A simple QSPR model to predict aqueous solubility of drugs

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Aqueous solubility of a drug/drug candidate is essential data in drug discovery, and an in silico method for predicting the aqueous solubility of drug candidates provides a valuable tool to speed up the process of drug discovery and development. This paper describes a simple quantitative structure property relationship (QSPR) model for predicting the aqueous solubility of drugs which is validated by cross-validation methods. A data set of 220 drug or drug like molecules as a train set was employed and the accuracy of the proposed QSPR model was compared with those of the general solubility equation (GSE) and the linear solvation energy relationship (LSER). Also, a test set containing the aqueous solubility of 75 official drugs which are structurally and physico-chemically diverse, was proposed to compare the accuracy of the aqueous solubility prediction models as a reference data set. The developed model is: $\log S_w = -1.120E - 0.599ClogP$, in which S_w is the molar aqueous solubility of a drug, E is the excess molar refraction and ClogP is the computed logarithm of partition coefficient of drug. The E and ClogP values for a drug candidate could be computed using Pharma-Algorithms software. Average absolute error (AAE) and mean percentage deviation (MPD) were used as comparison criteria. The proposed QSPR provided better AAE and MPD for solubility prediction in comparison with GSE and LSER models.

Key words: Aqueous Solubility – Prediction – QSPR – Drug.

Aqueous solubility of a drug/drug candidate is essential data in drug discovery because poor soluble compounds have low absorption and failed to proceed in drug discovery processes. In addition, aqueous solubility investigations are important for oral or parenteral drug liquid formulations. Also the solubility in water shows its importance where it is necessary to make a solution to test pharmacological or toxicological activities of the compounds. Solubility data is required for determination of absorption, distribution, metabolism and excretion (ADME) and is an important topic in drug extraction and analysis [1, 2].

Determination of solubility values is time-consuming, costly and affected by various factors, e.g. the aqueous solubility of ionizable compounds measured at pH 7 or in unbuffered water, however total solubility is equal to intrinsic solubility when pH < pKa for acids and when pH > pKa for bases [2, 3]. The other factors which affect the experimental solubility measurement are solute purity, equilibration time, temperature, and laboratory technique [2]. As an alternative, a number of quantitative structure property relationships (QSPRs) have been reported for solubility prediction of chemical compounds in water. Due to economic and humanitarian pressures, these models can improve the efficiency of drug discovery but solubility is a difficult physicochemical parameter to be predicted [4]. One reason for this problem is the lack of high quality dataset for designing and comparing the solubility prediction models [2]. Another problem is the applicability of the model for solubility prediction by using the accessible calculated parameters which make it easier to use for the researchers of the pharmaceutical and chemical sciences.

The solubility prediction models could be classified in two categories; models using 1D or 2D descriptors and models using 3D descriptors. The models using 1D or 2D descriptors are simple and their calculations are straightforward. The most accurate and famous models are: i) general solubility equation (GSE) of Yalkowsky and ii) the linear solvation energy relationship (LSER) of Abraham. The GSE consists of two parameters; melting point (*mp*) and logarithm of partition coefficient (*logP*) and is expressed as:

$$\log S_w = 0.5 - 0.01(mp - 25) - \log P \qquad \textbf{Eq. 1}$$

where S_w is the molar aqueous solubility of a drug at 25 ºC. If the solute has a melting point of less than 25 ºC, the (*mp* - 25) term is set to zero [5]. The two parameters, *logP* and *mp* are good representatives of the effects of hydrophobicity and crystal packing on the solubility of a certain solute [5]. A possible disadvantage is the melting point as an experimental parameter which may not be available for some of the compounds in the early stages of drug discovery. Also, drugs with high melting points which decompose before melting are not suitable to be predicted by the GSE model [6, 7]. The *logP* can be measured using experimental methods such as HPLC [6], and/or calculated by some computational methods [8, 9], then applied to solubility prediction. The *logP* is the important parameter for solubility prediction where some models proposed are based on *logP*. For the first time, Hansch *et al*. proposed a linear relationship between aqueous solubility and *logP*. But for complex molecules addition of other parameters are required. A number of models based on *logP* could be found in the literature [2, 3, 6, 10].

