

## SOLUBILITY PREDICTION OF SULFONAMIDES AT VARIOUS TEMPERATURES USING A SINGLE DETERMINATION

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### ABSTRACT

Solubility of sulphamethoxazole, sulphisoxazole and sulphasalazine in six solvents namely water, methanol, ethanol, 1-propanol, acetone and chloroform were determined at 15, 25, 37 and 45 °C. Two models derived from the Hildebrand solubility approach are proposed for solubility prediction at different temperatures using a single determination. The experimental data of the present work as well as data gathered from the literature have been employed to investigate the accuracy and prediction capability of the proposed models. The overall percent deviations between the predicted and experimental values were 10.78 and 14.63% which were comparable to those of the classical two and three parameter models. The proposed models were much superior to the two pure predictive models i.e., the ones which do not require experimental solubility determination, as the overall percent deviations produced by the latter models were 150.09 and 161.00%.

**Keywords:** Solubility; Sulphonamides; Modeling; Temperature; Prediction

### INTRODUCTION AND THEORY

Solubility is one of the most important physicochemical properties of drugs. As a general rule, water-insoluble compounds may not act as a specific drug. The solubility of a solute could be affected by factors like pH, pKa, polarity etc. The modeling of solubility data provides not only a means of screening experimental data sets for possible outliers which require of re-determination, but also facilitates interpolation at other points falling between measured data. Solubility prediction employing models without a curve-fit parameter or the minimum number of curve-fit parameters is the final goal of the solubility data modeling. By using such models, researchers are able to estimate the unmeasured solubilities.

Some models were proposed for mathematical representation of solubility in mixed solvents at a constant (1-10) and different temperatures (11-16). Knowledge of solubility at various temperatures is useful in the physical stability

studies of liquid dosage forms, in processes involving temperature changes and in pre-formulation stage of a new drug where only small amount of the drug is available.

In the present report, the solubility of three sulphonamides, i.e. sulphamethoxazole, sulphisoxazole and sulphasalazine, in water, methanol, ethanol, 1-propanol, acetone and chloroform at 15-45 °C were measured. Sulfonamides have already been used by others (13) as model drugs for solubility investigations. Two models based on the Hildebrand solubility approach which can predict the solute solubility in the range of  $\pm 25$  °C with acceptable error using a single experimental data determined at 25 °C are proposed and the superiority of these models to previously published models (13) in which no experimental data has been used to train the model, are shown. The errors of the proposed models in comparison with other models employing more than one data point, were satisfactory.

Five models for solubility prediction at different

temperatures, i.e. the van't Hoff (17), the Hildebrand (17), the Grant-Prankerd (11, 12) and the extended Hildebrand-Scatchard models (13) which are expressed by the respective Eqs. I - V, have been reported.

$$\ln X_2 = \frac{-\Delta H_s}{RT} + A \quad (I)$$

$$\ln X_2 = \frac{\Delta S_s \ln T}{R} + B \quad (II)$$

$$\ln X_2 = C \ln T + \frac{D}{T} + E \quad (III)$$

$$-\ln X_2 = \frac{-\Delta H_f (T_m - T)}{RTT_m} + \frac{V_2 \phi_1^2 (\delta_1 - \delta_2)^2}{RT \ln [\epsilon \delta_1 (\delta_1 - \delta_2)^2]} \quad (IV)$$

$$-\ln X_2 = \frac{-\Delta H_f (T_m - T)}{RTT_m} + \frac{V_2 \phi_1^2 (\delta_1 - \delta_2)^2}{RT \ln [ET_{(30)} \delta_1 (\delta_1 - \delta_2)^2]} \quad (V)$$

In the above equations  $X_2$  is the mole fraction solubility of the solute,  $\Delta H_s$  and  $\Delta S_s$  are the enthalpy and the entropy of solution,  $\Delta H_f$  is enthalpy of solute fusion,  $R$  is the molar gas constant ( $1.9872 \text{ cal mol}^{-1} \text{ K}^{-1}$ ),  $T$  and  $T_m$  are the solution temperature and melting point of the solute (in K),  $A$ ,  $B$ ,  $C$ ,  $D$  and  $E$  stand for the models constants,  $V_2$  and  $\delta_2$  are the molar volume and solubility parameter of the solute,  $\phi_1$  and  $\delta_1$  denote the volume fraction and solubility parameter of the solvent, (represents dielectric constant and  $ET_{(30)}$  is the solvatochromic polarity parameter of the solvent. The value of  $\phi_1$  which is very close to 1 was assumed to be equal to one (18-21).

