Synthesis, Spectral Description, and Lipophilicity Parameters Determination of Phenylcarbamic Acid Derivatives with Integrated *N*-Phenylpiperazine Moiety in the Structure

[a]I. MALÍK, [a]E. SEDLÁROVÁ, [b]J. CSÖLLEI, [a]F. ANDRIAMAINTY, [b]P. KURFÜRST, and [b]J. VANČO

[a]*Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Comenius University, SK-832 32 Bratislava*
e-mail: malik@fpharm.uniba.sk

[b]*Institute of Chemical Drugs, Faculty of Pharmacy, University of Veterinary and Pharmacy, CZ-612 42 Brno*

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The phenylcarbamic acid derivatives with *N*-phenylpiperazine moiety in the molecule have been prepared. The structure has been confirmed by elemental analysis, IR, ^{1}H NMR, and mass spectral data. For the prepared set of the compounds the lipophilicity parameters have been determined. The experimentally obtained lipophilicity parameters have been correlated with theoretical entries obtained by different computer programs based on the neural network and fragmental methods.

In agreement with original Löfgren model there is the structure of phenylcarbamic acid derivatives adorned with lipophilic part, represented by cyclic aromatic or heterocyclic skeleton, connecting chain, mainly hydrogencarbon or substituted hydrogencarbon chain, and hydrophilic part, *i.e.* dimethyl, diethylamino, piperidin-1-yl, pyrrolidin-1-yl, or piperazin-1-yl group [1—3]. The piperazine moiety is present in the structure of compounds which show a various spectrum of biological activities [4—6] including cardiovascular system impact [7]. The *N*-phenylpiperazine (substituted *N*-phenylpiperazine) fragment insertion into the hydrophilic part of the molecule of phenylcarbamic acid means, except some other effects, α_1-antiadrenergic and Ca^{2+}-antagonistic activities with implication to blood pressure magnitude [8].

The aim of this paper is the synthesis, the identification, and the determination of some lipophilic properties of nine novel phenylcarbamate derivatives with substituted *N*-phenylpiperazine moiety in the basic part of the molecule. Except for experimental determination of log *P* there were used a few different computer programs with different calculation methods for the prediction of lipophilicity of prepared compounds.

EXPERIMENTAL

The derivatives of general structure *V* (see Scheme 1) were synthesized by the method described in [9, 10]. The compound 1-(3-trifluoromethyl)phenylpiperazine was used like the basic moiety.

2,3-Epoxypropan-1-yl esters of corresponding alkoxy-substituted phenylcarbamic acids as the intermediate products were prepared by addition of 2,3-epoxypropan-1-ol to corresponding alkoxyphenylisocyanates [10]. Mixture of the compounds was dissolved in benzene, then it was heated for 10 h at 60 ℃. After isolation and checking the identity and purity of 2,3-epoxypropan-1-yl esters by ^{1}H NMR, IR spectra, and thin-layer chromatography, the mixture mobile phases petroleum ether—diethyl ether ($\varphi_r = 2 : 1$), resp. acetone—petroleum ether ($\varphi_r = 2 : 3$) have been used, the basic piperazine moiety was added. Mixture was heated for 8 h [10]. After addition of ethereal hydrochloric acid solution the corresponding salts were isolated. The final products were purified by crystallization from propan-2-ol.

Melting points were determined using a Kofler hotplate apparatus (HMK Franz Küstner, Germany). Elemental analysis was made using elemental analyzer EA1108 (Erba Instruments).

Spectra in the UV region were measured on 8452 A diode array spectrophotometer, Vectra 286/12 Desk Jet 500 (Hewlett—Packard), IR spectra (KBr disc) of final compounds and *N*-phenylpiperazine derivative were recorded on FTIR spectrophotometer Nicolet Model Impact 410 in the 400—4000 cm^{-1} range. ^{1}H NMR spectra were scanned on spectrophotometer Varian Gemini 2000, 200 MHz, chemical shifts are in the δ-scale and the following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Mass spectra were recorded by mass spectrometer Agilent 1100, LC/MSD VL Trap with linear mechanic pump (KD Scientific, USA).

