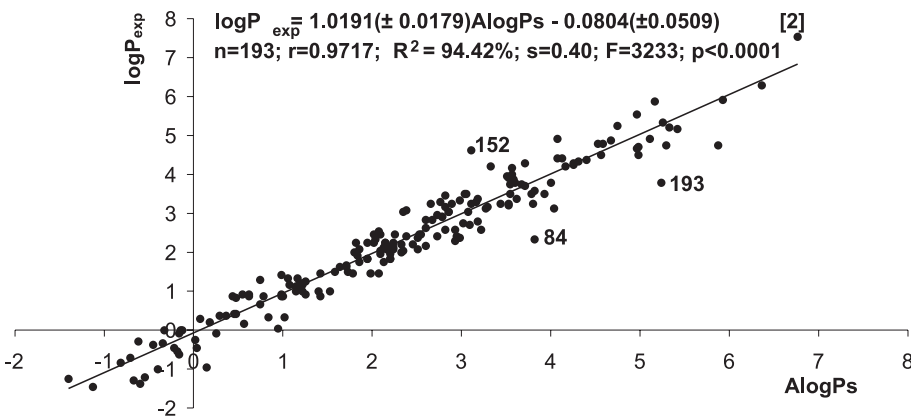

Figure 1. Relationships between the experimental *n*-octanol-water partition coefficients ($\log_{P_{exp}}$) and theoretical AlogPs values.

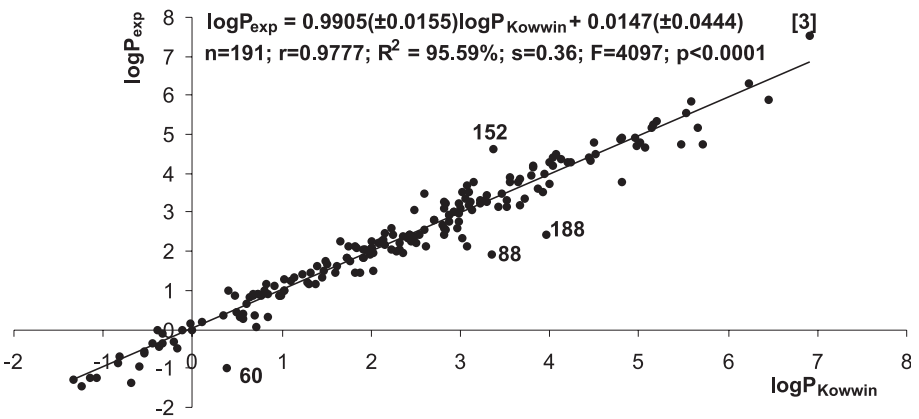

Figure 2. Relationships between the experimental *n*-octanol-water partition coefficients ($\log P_{exp}$) and theoretical $\log P_{Kowwin}$ values.

Table 1. Experimental (10,19,23,29-31) and theoretical partition coefficients (22-28) for examined drugs.