Eqs. I and II are two parameter models and a minimum number of two experimental solubilities which are determined at two different temperatures are required in order to predict solubilities at other temperatures. The constant terms of Eq. III are calculated by using a minimum number of three solubilities at three different temperatures. Eqs. IV and V are pure predictive models and require no experimental solubility data but require parameters related to solute structure and solvent which are easily calculated (22,23) or found in literature (24-27). The proposed models are as follows:

$$-\ln X_2 = -\ln X_2^i + \ln \left[ \frac{V_2 \phi_1^2 (\delta_1 - \delta_2)^2}{RT} \right] + F \quad (VI)$$

$$-\ln X_2 = -\ln X_2^i + \left[ \frac{V_2 \phi_1^2 (\delta_1 - \delta_2)^2}{RT} \right]^G \quad (VII)$$

Where  $X_2^i$  is ideal mole fraction solubility of the solute,  $F$  and  $G$  are the models constants which are calculated via a single solubility determination at  $25^\circ \text{C}$  by the following equations:

$$F = -\ln X_2 + \ln X_2^i - \ln \left[ \frac{V_2 \phi_1^2 (\delta_1 - \delta_2)^2}{RT} \right] \quad (VIII)$$

$$G = \frac{\ln \left( \ln \frac{X_2^i}{X_2} \right)}{\ln \left[ \frac{V_2 \phi_1^2 (\delta_1 - \delta_2)^2}{RT} \right]} \quad (IX)$$

Eq. VII is applicable only to those cases where  $X_2^i > X_2$  at  $25^\circ \text{C}$ .

The value of  $-\ln X_2^i$  in Eqs. VI and VII is given by Eq. X (28):

$$-\ln X_2^i = \frac{-\Delta H_f (T_m - T)}{RTT_m} \quad (X)$$

$\Delta H_f$  is calculated by Eq. XI:

$$\Delta H_f = \frac{0.02303 (T_m - T) RT_m}{\ln \left( \frac{T_m}{T} \right)} \quad (XI)$$

Substitution of  $\Delta H_f$  from Eq. XI into Eq. X yields Eq. XII.

$$-\ln X_2^i = \frac{0.02303 (T_m - T)^2}{T \ln \left( \frac{T_m}{T} \right)} \quad (XII)$$

The value of  $T$  in the latter equation is equal to  $298.15 \text{ K}$  (23). The value of  $X_2^i$  in the proposed models is calculated by means of Eq. XII.

To assess the prediction capability of the models, percent deviation (PD) for each data set, mean percent deviation (MPD) and number of sets with minimum PD values which are expressed as percentage of all sets (denoted as percent best adherence, PBA) are calculated. The latter two

criteria are employed for overall comparison of the models:

$$PD = \frac{100}{N} \sum \left( \frac{|X_2^{calculated} - X_2^{Observed}|}{X_2^{Observed}} \right) \quad (XIII)$$

$$MPD = \frac{\sum PD}{N_s} \quad (XIV)$$

$$PBA = \frac{N_{ba}}{N_s} \cdot 100 \quad (XV)$$

where N denotes the number of experimental data in each set,  $N_{ba}$  is number of sets with the best adherence for a model and  $N_s$  is the total number of sets.

