

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 (AlogPs, IALogP, miLogP, ClogP, $\log P_{\text{Kowwin}}$, and $x\log P$). Particular theoretical partition coefficients were compared with experimental *n*-octanol-water partition coefficients ($\log P_{\text{exp}}$) for all studied drugs. It was shown that experimental partition coefficients correlate the best with theoretical partition coefficients calculated by use of $\log P_{\text{Kowwin}}$ 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 $\log P_{\text{Kowwin}}$, AlogPs, and ClogP for fifteen drugs (adrenalin, clobazam, 5,5-dimethylbarbituric acid, ethyl nicotinate, fluphenazine, ibuprofen, methyllorazepam, pimozone, prednisolone, promethazine, spirinolactone, 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:

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

where a_i and b_j are regression coefficients, A_i is the number of occurrences of the i th atom type, and B_j is the number of occurrences of the j th 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-

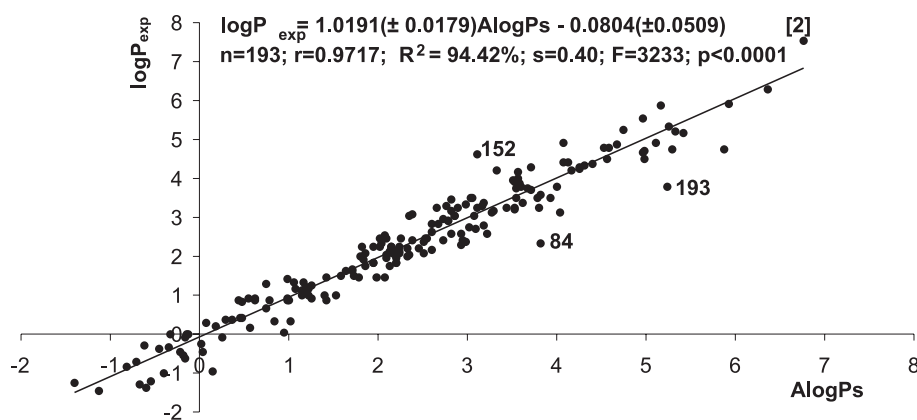


Figure 1. Relationships between the experimental *n*-octanol-water partition coefficients ($\log P_{\text{exp}}$) and theoretical AlogPs values.

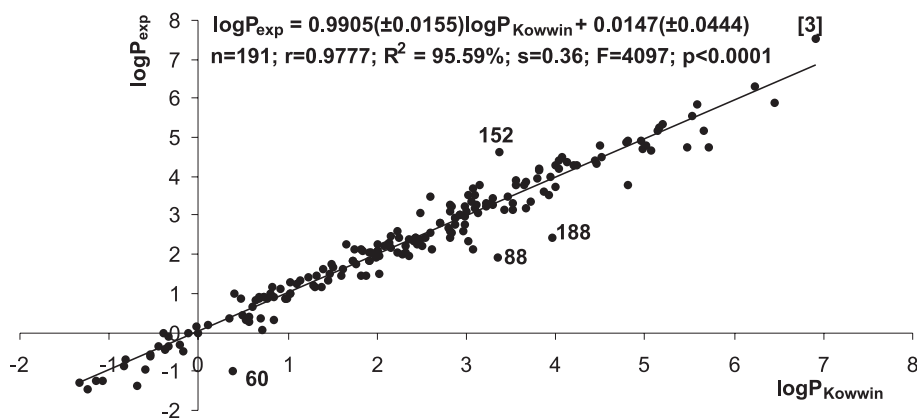


Figure 2. Relationships between the experimental *n*-octanol-water partition coefficients ($\log P_{\text{exp}}$) and theoretical $\log P_{\text{Kowwin}}$ values.