No.	*Drug*	$logP_{exp}$ (10, 19, 23, 29-31)	AlogPs	IAlogP	ClogP	miLogP	$logP_{Kowwin}$	xlogP
1	Adrenalin	-1.37	-0.60	-0.99	-0.69	-0.06	-0.69	0.55
2	Allopurinol	-0.55	-0.18	-0.06	0.63	-0.08	-0.55	0.91
3	5-Allyl-5-(1-methyl-1-butyl)barbituric acid	1.97	2.20	2.26	2.16	2.08	2.36	2.28
4	Alprazolam	2.12	2.23	3.20	2.56	2.29	3.07	4.89
5	Alprendol	3.10	2.38	2.81	2.65	2.58	2.81	2.84
6	Amantadine	2.44	2.53	2.24	2.00	2.65	2.43	2.31
7	Amfetamine	1.76	1.85	1.85	1.74	1.32	1.76	1.76
8	4-Aminosalicylic acid	0.89	0.62	0.66	1.06	0.92	0.98	1.61
9	Amitriptyline	4.92	5.10	5.15	4.85	4.19	4.95	4.93
10	Amobarbital	2.07	1.85	2.06	2.11	1.78	2.00	2.08
11	Amoxicillin	0.87	0.99	-2.21	-1.87	-1.35	0.97	0.03
12	Ampicillin	1.35	1.05	-1.10	-1.20	-0.87	1.45	0.43
13	Androstenedione	2.75	3.02	3.25	2.82	3.06	2.99	3.06
14	Androsterone	3.69	3.71	3.46	3.55	3.43	3.07	4.30
15	Aprobarbital	1.15	1.21	1.15	1.10	1.02	1.38	1.14
16	Atenolol	0.16	0.57	0.23	-0.11	0.72	-0.03	0.46
17	Atropine	1.83	2.20	1.76	1.30	1.77	1.91	1.83
18	Azoperone	3.30	2.76	2.35	3.34	2.88	3.23	3.35
19	Barbital	0.65	0.74	0.57	0.65	0.74	0.60	0.43
20	Barbituric acid	-1.47	-1.12	-1.27	-1.44	-1.48	-1.25	-1.63
21	Betamethasone	1.83	1.95	1.82	1.78	2.06	1.72	1.14
22	Benorylat	2.15	2.60	2.34	2.05	2.61	1.75	2.56
23	Benperidol	3.91	3.52	2.79	3.80	3.41	3.55	3.00
24	Benzyl nicotinate	2.40	2.39	2.00	2.60	2.13	2.35	2.42
25	Bifanazole	4.77	5.29	5.56	4.99	4.97	5.71	5.49
26	Bromazepam	2.05	2.09	2.22	1.70	2.41	1.93	1.79
27	Buthabarbital	1.65	1.70	1.38	1.58	1.49	1.51	1.51
28	Butyl nicotinate	2.27	2.24	2.29	2.35	1.97	2.11	2.06
29	Captopril	0.34	1.02	0.25	0.89	-1.09	0.84	0.64
30	Carbamazepine	2.45	2.10	2.76	2.38	2.84	2.25	2.30
31	Chloramphenicol	1.14	1.15	0.61	1.28	0.73	0.92	0.69
32	Chloropropamide	2.27	2.15	2.24	2.35	2.21	2.01	1.80
33	Chlorothiazide	-0.24	0.01	0.34	-0.29	0.02	-	-0.50
34	Chlorpromazine	5.35	5.26	5.40	5.30	5.03	5.20	4.92
35	Chlorprothixene	5.18	5.42	5.07	5.48	5.43	5.14	5.19
36	Cimetidine	0.40	0.48	0.41	0.38	0.14	0.57	0.74
37	Clobazam	2.12	2.13	2.20	2.44	2.55	1.82	2.28
38	Clofibric acid	2.57	2.81	2.93	2.82	2.73	2.84	2.58
39	Clomipramine	5.19	5.33	5.09	5.92	4.82	5.65	4.65
40	Clonazepam	2.41	2.73	2.59	2.38	2.77	2.53	2.67
41	Clozapine	3.23	3.80	3.20	3.71	4.14	2.84	3.74
42	Codeine	1.19	1.20	1.03	0.98	1.41	1.28	1.08
43	Corticosterone	1.94	2.09	3.47	2.32	1.88	1.99	1.67
44	Cortisone	1.47	1.99	2.46	1.29	1.43	1.81	0.10
45	3-Cyanopyridine	0.36	0.36	0.57	0.27	0.46	0.35	0.49
46	Cyclopal	1.51	1.58	1.19	1.16	1.19	2.03	1.42
47	Dehydroepiandrosterone	3.23	3.53	2.29	3.07	3.24	2.98	3.04
48	N-Demethyldiazepam	2.93	2.79	2.90	3.02	2.86	2.87	2.78
49	Demoxepam	1.41	0.99	2.35	1.07	1.23	1.23	2.42
50	Desipramine	4.90	4.07	4.10	4.47	3.92	4.80	3.79
51	Desmethyldiazepam	2.93	2.79	2.90	3.02	2.86	2.8	2.78

Table 1. cont.