In the present work we compared the accuracy and predictability of the proposed models (Eqs. VI and VII) with the classical two and three parameter models (Eqs. I–III) using the experimental solubility data of three sulfonamides in six solvents at various temperatures. Also the proposed models were compared with the pure predictive models (Eqs. IV and V). In addition to our data, the solubility data for different solutes with diverse structures in variety of solvents at various temperatures which are collected from the literature were employed to demonstrate the suitability and applicability of the proposed models.

## MATERIALS AND METHODS

### Chemicals:

All solvents were reagent grade from Merck (Germany). Double-distilled water was used throughout this investigation.

The solutes (sulphamethoxazole, sulphisoxazole and sulphasalazine) were kindly supplied by Daru-Pakhsh, Tehran, Iran. The purity of drugs was checked by infrared spectrophotometer (Shimadzu, Japan) and the IR spectra of the samples were the same as those of the references (29) and were above 99.3 %. Melting point of the compounds were 169, 194 and 253 °C for sulphamethoxazole, sulphisoxazole and sulphasalazine, respectively (29).

### Solubility determinations:

The solubilities of the sulfonamides were determined by equilibrating an excess amount of

solid with particular solvent at 15, 25, 37 and 45 °C using a thermostat incubator ( $\pm 1.7^\circ\text{C}$ ). After reaching equilibrium (5 days), the solutions were filtered using filters of pore size 0.5  $\mu\text{m}$  and diluted with solvents. The sulfonamide concentrations were quantified by a double-beam UV spectrophotometer (Shimadzu, Japan) at different wavelengths given in table 1. In order to convert molar concentrations into the mole fractions, the densities of the saturated solutions were determined in 5 ml pycnometer.

## RESULTS AND DISCUSSION

Table 1 shows the natural logarithm of mole fraction solubility of three sulfonamides in individual solvents at different temperatures together with  $\lambda_{\text{max}}$  values used for determination of the solutes concentration. For the all solvent systems, the higher temperature means higher solubility. The solutes exhibited maximum solubility in acetone and minimum in water.

Table 2 presents names of solutes and solvents used in our experiment as well as those which were taken from the literature, their physicochemical characteristics and the range of temperatures used in °C and number of data in each set (N). The mentioned parameters and quantities with the exception of N were used for calculation of the solutes solubility by means of Eqs. IV and V. Also some of these parameters are necessary for the solubility calculations via the proposed models.

In table 3 the values of PD, MPD and PBA for Eqs. I – VII calculated by Eqs. XIII and XIV together with the parameters of the proposed models i.e. F and G are listed. This table contains not only the results of our experimental data but also includes the results of data collected from the literature (12, 13, 26, 27, 30 -32). In the application of Eqs. I and II the solubility data at 25° and 37 °C were used in order to predict solubilities at other temperatures. In the data sets where the solubility value at 37 °C was not available, the value at the nearest temperature (35° or 40 °C) was used. The constant terms of Eq. III were calculated by solubility data at 25°, 37°, 50 °C or 0 °C in the absence of 50 °C datum. As mentioned above in the application of Eqs. IV and V no solubility data were required. The errors associated with the predicted solubilities by the

latter models were generally very high and above the acceptable 30% level (33, 34). The corresponding MPD values were 150.09 and 161.00%.

Eq. VI produced only one error higher than 30%. In contrast Eq. VII produced six PD values above 30% level. The number of PDs above 30% for Eqs. I – V were 2, 2, 4, 38 and 41, respectively. However, the MPD values for Eqs. VI and VII were 10.78 and 14.63, respectively which were comparable with those of two and three parameter models I - III (the corresponding MPD values were 9.64, 9.91 and 13.83%). Considering PBA criterion Eq. VII was the best as its PBA was 32.7% while suffering from the disadvantage that it could not be applied to 8 out of 51 sets because of its mathematical character. The corresponding criteria for Eqs. VI and I were 19.61%. This can be an advantage for Eq. VI which requires only a single solubility datum for predictions. In addition, Eq. VI does not have the limitation of

Eq. VII in that it is applicable for all data sets. Eqs. IV and V gave the lowest PBA values (1.96% and 0%) while the corresponding values of Eqs. II and III were 15.69 and 16.67% which were slightly less than those of Eq. I and VI.