Solubility of prepared compounds was determined in distilled water, 96 % ethanol, and in chloroform medium.

The Lipophilicity Parameters Determination

The apparent partition coefficient of prepared final compounds was measured by the *shake-flask* method according to [11], the reversed-phase thin-layer analysis was made also according to [11] where the mobile phase was a mixture of 1 M-HCl—acetone (φ_r = 4 : 1). The chromatographic system for HPLC analysis for capacity factor k determination consisted of a pump DeltaChrom SDS (Watrex, Slovakia) with injection valve and UV detector DeltaChrom UVD 200 (Watrex, Slovakia). The analytical chromatography column: Separon SGX C_{18} (250 mm × 4 mm, particle size 7 μm). Mobile phase a mixture of methanol—sodium acetate (φ_r = 95 : 1), the pH value was adjusted with acetic acid to pH = 6. The flow rate of mobile phase was 0.6 cm^3 min^{-1}, injection volume 10 mm^3, the chromatograms were scanned at 248 nm. The concentration of analyzed drugs was 0.2 mg cm^{-3}. A solution of $NaNO_2$ ($c = 0.1$ mol dm^{-3}) was used for determination of dead time (t_0).

Computational Calculation of Partition Coefficient *P* (resp. log *P*) Values

For the calculation (prediction) of log P values the following computer programs were used: ALOGPs 2.1, IA LogP, CLOGP, KowWin, XLOGP, miLogP 1.2, and ChemDraw Ultra 8. All mentioned programs calculate the log P values for the octan-1-ol—water medium.

The ALOGPs 2.1 package included a program for predicting the lipophilicity of chemical compounds. A method for predicting log P values is based on atom-type electropological-state (E-state) indices and neural network modeling developed by *Tetko* [12]. The analyzed compound was entered using the Simplified Molecular Input Line Entry System (SMILES) notation.

The IA LogP program predicts lipophilicity using neural network algorithms and E-state atom indices [13].

The CLOGP program is based on the fragmental method. The calculation result is accompanied by the picture of chemical structure as generated by the DEPICT algorithm. The result of log P value is displayed in the *Map Box*, where the first line is the SMILES notation of the compound [14].

The KowWin program calculates the log P values of organic chemicals using the atom/fragment method. The log P value of analyzed compound is calculated by simply summing up all atom/fragment contribution values, correction factors, and the linear equation constant [13].

The XLOGP program is another atom-additive method based on summation of atomic contributions, but it includes ten additive correction factors for some intramolecular interactions. Atoms are classified by their hybridization states and neighbouring atoms [15].

The miLogP 1.2 program is based on the group contributions. Group contributions have been obtained by fitting calculated log P with experimental log P for a training set of several thousands of drug-like molecules (according to www.molinspiration.com).

The ChemDraw Ultra 8 program (in Table 3 marked as ChemDraw) can calculate the log P values by three fragmentation methods.

The method one is based on 94 atomic contributions evaluated from 830 molecules by the least-squares analysis. This method works with a standard deviation of 0.47 log P units and can handle molecules containing hydrogen, oxygen, nitrogen, sulfur, and halogens. Method two is an extension of method one that is based on 120 atomic contributions evaluated from 893 molecules by the least-squares analysis. In addition to the atoms introduced for method one, it can handle molecules that contain phosphorus and selenium atoms. This method works with a standard deviation of 0.50 log P units. Method three is based on 222 atomic contributions calculated from 1868 molecules by the least-squares analysis. This method allows a calculation of log P with a standard deviation of 0.43 log P units and can handle molecules containing hydrogen, oxygen, nitrogen, sulfur, halogen, and phosphorus atoms. If this method is applied to molecules with internal hydrogen bonds, the standard deviation is 0.83 log P units (method evidences according to ChemDraw Ultra Contents).