No.	*Drug*	$logP_{exp}$ (10, 19, 23, 29-31)	AlogPs	IAlogP	ClogP	miLogP	$logP_{Kowwin}$	xlogP
52	Dexamethasone	1.83	1.95	2.58	1.78	2.06	1.72	1.14
53	5,5-Diallylbarbituric acid	1.15	1.07	0.92	0.75	0.81	1.31	0.84
54	Diazepam	2.82	2.60	2.95	2.96	2.74	2.70	2.92
55	N,N-Diethylnicotinamide	0.33	0.83	1.58	0.56	0.42	0.52	1.16
56	Diltiazem hydrochloride	2.70	3.09	2.65	3.65	3.34	2.79	2.84
57	5,5-Dimethylbarbituric acid	-0.44	-0.21	0.34	-0.40	0.07	-0.38	-0.70
58	Diphenhydramine	3.27	3.44	3.39	3.45	3.50	3.11	3.16
59	Disopyramide	2.58	3.21	2.97	2.58	2.78	2.96	3.49
60	Dopamine	-0.98	-0.40	-0.48	0.17	-0.05	0.38	0.92
61	Dothiepin	4.49	4.98	4.83	4.53	4.23	4.51	4.56
62	Dozepine	4.29	4.25	4.08	4.09	3.86	3.99	3.99
63	Droperidol	3.50	3.92	2.61	3.06	3.40	3.46	2.75
64	Erythromycin	3.06	2.34	2.15	1.61	2.28	2.48	1.14
65	Estradiol	4.01	3.57	2.73	3.78	3.43	3.94	4.23
66	Estriol	2.45	2.54	1.67	3.20	2.51	2.81	3.63
67	Estrone	3.13	4.03	2.08	3.38	3.24	3.43	3.63
68	Ethopropazine	4.77	5.88	5.13	5.46	5.19	5.47	5.25
69	Ethyl nicotinate	1.32	1.17	1.33	1.30	0.91	1.13	1.13
70	5-Ethyl-5-heptyl barbituric acid	3.37	3.18	3.16	3.30	3.32	3.06	3.28
71	5-Ethyl-5-methyl barbituric acid	0.19	0.19	0.19	0.13	0.40	0.11	-0.14
72	5-Ethyl-5-nonyl barbituric acid	4.43	4.12	4.18	4.36	4.33	4.04	4.42
73	5-Ethyl-5-octylbarbituric acid	3.78	3.60	3.66	3.83	3.82	3.55	3.85
74	5-Ethyl-5-pentylbarbituric acid	2.24	2.15	2.09	2.24	2.31	2.08	2.14
75	5-Ethyl-5-propyl barbituric acid	1.25	1.25	1.02	1.18	1.30	1.10	1.00