### CONCLUSION

Solubility prediction based upon the minimum number of experiments is valuable from practical point of view, especially in the preformulation studies of a new drug that only small amount of the drug is available and in the processes involving temperature changes. The solubility predictions at different temperatures using the solubility at 25 °C are proposed employing Eqs. VI and VII, which have a single constant term and their accuracy and prediction capability were much superior to those of pure predictive models (Eqs. IV and V) but overall comparable to those of two and three parameter models (Eqs. I – III) requiring two and three experimental solubilities.

**Table 1** Natural logarithm of experimental mole fraction solubility data of sulphonamides in individual solvents at different temperatures and the corresponding  $\lambda_{\max}$  values

	T(°C)	Acetone	Chloroform	Ethanol	Methanol	1-Propanol	Water
Sulphamethoxazole	15	-2.53	-7.35	-5.35	-4.62	-6.21	-11.37
	25	-2.26	-7.15	-5.01	-4.24	-5.86	-10.83
	37	-1.96	-6.79	-4.66	-3.78	-5.42	-10.22
	45	-a	-6.39	-4.43	-3.58	-5.21	-9.91
$\lambda_{\max}$ (nm)		209.2	266.6	270.4	269.2	269.8	267.8
Sulphasalazine	15	-9.39	-a	-9.83	-10.67	-10.02	-13.33
	25	-9.22	-a	-9.54	-9.82	-9.85	-12.23
	37	-8.83	-a	-9.32	-9.51	-9.47	-11.77
	45	-a	-a	-9.06	-9.26	-9.20	-11.64
$\lambda_{\max}$ (nm)		349.4	-	349.2	349.2	349.2	350.0
Sulphisoxazole	15	-3.59	-8.42	-5.92	-5.39	-6.53	-11.95
	25	-3.22	-8.12	-5.51	-4.97	-6.20	-11.45
	37	-2.96	-7.75	-5.09	-4.55	-5.74	-10.93
	45	-a	-7.45	-4.83	-4.16	-5.47	-10.54
$\lambda_{\max}$ (nm)		209.4	266.6	270.8	269.6	271.2	263.2

<sup>a</sup>Not determined.

**Table 2** The details of solutes and solvents characteristics used for solubility calculations at different temperatures