The LSER is another model developed by Abraham that composed of five properties of the solute [11]:

$$\log S_w = 0.318 - 1.004E + 0.77S + 2.168A + 4.238B - 3.362A \cdot B - 3.987V \qquad \textbf{Eq. 2}$$

and was updated as [12]:

$$\log S_w = 0.395 - 0.955E + 0.320S + 1.155A + 3.255B - 0.785A \cdot B - 3.330V \qquad \textbf{Eq. 3}$$

in which *E* is the excess molar refraction of the compound, *S* is the dipolarity/polarizability, *A* and *B* are hydrogen bond acidity and basicity, respectively [13]. These last three parameters (*S*, *A* and *B*) are determined from solubility data of a compound in water and different organic solvents, the *A·B* term is representative of hydrogen-bond interactions between acidic and basic functional groups of the drug in its pure solid or liquid [11] and *V* is one percent of the McGowan volume and can be calculated simply using a group contribution method [13]. In this work, an updated version of LSER (*Equation 3*) was used for comparing with other models.

The *E* descriptor is defined as:

$$E = MRx - aV + b \qquad \text{Eq. 4}$$

in which *MRx* is molar refraction and the units of *E* and *MRx* are (cm^3 mol^{-1})/10, *a* and *b* are the model constant. *MRx* is calculated by [13]:

$$MRx = 10[(\eta^2 - 1)/(\eta^2 + 2)]V \qquad \text{Eq. 5}$$

where η is the refractive index of the compound as a pure liquid at 20 °C.

Unfortunately, experimental Abraham's solute parameters are not available for some drugs but the parameters can be calculated by Pharma-Algorithms software [14], thus with calculated parameters, the LSER model can be considered as a computational model.

The GSE and LSER approaches are the golden and famous models for predicting aqueous solubility of chemical compounds, but prediction error of these models are relatively high for solubility prediction of drug and drug like molecules [1].

The models based on 3D descriptors were reviewed by Balakin *et al*. [15]. These descriptors have some problems such as difficulties in calculation and optimization of molecular geometry which can influence the capability of the prediction methods [15]. Also there are few examples of 3D methods which show good prediction in comparison with other descriptors [6]. Recently, Duchowicz *et al*. proposed a new QSPR model for the prediction of aqueous solubility using three DRAGON descriptors. One of the descriptors is a radial distribution function-6.0/unweighted (a 3D descriptor) [16].

The number of articles dealing with the aqueous solubility prediction methods has increased in recent years, revealing the importance of the subject in the pharmaceutical area [5]. Most of the presented methods were reviewed by Taskinen and Norinder [3]. In these articles, different data sets have been reported as test sets and as a consequence the accuracy of the models could not be directly compared. To cover this, structurally and physico-chemically diverse drugs as a test set are required. For the first time, a data set is developed by Yalkowsky consisting of 21 chemical and pharmaceutical compounds and is used by other researchers to compare the accuracies of aqueous solubility prediction models [6]. These 21 compounds are not more pharmaceutically interested compounds and also are not structurally and physico-chemically diverse.

The aims of this work are to propose a simple QSPR for predicting the aqueous solubility of drugs and also to provide a diverse test set for comparing the accuracies of the aqueous solubility prediction methods.