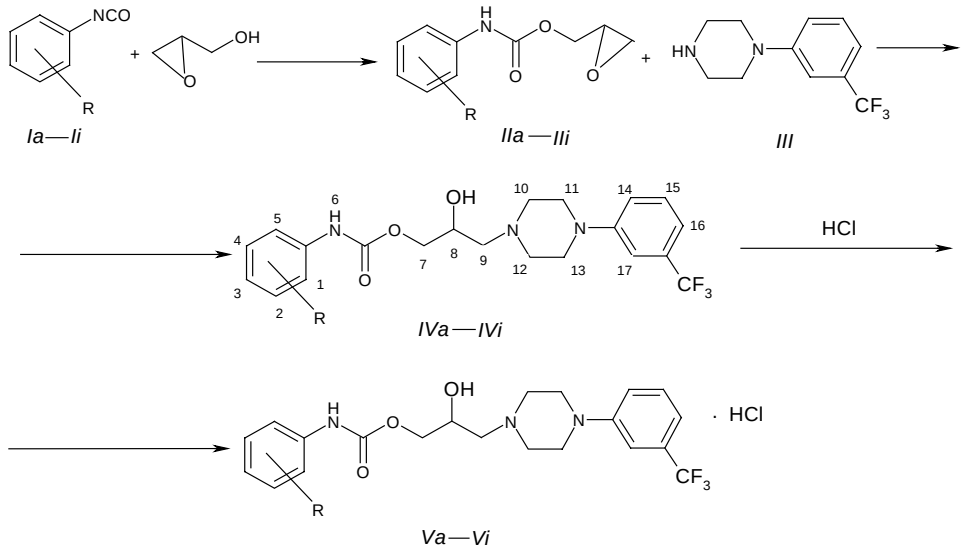
Correlation between Lipophilicity Parameters

Finally the number of carbon atoms in the alkoxy side chain and all estimated lipophilicity parameters were correlated mutually for the series of *m*- and *p*-substituted compounds. The regression coefficients were obtained as the results of regression analysis.

RESULTS AND DISCUSSION

The synthesis, spectral data, and lipophilicity parameters of 1-[(3-trifluoromethyl)phenyl]-4-[3-(2-/3-/4-alkoxyphenylcarbamoyloxy)-2-hydroxypropan-1-yl]piperazinium chlorides (*Va*—*Vi*) with one to four carbon atoms in the alkoxy group on aromatic ring were studied. The mentioned compounds have been synthesized by reaction of 4-(3-trifluoromethyl)phenylpiperazin-1-yl moiety with corresponding 2,3-epoxypropan-1-yl esters of 2-, 3-, and 4-alkoxyphenylcarbamic acids according to similar procedure which was described in the literature [10]. The obtained basic esters were not crystalline substances. The final compounds were isolated as the salts of hydrochloric acid (Scheme 1).

The methods of identification included elemental



R = 2-OCH_3 (*Ia*, *IIa*, *IVa*, *Va*), 2-OC_2H_5 (*Ib*, *IIb*, *IVb*, *Vb*), 3-OCH_3 (*Ic*, *IIc*, *IVc*, *Vc*),

3-OC_2H_5 (*Id*, *IId*, *IVd*, *Vd*), 3-OC_3H_7 (*Ie*, *IIe*, *IVe*, *Ve*), 4-OCH_3 (*If*, *IIf*, *IVf*, *Vf*),

4-OC_2H_5 (*Ig*, *IIg*, *IVg*, *Vg*), 4-OC_3H_7 (*Ih*, *IIh*, *IVh*, *Vh*), 4-OC_4H_9 (*Ii*, *IIi*, *IVi*, *Vi*)

Scheme 1. Synthetic route of the compounds, ring labelling from the point of ^{1}H NMR spectra.