No.	Solute	Solvent	t(°C)	N	$\delta_1$	$\epsilon^b$	$ET_{b(30)}$	$\delta_2$	$V_2$	$T_m(K)$	$\Delta H_f$	Reference
1	Sulphamethoxazole	Acetone	15-45	3	9.07 <sup>a</sup>	20.56	42.2	13.19 <sup>c</sup>	152.10 <sup>c</sup>	169.0	7393 <sup>d</sup>	This work
2	Sulphamethoxazole	Chloroform	15-45	4	8.77 <sup>a</sup>	4.81	39.1	13.19 <sup>c</sup>	152.10 <sup>c</sup>	169.0	7393 <sup>d</sup>	This work
3	Sulphamethoxazole	Ethanol	15-45	4	12.58 <sup>a</sup>	24.55	51.9	13.19 <sup>c</sup>	152.10 <sup>c</sup>	169.0	7393 <sup>d</sup>	This work
4	Sulphamethoxazole	Methanol	15-45	4	13.77 <sup>a</sup>	32.66	55.4	13.19 <sup>c</sup>	152.10 <sup>c</sup>	169.0	7393 <sup>d</sup>	This work
5	Sulphamethoxazole	1-Propanol	15-45	4	11.84 <sup>a</sup>	20.45	50.7	13.19 <sup>c</sup>	152.10 <sup>c</sup>	169.0	7393 <sup>d</sup>	This work
6	Sulphamethoxazole	Water	15-45	4	24.52 <sup>a</sup>	78.54	63.1	13.19 <sup>c</sup>	152.10 <sup>c</sup>	169.0	7393 <sup>d</sup>	This work
7	Sulphasalazine	Acetone	15-45	3	9.07 <sup>a</sup>	20.56	42.2	15.40 <sup>c</sup>	207.30 <sup>c</sup>	253.0	9666 <sup>g</sup>	This work
8	Sulphasalazine	Ethanol	15-45	4	12.58 <sup>a</sup>	24.55	51.9	15.40 <sup>c</sup>	207.30 <sup>c</sup>	253.0	9666 <sup>g</sup>	This work
9	Sulphasalazine	Methanol	15-45	4	13.77 <sup>a</sup>	32.66	55.4	15.40 <sup>c</sup>	207.30 <sup>c</sup>	253.0	9666 <sup>g</sup>	This work
10	Sulphasalazine	1-Propanol	15-45	4	12.58 <sup>a</sup>	20.45	50.7	15.40 <sup>c</sup>	207.30 <sup>c</sup>	253.0	9666 <sup>g</sup>	This work
11	Sulphasalazine	Water	15-45	4	24.52 <sup>a</sup>	78.54	63.1	15.40 <sup>c</sup>	207.30 <sup>c</sup>	253.0	9666 <sup>g</sup>	This work
12	Sulphisoxazole	Acetone	15-45	3	9.07 <sup>a</sup>	20.56	42.2	12.87 <sup>c</sup>	166.60 <sup>c</sup>	194.0	8035 <sup>d</sup>	This work
13	Sulphisoxazole	Chloroform	15-45	4	8.77 <sup>a</sup>	4.81	39.1	12.87 <sup>c</sup>	166.60 <sup>c</sup>	194.0	8035 <sup>d</sup>	This work
14	Sulphisoxazole	Ethanol	15-45	4	12.58 <sup>a</sup>	24.55	51.9	12.87 <sup>c</sup>	166.60 <sup>c</sup>	194.0	8035 <sup>d</sup>	This work
15	Sulphisoxazole	Methanol	15-45	4	13.77 <sup>a</sup>	32.66	55.4	12.87 <sup>c</sup>	166.60 <sup>c</sup>	194.0	8035 <sup>d</sup>	This work
16	Sulphisoxazole	1-Propanol	15-45	4	11.84 <sup>a</sup>	20.45	50.7	12.87 <sup>c</sup>	166.60 <sup>c</sup>	194.0	8035 <sup>d</sup>	This work
17	Sulphisoxazole	Water	15-45	4	24.52 <sup>a</sup>	78.54	63.1	12.87 <sup>c</sup>	166.60 <sup>c</sup>	194.0	8035 <sup>d</sup>	This work
18	Sulfanilamide	Water	20-75	7	24.52	78.54	63.1	12.98	110.40	438.54	7304	13
19	Acetylsulfanilamide	Water	20-75	7	24.52	78.54	63.1	13.58	134.20	454.28	7702	13
20	Sulfapyridine	Water	20-75	7	24.52	78.54	63.1	13.05	158.60	464.53	7978	13
21	Sulfadiazine	Water	20-75	7	24.52	78.54	63.1	13.85	151.10	528.28	9723	13
22	Sulfatiazole	Water	20-75	7	24.52	78.54	63.1	13.84	145.80	474.31	8231	13
23	Sulfamerazine	Water	20-75	7	24.52	78.54	63.1	13.48	164.60	509.11	9185	13
24	Sulfafurazole	Water	20-75	7	24.52	78.54	63.1	12.87	166.60	469.69	8111	13
25	Sulfamethylthiazole	Water	20-75	7	24.52	78.54	63.1	13.46	160.30	523.24	9579	13
26	Sulfadimidine	Water	20-75	7	24.52	78.54	63.1	13.16	179.10	471.12	8152	13
27	Sulfamethoxy pyridazine	Water	20-75	7	24.52	78.54	63.1	13.50	168.40	454.52	7720	13