76	5-Ethylbarbituric acid	-0.35	-0.34	-0.41	-0.39	-0.50	-0.34	-0.85
77	Fluanisone	3.60	3.82	3.00	4.22	3.79	3.86	3.79
78	Flufenamic acid	5.25	4.74	4.89	5.53	4.84	5.15	4.42
79	Flumazenil	1.00	1.52	1.23	1.29	0.86	1.03	1.92
80	Flunitrazepam	2.06	2.20	1.92	1.78	2.13	1.91	2.35
81	Fluoxymesterone	2.38	2.50	2.41	2.65	2.76	2.49	1.96
82	Flupenthixol	4.51	4.56	4.53	4.34	4.91	4.07	4.42
83	Fluphenazine	4.36	4.40	4.05	4.12	4.51	4.13	4.16
84	Flurazepam	2.35	3.81	4.02	4.22	3.64	3.02	3.78
85	Flurbiprofen	4.16	3.57	3.59	3.75	4.05	3.81	3.76
86	Fluspirilene	5.86	5.17	4.81	5.42	5.54	5.59	6.09
87	Furosemide	2.03	2.35	1.76	1.90	1.77	2.32	1.41
88	Glipizide	1.91	1.83	2.47	2.57	2.31	3.35	2.53
89	Haloperidol	4.30	3.70	3.41	3.85	4.30	4.20	3.98
90	Hexachlorophene	7.54	6.77	7.06	7.03	7.10	6.92	6.27
91	Hexobarbital	1.98	1.80	1.35	1.63	2.10	2.02	1.18
92	Hexyl nicotinate	3.51	3.06	3.27	3.41	2.98	3.10	3.19
93	Hydrochlorothiazide	-0.07	-0.16	0.05	-0.37	-0.06		--0.47
94	Hydrocortisone	1.61	1.71	2.91	1.70	1.62	1.62	0.52
95	Hyoscine	0.98	1.40	0.90	0.29	1.05	0.39	0.79
96	Hyoscyamine	1.83	2.20	1.76	1.30	1.77	1.91	1.83
97	Ibuprofen	3.97	3.50	3.54	3.68	3.46	3.79	3.64
98	Imipramine	4.80	4.58	4.62	5.04	4.16	5.01	4.03
99	Indomethacin	4.27	4.25	3.58	4.18	3.99	4.23	4.18
100	Isoniazid	-0.70	-0.71	-0.58	-0.67	-0.97	-0.81	-0.82
101	Ketoconazole	4.35	4.30	4.11	3.63	3.77	4.45	3.96
102	Ketoprofen	3.12	3.28	2.78	2.76	3.59	3.00	3.22