Table 1. 1-[(3-Trifluoromethyl)phenyl]-4-[3-(2-/3-/4-alkoxyphenylcarbamoyloxy)-2-hydroxypropan-1-yl]piperazinium Chlorides

Compound	Yield	M.p.	R_f
	%	°C	
Va	73	181—185	0.35
Vb	69	137—141	0.54
Vc	75	192—195	0.27
Vd	62	168—172	0.33
Ve	69	163—166	0.36
Vf	81	201—205	0.22
Vg	74	145—149	0.31
Vh	71	159—162	0.39
Vi	68	136—140	0.44

analysis, the ultraviolet, infrared, mass, and ^{1}H NMR spectra and thin-layer chromatography.

The prepared phenylcarbamates were solid, colourless compounds and their melting points and retention factors are given in Table 1. Mobile phase for R_f values determination on the silica gel plates Silufol UV_{254} was the mixture of petroleum ether—diethylamine (φ_r = 8 : 3).

The structure of prepared compounds was confirmed by elemental analysis, the values were generally in good agreement with respective structure for carbon, hydrogen, and nitrogen. The differences between calculated and experimentally obtained data were in the range of ± 0.4 %.

The spectrum in ultraviolet region showed three absorption maxima at the wavelengths (λ) 200 nm, 240 nm, and 280 nm in distilled water. In methanol medium there was observed a slight shift to the higher absorption maxima at 212 nm, 244 nm, and 282 nm. IR spectra of the prepared final compounds *Va*—*Vi* showed absorption bands around 3300 cm^{-1} (N—H stretching), 2600 cm^{-1} (N^+—H str.), 1730 cm^{-1} (C═O str.), 1600 cm^{-1} (aromatic C—C str.), and 1200 cm^{-1} (NHC deformation). IR spectrum of 1-(3-trifluoromethyl)phenylpiperazine (*III*) showed absorption bands at 3260 cm^{-1} (N—H str.), 2948 cm^{-1} (C—H str.), 1499 cm^{-1} (N—H deformation str.), 1318 cm^{-1} (C—N str.), and 1241 cm^{-1} (C—F str.). The mass spectra of prepared salts *Va*—*Vi* revealed the presence of $[M + H^+]^+$ ions in all cases, the value m/z = 454.2 for the compounds *Va*, *Vc*, *Vf*, m/z = 468.2 for *Vb*, *Vd*, *Vg*, m/z = 482.2 for *Ve*, *Vh*, and m/z = 496.2 for *Vi*. The ^{1}H NMR spectra of the basic esters of 2-, 3-, 4-phenylcarbamic acids agreed with the proposed structures (Table 2).

All the compounds were checked for purity also by thin-layer chromatography. With the prolongation of alkoxy chain in lipophilic part of the molecules the increase of the R_f values in the mentioned mobile phase was observed.

The solubility of liquids and solids in water is no doubt one of the most important molecular properties that affects their biological activity [16]. Solubility of solid compounds depends on the free energy changes involved in changing the solid state to liquid state, in addition to the interactions in the liquid phase