Table 2 continued

28	Sulfaproxyline	Water	20-75	7	24.52	78.54	63.1	12.55	222.90	460.31	7859	13
29	Sulphamethoxypyridazine	Ethyl acetate	20-40	5	8.85	6.02	38.1	13.50 <sup>d</sup>	168.40 <sup>d</sup>	454.52 <sup>d</sup>	7720 <sup>d</sup>	26
30	Sulphamethoxypyridazine	Ethanol	20-40	5	12.58 <sup>a</sup>	24.55	51.9	13.50 <sup>d</sup>	168.40 <sup>d</sup>	454.52 <sup>d</sup>	7720 <sup>d</sup>	26
31	Sulphamethoxypyridazine	Water	20-40	5	24.52	78.54	63.1	13.50 <sup>d</sup>	168.40 <sup>d</sup>	454.52 <sup>d</sup>	7720 <sup>d</sup>	26
32	Paracetamol	Ethyl acetate	20-40	5	8.85 <sup>a</sup>	6.02	38.1	13.40 <sup>e</sup>	118.66 <sup>e</sup>	442.28	6274	27
33	Paracetamol	Ethanol	20-40	5	12.58 <sup>a</sup>	24.55	51.9	13.40 <sup>e</sup>	118.66 <sup>e</sup>	442.28	6274	27
34	Paracetamol	Water	20-40	5	24.52	78.54	63.1	13.40 <sup>e</sup>	118.66 <sup>e</sup>	442.28	6274	27
35	Phenacetin	Water	20-40	5	24.52	78.54	63.1	11.55	148.40	407.40	6523 <sup>g</sup>	30
36	Phenacetin	Dioxane	20-40	5	10.01 <sup>a</sup>	2.21	36.0	11.55	148.40	407.40	6523 <sup>g</sup>	30
37	Naphthalene	Hexane	0-50	6	7.30 <sup>a</sup>	1.88	31.0	9.89 <sup>a</sup>	111.50 <sup>a</sup>	353.15	5250 <sup>g</sup>	32
38	Naphthalene	Carbon tetrachloride	0-50	6	8.71 <sup>a</sup>	2.23	32.4	9.89 <sup>a</sup>	111.50 <sup>a</sup>	353.15	5250 <sup>g</sup>	32
39	Naphthalene	Toluene	0-50	6	8.88 <sup>a</sup>	2.38	33.9	9.89 <sup>a</sup>	111.50 <sup>a</sup>	353.15	5250 <sup>g</sup>	32
40	Naphthalene	Benzene	0-50	6	9.06 <sup>a</sup>	2.27	34.3	9.89 <sup>a</sup>	111.50 <sup>a</sup>	353.15	5250 <sup>g</sup>	32
41	Naphthalene	Chloroform	0-50	6	8.77 <sup>a</sup>	4.81	39.1	9.89 <sup>a</sup>	111.50 <sup>a</sup>	353.15	5250 <sup>g</sup>	32
42	Naphthalene	Chlorobenzene	0-50	6	9.59 <sup>a</sup>	5.62	36.8	9.89 <sup>a</sup>	111.50 <sup>a</sup>	353.15	5250 <sup>g</sup>	32
43	Naphthalene	Carbon disulfide	0-50	6	10.00 <sup>a</sup>	2.64	32.8	9.89 <sup>a</sup>	111.50 <sup>a</sup>	353.15	5250 <sup>g</sup>	32
44	Methyl paraben	Water	0-58	13	24.52	78.54	63.1	13.31 <sup>f</sup>	113.90 <sup>f</sup>	404.15	6143	12
45	Ethylparaben	Water	0-58	14	24.52	78.54	63.1	12.82 <sup>f</sup>	130.00 <sup>f</sup>	389.15	6334	12
46	Propyl paraben	Water	0-50	12	24.52	78.54	63.1	12.42 <sup>f</sup>	146.10 <sup>f</sup>	369.65	6692	12
47	Butylparaben	Water	0-35	8	24.52	78.54	63.1	12.09 <sup>f</sup>	162.20 <sup>f</sup>	341.65	5760	12
48	5-5-Diethyl barbituric acid	Water	10-50	9	24.52	78.54	63.1	14.20 <sup>f</sup>	125.80 <sup>f</sup>	463.15	5710	12
49	5-5-Diisopropyl barbituric acid	Water	10-50	9	24.52	78.54	63.1	13.02 <sup>f</sup>	158.60 <sup>f</sup>	496.15	7978	12
50	5-Ethyl 5-phenyl barbituric acid	Water	25-50	6	24.52	78.54	63.1	14.42 <sup>f</sup>	147.60 <sup>f</sup>	450.15	6058	12
51	Paracetamol	Water	5-70	17	24.52	78.54	63.1	13.40 <sup>e</sup>	118.66 <sup>e</sup>	443.15	7720	12