Table 1. cont.

No.	*Drug*	$logP_{exp}$ (10, 19, 23, 29-31)	AlogPs	IAlogP	ClogP	miLogP	$logP_{Kowwin}$	xlogP
103	Librium	2.44	2.01	0.43	3.79	2.12	2.42	3.39
104	Lidocaine	2.26	1.81	2.21	1.95	2.13	1.66	2.10
105	Lorazepam	2.39	2.98	2.53	2.37	2.47	2.41	3.47
106	Metamphetamine	2.07	2.23	2.15	1.89	2.23	2.22	2.15
107	Mebendazole	2.83	2.67	2.72	3.08	2.89	2.71	2.79
108	Medazepam	4.41	4.08	3.93	4.12	3.42	4.43	4.40
109	Metharbital	1.15	1.18	0.82	1.14	1.21	0.82	0.58
110	Methotripremazine	4.68	4.97	4.93	4.83	4.89	5.06	4.51
111	Methyl nicotinate	0.83	0.47	0.82	0.77	0.53	0.64	0.71
112	Methyl salicylate	2.55	2.07	1.98	2.34	2.13	2.60	2.54
113	5-Methylbarbituric acid	-0.84	-0.82	-0.87	-0.92	-1.00	-0.83	-1.41
114	Methyllorazepam	2.58	2.92	3.10	2.40	2.71	2.23	3.61
115	17a-Methyltestosterone	3.36	3.62	2.41	3.74	3.69	3.72	4.01
116	Metronidazole	-0.02	-0.15	-0.79	-0.46	-0.47	0.00	-0.14
117	Mexiletine	2.15	2.17	2.23	2.57	2.00	2.61	2.07
118	Naproxen	3.18	3.29	3.32	2.82	3.38	3.10	2.84
119	Nembutal	2.10	2.17	1.92	2.11	2.04	2.00	2.08
120	Nicotinamide	-0.37	-0.45	-0.16	-0.21	-0.48	-0.45	-0.34
121	Nicotinic acid	0.36	0.29	0.59	0.80	0.27	0.69	0.39
122	Nifedipine	2.20	2.32	1.52	3.13	3.07	2.50	2.37
123	Nimodipine	3.05	3.08	2.93	4.00	4.10	3.13	3.07
124	Nitrazepam	2.25	1.95	1.79	2.32	2.14	2.45	2.05
125	Nitrofurantoin	-0.47	0.03	-0.37	-0.47	-0.05	-0.17	-0.09
126	Norepinephrine	-1.24	-1.40	-1.65	0.99	-1.04	-1.16	0.16
127	Norethindrone	2.97	2.72	3.45	2.78	3.23	2.99	3.21
128	19-Nortestosterone	2.62	2.60	2.68	2.70	3.00	2.82	3.19
129	Orphenandrine	3.77	3.55	3.69	3.90	3.90	3.65	3.59
130	Oxaproxin	4.19	3.33	3.56	2.95	3.75	4.04	3.67
131	Oxazepam	2.24	2.01	2.64	2.31	1.84	2.32	2.84
132	Oxprendol	2.10	2.50	2.07	2.09	2.07	1.83	2.02
133	Pentobarbital	2.10	2.17	1.92	2.11	2.04	2.00	2.08
134	Pentoxifylline	0.29	0.08	0.17	0.12	0.65	0.56	0.03
135	Pericyazine	3.52	3.78	3.53	3.23	3.13	3.93	3.86
136	Phenobarbital	1.47	1.41	1.80	1.37	0.80	1.33	1.32
137	Phenylbutazone	3.16	2.81	3.39	3.38	4.56	3.52	3.71
138	Phenylephrine	-0.31	-0.62	-0.13	-0.09	0.41	-0.21	0.52
139	Phenytoin	2.47	2.26	2.52	2.09	2.18	2.16	2.22
140	Perphenazine	4.20	4.16	4.31	3.81	4.29	3.82	3.86
141	Pimozide	6.30	6.37	4.92	6.40	5.62	6.23	5.60
142	Pindolol	1.75	2.13	1.41	1.67	1.98	1.48	1.92
143	Pipamperone	2.02	2.32	2.71	2.24	2.33	2.28	1.73
144	Pirimidone	0.91	0.62	1.15	0.88	0.92	0.73	1.57
145	Prazepam	3.73	3.68	3.82	3.93	3.61	3.99	3.66
146	Prednisolone	1.62	1.64	1.23	1.42	1.60	1.40	1.02
147	Prednisone	1.46	2.07	1.28	1.66	1.41	1.59	0.61
148	Procainamide	0.88	1.42	1.34	1.42	0.99	0.97	1.31
149	Prochlorperazine	4.88	4.67	4.99	4.38	4.92	4.79	4.57
150	Progesterone	3.87	3.58	3.33	3.78	3.81	3.67	3.52
151	Promethazine	4.81	4.52	4.70	4.40	4.44	4.49	4.40
152	Propafenone	4.63	3.11	3.25	3.64	3.46	3.37	3.20
153	Propanolol	3.48	3.03	2.96	2.75	2.97	2.60	3.03