Table 2. ^{1}H NMR Spectral Data of Prepared Final Compounds

Compound	Chemical shift, δ
Va	2.62 (t, 4H, H-10, H-12), 3.05 (t, 4H, H-11, H-13), 3.86 (s, 3H, O-CH_3), 4.06 (m, 1H, H-8), 4.32 (d, 2H, H-9), 4.37 (d, 2H, H-7), 6.90 (s, 1H, O<u>H</u>) vs 7.40 (s, 1H, O<u>H</u>), 7.00—7.30 (m, 8H, Ar<u>H</u>), 8.00 (s, 1H, N<u>H</u>, H-5)
Vb	1.45 (t, 3H, O-CH_2-C<u>H</u>$_3$), 2.54 (t, 4H, H-10, H-12), 3.05 (t, 4H, H-11, H-13), 3.26 (q, 2H, O-C<u>H</u>$_2$-CH_3), 4.12 (m, 1H, H-8), 4.33 (d, 2H, H-9), 4.38 (d, 2H, H-7), 6.80 (s, 1H, O<u>H</u>) vs 7.40 (s, 1H, O<u>H</u>), 6.90—7.60 (m, 8H, Ar<u>H</u>), 8.10 (s, 1H, N<u>H</u>, H-5)
Vc	2.63 (t, 4H, H-10, H-12), 3.04 (t, 4H, H-11, H-13), 3.80 (s, 3H, O-CH_3), 4.13 (m, 1H, H-8), 4.30 (d, 2H, H-9), 4.49 (d, 2H, H-7), 6.60 (s, 1H, O<u>H</u>) vs 7.40 (s, 1H, O<u>H</u>), 6.80—7.30 (m, 8H, Ar<u>H</u>), 7.50 (s, 1H, N<u>H</u>, H-5)
Vd	1.39 (t, 3H, O-CH_2-C<u>H</u>$_3$), 2.58 (t, 4H, H-10, H-12), 2.83 (t, 4H, H-11, H-13), 4.024 (m, 1H, H-8), 4.12 (q, 2H, O-C<u>H</u>$_2$-CH_3), 4.30 (d, 2H, H-9), 4.36 (d, 2H, H-7), 7.00—7.20 (m, 8H, Ar<u>H</u>), 6.90 (s, 1H, O<u>H</u>) vs 7.20 (s, 1H, O<u>H</u>), 7.60 (s, 1H, N<u>H</u>, H-5)
Ve	1.01 (t, 3H, O-CH_2-CH_2-C<u>H</u>$_3$), 2.60 (t, 4H, H-10, H-12), 2.80 (t, 4H, H-11, H-13), 3.01 (m, 2H, O-CH_2-C<u>H</u>$_2$-CH_3), 3.28 (t, 2H, O-C<u>H</u>$_2$-CH_2-CH_3), 4.10 (m, 1H, H-8), 4.33 (d, 2H, H-9), 4.35 (d, 2H, H-7), 6.80 (s, 1H, O<u>H</u>) vs 7.00 (s, 1H, O<u>H</u>), 6.80—7.10 (m, 8H, Ar<u>H</u>), 7.45 (s, 1H, N<u>H</u>, H-5)
Vf	2.60 (t, 4H, H-10, H-12), 2.90 (t, 4H, H-11, H-13), 3.82 (s, 3H, O-C<u>H</u>$_3$), 4.02 (m, 1H, H-8), 4.34 (d, 2H, H-9), 4.40 (d, 2H, H-7), 6.95 (s, 1H, O<u>H</u>) vs 7.30 (s, 1H, O<u>H</u>), 7.00—7.20 (m, 8H, Ar<u>H</u>), 7.90 (s, 1H, N<u>H</u>, H-5)
Vg	1.37 (t, 3H, O-CH_2-C<u>H</u>$_3$), 2.63 (t, 4H, H-10, H-12), 2.81 (t, 4H, H-11, H-13), 3.74 (q, 2H, O-C<u>H</u>$_2$-CH_3), 4.02 (m, 1H, H-8), 4.30 (d, 2H, H-9), 4.35 (d, 2H, H-7), 6.70 (s, 1H, O<u>H</u>) vs 6.95 (s, 1H, O<u>H</u>), 6.80—7.30 (m, 8H, Ar<u>H</u>), 7.40 (s, 1H, N<u>H</u>, H-5)
Vh	1.026 (t, 3H, O-CH_2-CH_2-C<u>H</u>$_3$), 2.64 (t, 4H, H-10, H-12), 2.84 (t, 4H, H-11, H-13), 3.06 (m, 2H, O-CH_2-C<u>H</u>$_2$-CH_3), 3.26 (t, 2H, O-C<u>H</u>$_2$-CH_2-CH_3), 4.07 (m, 1H, H-8), 4.30 (d, 2H, H-9), 4.35 (d, 2H, H-7), 6.81 (s, 1H, O<u>H</u>) vs 7.10 (s, 1H, O<u>H</u>), 6.85—7.15 (m, 8H, Ar<u>H</u>), 7.40 (s, 1H, N<u>H</u>, H-5)
Vi	0.97 (t, 3H, O-CH_2-CH_2-CH_2-C<u>H</u>$_3$), 1.46 (m, 2H, O-CH_2-CH_2-C<u>H</u>$_2$-CH_3), 1.75 (m, 2H, O-CH_2-C<u>H</u>$_2$-CH_2-CH_3), 2.64 (t, 4H, H-10, H-12), 3.19 (t, 2H, O-C<u>H</u>$_2$-CH_2-CH_2-CH_3), 3.26 (t, 4H, H-11, H-13), 4.08 (m, 1H, H-8), 4.29 (d, 2H, H-9), 4.34 (d, 2H, H-7), 6.90—7.30 (m, 8H, Ar<u>H</u>), 6.80 (s, 1H, O<u>H</u>) vs 7.35 (s, 1H, O<u>H</u>), 7.45 (s, 1H, N<u>H</u>, H-5)