I. EXPERIMENTAL

The experimental aqueous solubilities of 220 drugs and/or drug like molecules at 25 °C were collected from the literature as a train data set (data points dealing with the intrinsic solubility were excluded) [2, 16-20]. The selected solutes for the train set including drug and/or drug like molecules were also extracted from recently published works. Melting points and experimental *logP* (*ElogP*) values of the studied solutes were taken from ChemIDplus (National Library of Medicine) [21], and calculated Abraham solvation parameters and calculated *logP* (*ClogP*) from Pharma-Algorithms software [14]. We selected Abraham solvation parameters, *ClogP* and melting points for developing a new QSPR model by stepwise multiple linear regression (MLR). To validate the proposed model and in order to assess its prediction capability, cross validation methods were used. The data is sorted by aqueous solubility and divided into two, four and ten groups. Each group was excluded from the training process and the excluded data was considered as a validation set. The predictive squared correlation coefficient (Q^2) calculated by *Equations 6 to 8* were considered to deal with the validity of the model [22]:

$$Q_{F1}^2 = 1 - \frac{\displaystyle\sum_{i=1}^{n\,Validation\,set}(y_i' - y_i)^2}{\displaystyle\sum_{i=1}^{n\,Validation\,set}(y_i - \bar{y}_{Train\,set})^2} \qquad \text{Eq. 6}$$

$$Q_{F2}^2 = 1 - \frac{\displaystyle\sum_{i=1}^{n\,Validation\,set}(y_i' - y_i)^2}{\displaystyle\sum_{i=1}^{n\,Validation\,set}(y_i - \bar{y}_{Validation\,set})^2} \qquad \text{Eq. 7}$$

$$Q_{F3}^2 = 1 - \frac{\left[\displaystyle\sum_{i=1}^{n\,Validation\,set}(y_i' - y_i)^2\right]/n_{Validation\,set}}{\left[\displaystyle\sum_{i=1}^{n\,Train\,set}(y_i - \bar{y}_{Train\,set})^2\right]/n_{Train\,set}} \qquad \text{Eq. 8}$$

In these equations, y_i and y_i' are experimental and predicted values respectively, *n* is number of the compounds in the validation set and $\bar{y}$ indicate the means of the training and validation sets.

To compare the accuracy of aqueous solubility prediction using GSE, LSER and the proposed models, a data set composed of 75 structurally and physico-chemically diverse drugs as a test set is proposed. Normal distribution of aqueous solubility data and solute's parameters were checked by Kolmogorov-Smirov and Shapiro-Wilk tests. The range of the experimental solubility and physicochemical properties (e.g. *logP, mp*) are as wide as possible and approximately equal numbers of acidic, basic and neutral drugs were employed.

An external validation method employing the proposed test set was used to check the validity of QSPR model considering the following criteria taken from the literature [23, 24]:
1) R^2 > 0.6 and Q^2 > 0.5, where R^2 is the squared correlation coefficient between the predicted (y_i'') and experimental (y_i) solubilities of compounds in the test set and Q^2 is defined as:

$$Q^2 = 1 - \frac{\displaystyle\sum_{i=1}^{n\,Test\,set}(y_i - y_i'')^2}{\displaystyle\sum_{i=1}^{n\,Test\,set}(y_i - \bar{y}_{Train\,set})^2} \qquad \text{Eq. 9}$$

in which $n_{Test\,set}$ is the number of compounds in the test set and $\bar{y}_{Train\,set}$ indicates the mean of the train set;
2) $[(R^2 - R_0^2)/R^2]$ or $[(R^2 - R_0'^2)/R^2] < 0.1$, where R^2 from a test set should be close to R_0^2 or $R_0'^2$ (R_0^2 is the squared correlation coefficient of the predicted versus experimental values using with intercept analysis and $R_0'^2$ is that of a no intercept regression analysis);
3) k (slope of the regression line of the predicted versus experimental solubilities using intercept regression) or k' (slope of the regression line of the predicted versus experimental solubilities using with no intercept regression) value should be between 0.85 to 1.15 [23, 24].