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-Aminosalicic 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 | Chlorpropamide | 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. | <i>Drug</i> | $\log P_{\text{exp}}$ (10, 19, 23, 29-31) | AlogPs | IAlogP | ClogP | miLogP | $\log P_{\text{Kowwin}}$ | 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. | <i>Drug</i> | $\log P_{\text{exp}}$ (10, 19, 23, 29-31) | AlogPs | IAlogP | ClogP | miLogP | $\log P_{\text{Kowwin}}$ | 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 | Methyllozepam | 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 | Propranolol | 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 | IAllogP | 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 | Pyrimidine | 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 | Spiroperone | 3.03 | 2.86 | 2.45 | 2.82 | 3.34 | 2.92 | 3.48 |
| 163 | Spiroolactone | 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 | Trifluoperidol 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 | IAllogP | 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 |
| IAllogP | | | 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} | $\Delta\log P = \log P_{pred} - \log P_{exp}$ | logP _{pred} | $\Delta\log P = \log P_{pred} - \log P_{Known}$ | logP _{pred} | $\Delta\log P = \log P_{pred} - C\log P$ | logP _{pred} | $\Delta\log P = \log P_{pred} - m\log P$ |
| 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-Dimethylbarbituric 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 | Methylorazepam | 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 | Spirolactone | 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 ($\log P_{\text{exp}}$) with the theoretical partition coefficients (AlogPs, IlogP, ClogP, miLogP, $\log P_{\text{Kowwin}}$ and xlogP) for the studied drugs were compared. The linear dependencies were received between experimental *n*-octanol-water partition coefficients ($\log P_{\text{exp}}$) and particular theoretical partition coefficients (AlogPs, IlogP, ClogP, miLogP, $\log P_{\text{Kowwin}}$ 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 IlogP and xlogP methods are the least agreed with the experimental partition coefficients ($\log P_{\text{exp}}$) ($r=0.9315$, $r^2=86.77\%$ and $r=0.9295$, $r^2=86.40\%$, respectively). The remaining theoretical partition coefficients (AlogPs, ClogP, miLogP, and $\log P_{\text{Kowwin}}$) show high agreement with experimental partition coefficients ($\log P_{\text{exp}}$). 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 $\log P_{\text{Kowwin}}$ and AlogPs values. The relationships between experimental *n*-octanol-water partition coefficients ($\log P_{\text{exp}}$) and AlogPs as well as $\log P_{\text{Kowwin}}$ are presented in Figs. 1 and 2, respectively. The computer program $\log P_{\text{Kowwin}}$ 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:

$$\log P_{\text{exp}} = 0.1148(\pm 0.0614) + 0.9539(\pm 0.0215) \times \text{ClogP} \quad [4]$$

$n=193$; $r=0.9546$; $r^2=91.13\%$; $F=1963$; $s=0.51$; $p<0.0001$

$$\log P_{\text{exp}} = 0.0496(\pm 0.0581) + 0.9838(\pm 0.0206) \times \text{miLogP} \quad [5]$$

$n=193$; $r=0.9607$; $r^2=92.30\%$; $F=2290$; $s=0.47$; $p<0.0001$

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, methylflorazepam, pimozide, prednisolone, promethazine, spironolactone, surital, theophylline, triamterene, and trimethoprim) and the subset of equations were recalculated:

$$\log P_{\text{exp}} = -0.0679(\pm 0.0546) + 1.0152(\pm 0.0193) \times \text{AlogPs} \quad [6]$$

$n=178$; $r=0.9696$; $r^2=94.01\%$; $F=2763$; $s=0.41$; $p<0.0001$

$$\log P_{\text{exp}} = 0.0146(\pm 0.0477) + 0.9861(\pm 0.0166) \times \log P_{\text{Kowwin}} \quad [7]$$

$n=176$; $r=0.9762$; $r^2=95.29\%$; $F=3519$; $s=0.36$; $p<0.0001$

$$\log P_{\text{exp}} = 0.1451(\pm 0.0657) + 0.9415(\pm 0.0231) \times \text{ClogP} \quad [8]$$

$n=178$; $r=0.9510$; $r^2=90.43\%$; $F=1663$; $s=0.52$; $p<0.0001$

$$\log P_{\text{exp}} = 0.0861(\pm 0.0602) + 0.9687(\pm 0.0212) \times \text{miLogP} \quad [9]$$

$n=178$; $r=0.9600$; $r^2=92.16\%$; $F=2068$; $s=0.47$; $p<0.0001$

The comparison of predicted experimental partition coefficients ($\log P_{\text{pred}}$), 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 AlogPs, $\log P_{\text{Kowwin}}$ and ClogP ($r>0.989$, $r^2>97.8\%$) (Table 3). There is high compatibility between experimental and predicted $\log P$ 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 (AlogP_s, IlogP, ClogP, miLogP, logP_{Kowwin}, and xlogP) 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 IlogP 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, methylorazepam, pimozide, prednisolone, promethazine, spironolactone, surital, theophylline, triamterene, and trimethoprim).

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