Table 1. cont.

No.	*Drug*	$logP_{exp}$ (10, 19, 23, 29-31)	AlogPs	IAlogP	ClogP	miLogP	$logP_{Kowwin}$	xlogP
154	Pseudoephedrine	0.89	1.00	1.03	0.89	1.24	0.68	1.39
155	3-Pyridinemethanol	-0.02	-0.13	0.18	0.06	0.04	-0.11	-0.04
156	1-(3-Pyridinyl)etanone	0.43	0.45	0.65	0.48	0.60	0.49	0.61
157	Pyrilamine	3.27	2.89	2.46	3.22	2.63	2.81	3.18
158	Quinidine	3.44	2.82	3.26	2.79	3.06	3.29	2.60
159	Rutinal	0.91	0.99	1.35	0.84	0.47	0.84	0.75
160	Salicylamide	1.28	0.74	1.01	1.28	1.25	1.03	0.93
161	Salicylanilide	3.27	2.65	3.26	3.27	3.32	3.30	3.02
162	Spiperone	3.03	2.86	2.45	2.82	3.34	2.92	3.48
163	Spironolactone	2.78	3.18	2.44	2.65	3.03	2.88	3.41
164	Sulfadiazine	-0.09	0.25	0.29	0.10	-0.04	-0.34	-0.17
165	Sulfadimidine	0.89	0.43	0.79	1.10	0.83	0.76	0.46
166	Sulfaguanidine	-1.22	-0.55	-1.37	-1.24	-0.84	-1.07	-0.45
167	Sulfamethoxazole	0.89	0.79	0.75	0.56	0.61	0.48	0.68
168	Sulfanilamide	-0.62	-0.16	-0.41	-0.57	-0.29	-0.55	-0.84
169	Sulfathiazole	0.05	0.94	0.85	0.73	0.83	0.72	-0.03
170	Sulfisoxazole	1.01	1.14	0.95	0.22	0.99	1.03	0.90
171	Sulfoxyphenyl pyrazolidine	2.30	2.92	2.12	1.65	3.35	2.14	2.40
172	Sultrin	-0.96	0.15	-0.25	-0.98	-0.56	-0.60	-0.56
173	Surital	3.23	3.11	3.18	3.03	2.62	3.23	2.53
174	Talbutal	1.47	1.79	1.50	1.63	1.52	1.87	1.71
175	Temazepam	2.19	2.46	2.20	2.34	2.08	2.15	2.99
176	Tertbutaline	0.90	0.55	0.77	0.48	1.07	0.67	1.42
177	Testosterone	3.32	2.99	2.39	3.22	3.24	3.27	3.60
178	Tetracaine	3.51	3.54	3.10	3.83	3.43	3.02	2.81
179	Tetracycline	-1.30	-0.68	-1.73	-0.91	-0.69	-1.33	-0.93
180	Tetrazepam	3.20	3.53	3.34	3.68	3.84	3.67	2.75
181	Theophylline	-0.02	-0.32	-0.49	-0.03	0.00	-0.39	-0.48
182	Thiobarbital	1.50	1.72	1.49	1.52	1.28	1.47	0.68
183	Thioridazine	5.90	5.93	5.69	6.00	5.68	6.45	5.94
184	Thiothixene	3.78	4.00	3.81	3.23	3.95	3.14	3.30
185	Thymol	3.30	3.16	3.06	3.20	3.34	3.52	3.25
186	Tolbutamide	2.34	2.04	2.05	2.50	2.54	2.41	2.18
187	Triamterene	0.98	1.21	-0.03	1.61	0.82	0.80	0.28
188	Triazolam	2.42	2.94	3.56	2.62	2.92	3.96	5.51
189	Trifluoperazine	5.54	4.96	4.94	5.61	5.25	5.52	5.23
190	Trifluperidol hydrochloride	3.03	2.86	2.19	2.82	3.34	2.92	3.48
191	Trimeprazine	4.71	4.99	5.08	4.80	4.85	4.98	4.60
192	Trimethoprim	0.91	1.26	1.21	0.98	1.00	0.73	0.65
193	Verapamil	3.79	5.23	6.93	4.47	4.55	4.80	4.70

Table 2. Matrix of correlation coefficients of linear dependences between particular partition coefficients (n = 193).

	$logP_{exp}$	AlogPs	IAlogP	ClogP	miLogP	$logP_{Kowwin}$*	xlogP
$logP_{exp}$ *	1	0.9717	0.9315	0.9546	0.9607	0.9777	0.9295
AlogPs		1	0.9435	0.9523	0.9623	0.9740	0.9350
IAlogP			1	0.9328	0.9462	0.9380	0.9085
ClogP				1	0.9626	0.9574	0.9387
miLogP					1	0.9553	0.9376
$logP_{Kowwin}$						1	0.9465
xlogP							1

* for $logP_{Kowwin}$ n =191

Table 3. Experimental *n*-octanol-water partition coefficients of drugs omitted from eqs. [6]-[9], and predicted by these equations.