Accuracy of the solubility prediction by the proposed model in train and test sets was compared with those of GSE and LSER by performing a paired t-test. Abraham *et al*. used the experimental Abraham's solvation parameters but these parameters have not been reported for some compounds therefore, we used the Abraham's solvation parameters computed by Pharma-Algorithms software. Different *logP* values are available for a given solute and the impact of the experimental *logP* and calculated *logP* by Pharma-Algorithms [14], KowWin [25], ACD/Labs [26], and *alogPs* [27] values on the prediction capability of the proposed model and GSE for test set was also studied.

The accuracy of the predicted solubilities is calculated by average absolute error (AAE) and mean percentage deviation (MPD) criteria, defined as:

$$AAE = \frac{\sum \left| \log S_w^{Calculated} - \log S_w^{Observed} \right|}{N}$$

Eq. 10

$$MPD = \frac{100}{N} \sum \frac{\left| S_w^{Calculated} - S_w^{Observed} \right|}{S_w^{Observed}}$$

Eq. 11

in which N is the number of data points. All analyses were performed by Excel 2003 software.

II. RESULTS AND DISCUSSION

The $\log S_w$ of 220 drugs (details listed in *Table I*) are regressed against seven investigated descriptors (Abraham solvation parameters, *MP* and *ClogP*), *E* and *ClogP* were selected by stepwise MLR method to develop a two variable model for aqueous solubility prediction. The two parameters made a significant (p < 0.0005) contribution to the model as:

$\log S_w = -1.120E - 0.599 ClogP$
$N = 220, R^2 = 0.934, s = 0.893, F = 1538$

Eq. 12

N is the number of drugs in the training set, R^2 is the squared correlation coefficient, s is the standard error of estimate and F is F-value (Fisher variance ratio). The inverse relation between *ClogP* and aqueous solubility has been reported earlier and shows the relation between solubility and lipophilicity of the solute [2]. The *E* parameter or excess molar refraction which could be calculated by Pharma-Algorithms software or according to *Equation 4* is composed of two parameters: the *V* and *MRx* that are indicators of the aqueous solubility of a molecule because these parameters can be calculated by atomic fragmental and the number of bonds in the molecule [13, 28]. A mechanistic interpretation is required for a valid QSPR model [29]. In this work, the employed descriptors have physicochemical interpretations as explained above, that are in agreement with the solubility mechanism and shows the validity of model. The *ClogP* and *E* values are scattered and there is no cross correlation between the employed independent variables as shown in *Figure 1*.

Tables I and II listed the details of train and test sets. The overall errors in correlation and prediction analyses for the investigated models for train and test sets are shown in *Tables III and IV*, respectively. Graphs of the estimates from three methods for train and test sets are shown in *Figures 2 and 3*. The proposed model shows better correlation between experimental and predicted aqueous solubility and AAE and MPD values of the proposed model are less than those of the GSE and LSER models. The overall deviations of these models have high standard deviations, because of some outliers of the predicted aqueous solubility data. Possible reasons for these outliers in predictions could be any impurity of drugs, polymorphism, any systematic errors in solubility experiments, inadequate equilibration time and temperature variations [1]. As an example, different polymorphs possess different solubilities [1], however, this is not considered in the independent variables of the GSE, LSER and the proposed models. Computational weakness of the model is another reason for the predicted outliers. To further investigate on the models' accuracies, the 10 % highest and lowest MPDs or AAEs from train and test sets for each model are excluded and the overall deviations are shown in *Tables III and IV*. In this case, the proposed model provided better results when compared with the AAE and MPD of GSE and LSER models.