[17]. *Yalkowsky* has introduced a model of solubility of nonelectrolytes based on thermodynamic grounds. The model contains only two parameters, log P_{oct} and melting point [18].

Despite the fact that the prepared compounds are the salts with hydrochloric acid, their solubility in water was very limited. It is the consequence of relatively bulky substituent abundance in the basic part of molecule. In ethanol the analyzed compounds show relatively good solubility, on the contrary in chloroform they were practically indissoluble.

Lipophilicity of a substance is one of the parameters which influences its biological activity and is well known as a prime physicochemical descriptor of xenobiotics with relevance to their biological properties [11]. The parameters obtained from reverse-phase thin-layer chromatography can be used for definition of drug lipophilicity [11].

With side alkyl chain elongation the R_{M} values decreased, so there is the evident influence of the methylene group on a compound lipophilicity, taking into account that accuracy and reproducibility of chromatographically obtained R_{M} values is closely linked with the application of standard conditions.

The log k parameter obtained from HPLC became a very important parameter of lipophilicity. Retention times of evaluated compounds increase with increasing number of carbon atoms in the alkoxy side chain. Study [19] has shown that the log k values of basic esters of 2-, 3-, and 4-alkoxyphenylcarbamic acid can be used for determination of their local anaesthetic activity; there was observed that the relation between k and relative activity of surface and infiltration anaesthesia is statistically significant.

The logarithm of the partition coefficient between octan-1-ol and water is a leading physicochemical descriptor in many quantitative structure—activity relationship (QSAR) studies for modeling transport across biological membranes, biochemical and pharmacokinetic processes, and toxicity of organic compounds [20].

Partition coefficient was determined by the *shake-flask* method in octan-1-ol—phosphate medium. The amount of organic solvent was relatively small (0.05 cm^3) because of relatively high lipophilicity of evaluated compounds. Partition coefficient, as well as the value of its logarithm, increases by elongation of the side chain. There was no significant deviation of values between positional isomers at lipophilic aromatic ring in *o*-, *m*-, and *p*-position.

According to [21] the experimental log P values are limited to the range $-3 < \log P < 3$. The given literature mentioned some difficulties with log P determination for relatively polar or highly lipophilic compounds if the log P value is higher than 4. Correspondingly, there is a great interest in medicinal chemistry in developing methods for deriving the quantitative descriptor of lipophilicity, the partition coefficient P, from molecular structure.