Drug No.	Omitted drug	$logP_{exp}$	logP predicted by use of eq. [6]		logP predicted by use of eq. [7]		logP predicted by use of eq. [8]		logP predicted] by use of eq. [9	
			$logP_{pred}$	$\Delta logP = logP_{pred}$-AlogPs	$logP_{pred}$	$\Delta logP = logP_{pred}$-$logP_{Kowwin}$	$logP_{pred}$	$\Delta logP = logP_{pred}$-ClogP	$logP_{pred}$	$\Delta logP = logP_{pred}$-miLogP
1	Adrenalin	-1.37	-0.68	-0.69	-0.67	-0.70	-0.50	-0.87	0.03	-1.40
37	Clobazam	2.12	2.09	0.03	1.81	0.31	2.44	-0.32	2.56	-0.44
57	5,5-Dimethylbarbutiric acid	-0.44	-0.28	-0.16	-0.36	-0.08	-0.23	-0.21	0.15	-0.59
69	Ethyl nicotinate	1.32	1.12	0.20	1.13	0.19	1.37	-0.05	0.97	0.35
83	Fluphenazine	4.36	4.40	-0.04	4.09	0.27	4.02	0.34	4.45	-0.09
97	Ibuprofen	3.97	3.49	0.48	3.75	0.22	3.61	0.36	3.44	0.53
114	Methyllorazepam	2.58	2.90	-0.32	2.21	0.37	2.40	0.18	2.71	-0.13
141	Pimozide	6.30	6.40	-0.10	6.16	0.14	6.17	0.13	5.53	0.77
146	Prednisolone	1.62	1.60	0.02	1.40	0.22	1.48	0.14	1.64	-0.02
151	Promethazine	4.81	4.52	0.29	4.44	0.37	4.29	0.52	4.39	0.42
163	Spironolactone	2.78	3.16	-0.38	2.85	-0.07	2.64	0.14	3.02	-0.24
173	Surital	3.23	3.09	0.14	3.20	0.03	3.00	0.23	2.62	0.61
181	Theophylline	-0.02	-0.39	0.37	-0.37	0.35	0.12	-0.14	0.09	-0.11
187	Triamterene	0.98	1.16	-0.18	0.80	0.18	1.66	-0.68	0.88	0.10
192	Trimethoprim	0.91	1.21	-0.30	0.73	0.18	1.07	-0.16	1.05	-0.14
Agreement with experimental $logP_{(exp)}$ – correlation coefficient (r) and determination coefficient (r^2, %)			0.9895 97.91%		0.9928 98.57%		0.9908 98.17%		0.9781 95.67%	

ical partition coefficients were calculated by use of different methods (22-28). Numerical values of experimental *n*-octanol-water partition coefficients for all studied drugs were reported previously (10,19,23, 29-31) and together with theoretical partition coefficients (22-28) are presented in Table 1.

The experimental values of *n*-octanol-water partition coefficients ($logP_{exp}$) with the theoretical partition coefficients (AlogPs, IAlogP, ClogP, miLogP, $logP_{Kowwin}$, and xlogP) for the studied drugs were compared. The linear dependencies were received between experimental *n*-octanol-water partition coefficients ($logP_{exp}$) and particular theoretical partition coefficients (AlogPs, IAlogP, ClogP, miLogP, $logP_{Kowwin}$, and xlogP. The obtained correlation coefficient values for the linear dependencies between particular partition coefficients are presented in Table 2. They indicate, that theoretical partition coefficients calculated using IAlogP and xlogP methods are the least agreed with the experimental partition coefficients ($logP_{exp}$) (r=0.9315, r^2=86.77% and r=0.9295, r^2=86.40%, respectively). The remaining theoretical partition coefficients (AlogPs, ClogP, miLogP, and $logP_{Kowwin}$) show high agreement with experimental partition coefficients ($logP_{exp}$). For those dependencies correlation coefficients have larger values than 0.954. We have been affirmed that experimental values of *n*-octanol-water partition coefficients for all drugs correlate the best with $logP_{Kowwin}$ and AlogPs values. The relationships between experimental *n*-octanol-water partition coefficients ($logP_{exp}$) and AlogPs as well as $logP_{Kowwin}$ are presented in Figs. 1 and 2, respectively. The computer program $logP_{Kowwin}$ based on atom-fragmental contributions did not calculate the partition coefficients for chlorothiazide (33) and hydrochlorothiazide (93). The values of partition coefficients for these compounds calculated on the basis of equation [3] are equal –0.26 and –0.08, respectively.

For flurazepam (84), propafenone (152) , and verapamil (193), the Studentized residual for use of eq. [2] were –3.72, 3.95 and –3.76, respectively (Fig.1). For dopamine (60), glipizide (88), propafenone (152), and triazolam (188), the Studentized residual for use of eq. [3] were –4.00, -4.15, 3.69, and –4.46, respectively (Fig. 2). These points are particularly distant from straight lines (Figs. 1 and 2).