<sup>a</sup> The values were taken from reference (25), <sup>b</sup> The values of  $\epsilon$  and ET(30) were taken from reference (24), <sup>c</sup> The values of  $\delta_2$  and  $V_2$  were taken from reference (26), <sup>d</sup> Taken from reference (13), <sup>e</sup> Taken from reference (31)

**Table 3** Parameters of the proposed models(Eqs. VI and VII), percent deviation (PD) for each set, mean percent deviation(MPD) of all sets and percent best adherence(PBA) for Eqs. I - VII

No. <sup>a</sup>	The models constants		PD <sup>d</sup>						
	F <sup>b</sup>	G <sup>b</sup>	Eq. IV	Eq. V	Eq. VI	Eq. VII	Eq. I <sup>c</sup>	Eq. II <sup>c</sup>	Eq. III <sup>c</sup>
1	-3.2721	- <sup>c</sup>	95.14	94.62	9.52	- <sup>e</sup>	0.09	1.07	- <sup>f</sup>
2	1.4705	0.6982	298.73	499.48	7.21	10.87	13.81	12.98	16.39
3	3.2992	0.0215	163.48	165.19	8.83	5.16	1.88	2.11	4.48
4	2.6226	0.7155	17.75	18.21	2.88	2.29	6.17	5.96	15.60
5	2.5555	-0.7708	336.54	346.8	4.20	4.13	5.536	5.34	13.63
6	3.2705	0.5470	104.125	86.26	11.51	2.65	4.04	4.99	11.19
7	-0.4839	0.2910	76.64	69.31	14.77	13.89	16.45	15.40	- <sup>f</sup>
8	1.4505	0.8851	563.29	614.17	27.44	32.81	10.62	10.81	32.97
9	2.8221	-13.8535	1442.43	1476.33	28.63	125.50	41.32	41.91	93.54
10	1.7612	1.0007	414.23	486.59	18.66	25.63	9.46	9.12	11.28
11	1.7954	0.4872	23.64	27.59	32.65	35.38	59.49	61.52	55.34
12	-3.0937	- <sup>c</sup>	93.89	93.25	10.05	- <sup>e</sup>	14.66	15.63	- <sup>f</sup>
13	1.6588	0.7513	414.35	667.27	8.75	13.95	4.90	3.95	7.90
14	4.3414	0.1378	90.87	91.48	4.90	2.67	1.81	2.95	3.00
15	1.5377	1.9219	5.19	5.27	2.12	3.32	8.20	8.53	27.57
16	2.4986	-0.2099	228.44	234.29	4.56	2.36	4.84	4.64	10.40
17	2.8937	0.5155	31.66	38.28	5.54	2.64	4.86	5.23	14.54
18	0.0087	0.3641	73.20	75.22	17.51	16.93	9.56	13.83	11.31
19	1.0984	0.4489	40.08	45.04	11.38	7.37	6.04	3.31	5.07
20	2.4684	0.5045	33.11	37.41	19.86	11.25	20.67	26.62	15.39
21	1.7000	0.4818	33.35	32.10	10.01	16.05	21.12	25.76	25.54
22	1.8178	0.4917	9.86	11.72	15.52	9.51	3.13	1.30	1.21
23	1.4440	0.4550	60.67	64.66	9.71	10.34	17.65	16.59	24.16
24	3.0471	0.5218	34.78	36.22	5.30	10.94	13.44	17.62	17.20
25	1.3064	0.4486	65.30	68.74	9.82	4.75	1.57	2.22	1.16
26	1.7917	0.4631	64.03	68.07	24.30	35.87	5.92	4.40	16.23