The log P values were calculated by different com-

Table 3. Lipophilicity Parameters of Analyzed Compounds with the log P Values Obtained by Different Computer Programs

Compound	R_M	log k	log P_{exp}	ALOGPs	IA LogP	CLOGP	KowWin	XLOGP	miLogP	ChemDraw
Va	0.04	−0.229	3.57	3.13	2.79	4.21	3.16	3.28	3.52	3.62
Vb	0.18	−0.177	3.60	3.65	2.84	4.74	3.65	3.70	3.92	3.95
Vc	−0.02	−0.318	3.61	3.15	2.83	4.21	3.16	3.28	3.52	3.62
Vd	0.11	−0.276	3.72	3.67	2.74	4.74	3.65	3.70	3.92	3.95
Ve	0.23	−0.268	4.03	3.95	2.96	5.27	4.14	4.06	4.36	4.44
Vf	0.00	−0.347	3.60	3.19	2.86	4.21	3.16	3.28	3.52	3.62
Vg	0.12	−0.301	3.71	3.69	2.77	4.74	3.65	3.70	3.92	3.95
Vh	0.29	−0.222	3.92	4.00	3.00	5.27	4.14	4.06	4.36	4.44
Vi	0.45	−0.155	3.98	4.27	3.29	5.80	4.64	4.63	4.79	4.86

puter programs based on two main methods, *i.e.* the neural network and fragmental methods. All calculated log P values are for neutral forms of the compounds. Log P data obtained with the seven software packages are listed in Table 3 together with experimental partition coefficients (log P_{exp}).

Validity of the seven calculation procedures was compared as follows: As first statistical criterion, the averaged absolute residual sums (AARS) for the differences between experiment and calculation are given. Secondly, the differences (Δ log P) between log P_{exp} and calculated data in the range 0.00 to ± 0.49 are qualified as acceptable, Δ log P values of ± 0.50 to ± 0.99 are viewed as disputable and differences exceeding ± 1.00 are classified as unacceptable [22]. The comparison of calculated log P values for *o*-, *m*-, and *p*-isomers with those of the same substituent on lipophilic phenylcarbamate moiety showed that there were no significant deviations between *log P* values for *o*-, *m*-, and *p*-substituted analogues.

Before inspecting the observed differences, it should be admitted that the rather small number of tested molecules confines a generalization of such validity comparisons. On the basis of the AARS the following ranking of the seven included calculation programs is observed for the entire data set: XLOGP ∼ ALOGPs 2.1 > KowWin ∼ miLogP 1.2 > ChemDraw Ultra 8 > IA LogP > CLOGP.

The classification into acceptable, disputable, and unacceptable calculations more or less mirrors this view. Counting the negative and positive deviations of calculations from experimental partition coefficients demonstrates a rather equilibrated pattern for XLOGP and ALOGPs 2.1. The AARS data show that XLOGP and ALOGPs 2.1 are the best in calculating for the mentioned set of compounds. For this set of compounds we find that XLOGP, ALOGPs 2.1 produce similar results (XLOGP AARS = 0.20, ALOGPs 2.1 AARS = 0.21), KowWin, miLogP 1.2, and ChemDraw Ultra 8 produce slightly worse results (KowWin AARS = 0.27, miLogP 1.2 AARS = 0.28, ChemDraw Ultra 8 AARS = 0.30). The IA LogP and CLOGP programs seem to be the least convenient for log P values prediction of shown set of molecules.

Taking into account another experimentally estimated parameter – lipophilicity (except of log$P$) in both series of *m*- and *p*-substituted compounds there was the best correlation between the R_M values from reverse-phase thin-layer chromatography and theoretically calculated parameters of lipophilicity based on fragmental methods. The R_M values of *p*-substituted compounds showed the best correlation with log P values obtained by ChemDraw Ultra 8 program. In the same series of compounds there was better correlation beween R_M and log k values than for *m*-substituted derivatives.

For the series of *m*-substituted substances there was the best correlation between R_M and calculated log P values obtained by CLOGP and KowWin methods. The IA LogP method seems to be not convenient for QSAR studies.

In general, the log P values calculated by fragmental methods (KowWin, CLOGP) for presented set of compounds were more convenient for QSAR studies than the values obtained by neural networks-based methods (ALOGPs 2.1, IA LogP).

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