The experimental values of *n*-octanol-water partition coefficients for all studied drugs correlate also best with theoretical ClogP and miLogP:

$logP_{exp}$ =0.1148(±0.0614) + 0.9539(±0.0215)×ClogP [4]
n=193; r=0.9546; r^2=91.13%; F=1963; s=0.51; p<0.0001

$logP_{exp}$ =0.0496(±0.0581) + 0.9838(±0.0206)×miLogP [5]
n=193; r=0.9607; r^2=92.30%; F=2290; s=0.47; p<0.0001

For amoxicillin (11), ampicillin (12), flurazepam (84), and norepinephrine (126), the Studentized residual for use of eq. [4] were 5.42, 5.00, -3.63, and –4.76, respectively. For amoxicillin (11), and ampicillin (12), the Studentized residual for use of eq. [5] were 4.84, and 4.84, respectively. These points are particularly distant from straight lines.

Regression equations [2]-[5] can also be used to predict the experimental *n*-octanol-water partition coefficients of examined drugs, the measurement points of which have not been taken into consideration in the equations. A test was performed on equations [2] – [5] to determine how well they predict values of points not included in the training sets. Fifteen drugs were removed from the training sets (eqs. from [2] to [5]) (adrenalin, clobazam, 5,5-dimethylbarbituric acid, ethyl nicotinate, fluphenazine, ibuprofen, methyllorazepam, pimozide, prednisolone, promethazine, spironolactone, surital, theophylline, triamterene, and trimethoprim) and the subset of equations were recalculated:

$logP_{exp}$ =-0.0679(±0.0546) + 1.0152(±0.0193)×AlogPs [6]
n=178; r=0.9696; r^2=94.01%; F=2763; s=0.41; p<0.0001

$logP_{exp}$ =0.0146(±0.0477) + 0.9861(±0.0166)× $logP_{Kowwin}$ [7]
n=176; r=0.9762; r^2=95.29%; F=3519; s=0.36; p<0.0001

$logP_{exp}$ =0.1451(±0.0657) + 0.9415(±0.0231)×ClogP [8]
n=178; r=0.9510; r^2=90.43%; F=1663; s=0.52; p<0.0001

$logP_{exp}$ =0.0861(±0.0602) + 0.9687(±0.0212)×miLogP [9]
n=178; r=0.9600; r^2=92.16%; F=2068; s=0.47; p<0.0001

The comparison of predicted experimental partition coefficients ($logP_{pred}$), on the basis of equations [6]-[9], with experimental *n*-octanol-water partition coefficients for above-mentioned drugs is presented in Table 3. These equations are statistically significant and can be used for reasonably good prediction of the partition coefficient values of the drugs examined. We affirmed the best agreement between experimental *n*-octanol-water partition coefficients and partition coefficients calculated on the basis of $AlogP_s$, $logP_{Kowwin}$ and ClogP (r>0.989, r^2>97.8%) (Table 3). There is high compatibility between experimental and predicted logP values for drugs omitted in regression equations.

Theoretical determination of log*P* values of organic compounds, including drugs, has special significance if standards are not available. The method presented is very simple and can be recom-

mended for studies of quantitative structure-activity relationships for drugs.

CONCLUSIONS

Particular theoretical partition coefficients (Alog*P*s, IAlog*P*, Clog*P*, miLogP, logP_{Kowwin}, and xlog*P*) were compared with experimental *n*-octanol-water partition coefficients (logP_{exp}) for hundred ninety three studied drugs. It was shown that experimental partition coefficients correlate the best with theoretical partition coefficients calculated by use of logP_{Kowwin} and AlogP_s methods.

Remaining theoretical partition coefficients (ClogP, miLogP), except IAlogP and xlogP, show also high agreement with experimental *n*-octanol-water partition coefficients (logP_{exp}) ($r>0.954$).

It was shown that it exists the possibility of prediction of experimental *n*-octanol-water partition coefficients on the basis of logP_{Kowwin}, AlogP_s or ClogP for selected drugs (adrenalin, clobazam, 5,5-dimethylbarbituric acid, ethyl nicotinate, fluphenazine, ibuprofen, methyllorazepam, pimozide, prednisolone, promethazine, spironolactone, surital, theophylline, triamterene, and trimethoprim).

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