27	2.1727	0.4922	39.59	44.02	10.79	5.56	12.04	16.16	10.43
28	5.1353	0.5545	56.28	55.25	10.58	40.29	7.37	10.15	6.30
29	-0.1051	0.2957	21.96	17.94	3.98	3.79	5.69	5.38	1.49
30	3.4854	-0.5075	693.03	702.27	11.18	6.10	10.44	10.40	18.26
31	2.1792	0.4925	47.72	53.33	6.80	6.44	11.54	11.65	13.80
32	-0.5712	-0.1135	24.48	64.50	12.57	9.58	2.42	2.62	2.37
33	0.8509	- <sup>c</sup>	40.80	40.39	15.40	- <sup>e</sup>	3.87	3.90	5.38
34	-1.0185	0.2444	81.74	83.16	7.18	6.23	5.65	5.70	7.06
35	2.7149	0.4985	65.68	69.91	2.74	2.95	2.84	2.91	5.03
36	1.6331	-0.2042	109.96	141.64	3.97	6.62	3.04	3.10	5.28
37	0.4743	-1.4862	20.91	42.59	19.67	30.56	1.44	3.03	5.45
38	1.2985	- <sup>c</sup>	20.27	13.42	1.65	- <sup>e</sup>	3.84	2.04	10.36
39	1.7399	1.4625	14.03	8.50	8.13	7.88	19.10	19.57	36.23
40	1.9006	- <sup>c</sup>	23.07	18.55	5.35	- <sup>e</sup>	1.88	1.10	6.98
41	1.1601	- <sup>c</sup>	35.31	32.18	10.93	- <sup>e</sup>	3.50	2.17	7.80
42	3.8501	- <sup>c</sup>	23.27	22.23	9.25	- <sup>e</sup>	1.99	0.77	5.71
43	5.9322	- <sup>c</sup>	12.60	13.34	2.88	- <sup>e</sup>	2.23	4.89	4.15
44	2.1916	0.5282	184.83	163.17	3.60	6.14	7.50	6.26	12.95
45	3.4148	0.5642	245.25	213.61	9.17	8.31	11.38	9.89	11.31
46	4.9321	0.5973	302.73	258.54	15.70	15.61	23.11	21.35	22.69
47	5.8681	0.6043	368.51	307.85	5.32	13.23	16.05	13.80	5.24
48	-0.6272	0.2927	28.73	33.92	16.48	15.31	3.02	2.31	2.20
49	0.8703	0.4177	74.15	76.93	13.10	16.57	5.43	4.59	4.66
50	1.6483	0.4902	216.06	190.58	6.88	13.18	3.34	2.62	1.31
51	-0.9465	0.2545	88.70	89.55	10.62	8.56	15.75	15.36	16.25
MPD <sup>g</sup>	-	-	150.09	161.00	10.78	14.63	9.64	9.91	13.83
PBA <sup>h</sup>	-	-	1.96	0.00	19.61	32.56	19.61	15.69	16.67

<sup>a</sup> The set numbers are the same as Table 2, <sup>b</sup> The models constants obtained employing experimental solubility at 25°C and known  $T_m$  values by means of Eqs. VIII and IX, <sup>c</sup> The values of G could not be calculated due to  $X_2^i < X_2$  at 25 °C.

<sup>d</sup> Calculated with the aid of Eq. XIII, <sup>e</sup> Not determined because of  $X_2^i < X_2$  at 25 °C, <sup>f</sup> Prediction was not possible due to scarcity of data, <sup>g</sup> Calculated by means of Eq. XIV, <sup>h</sup> Calculated by Eq. XV

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