The *logP* is an experimental parameter but it can be calculated by some software. In this work, the impact of the various *logP* values on the prediction capability of the GSE and the proposed model was studied. The correlations between calculated *ClogPs* and *ElogP* for test set are investigated and shown in *Figure 4*. The aqueous solubilities are predicted by GSE and the proposed model using *ElogP* and *Clogp*
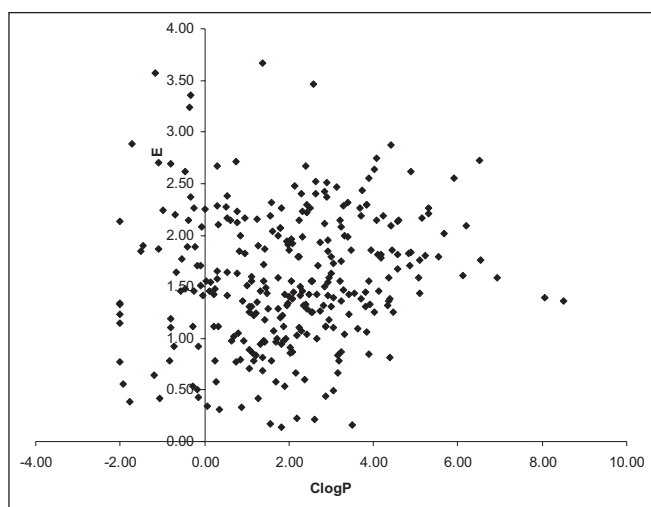

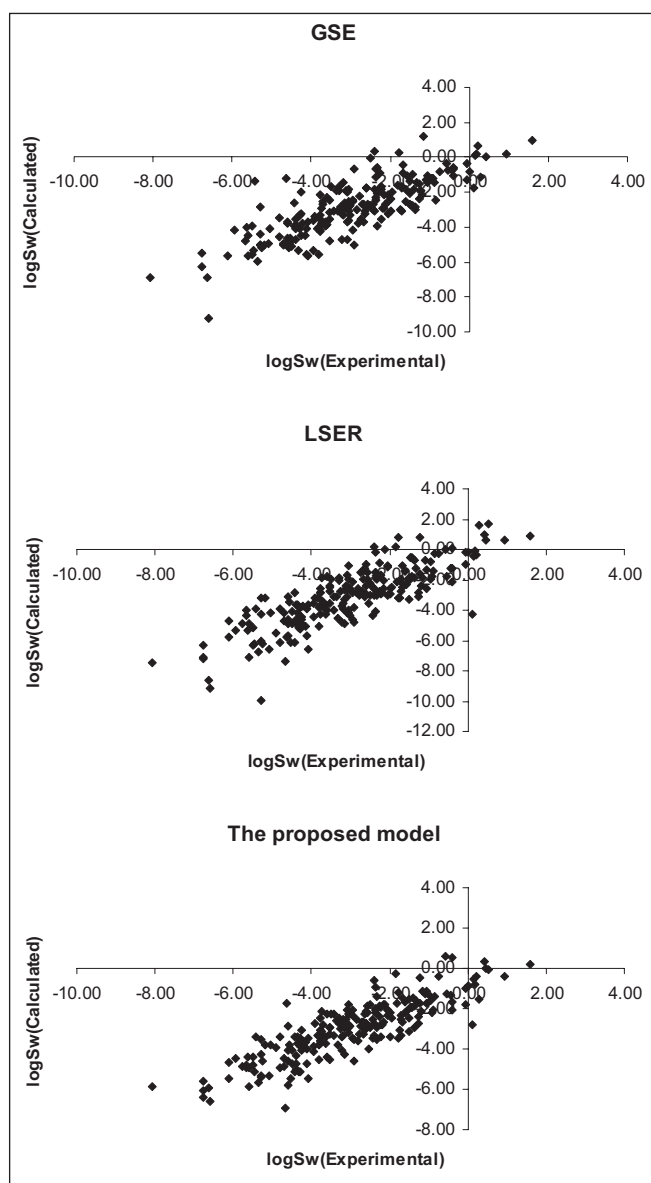**Figure 1 -** Scatter plot of *ClogP* versus *E* values for data points of train and test sets (N = 295).

Figure 2 - The correlation between experimental values versus predicted values using GSE ($R^2 = 0.65$), LSER ($R^2 = 0.68$), and the proposed model (*Equation 12*) ($R^2 = 0.73$) for train set.

Table I - The train set of experimental ($logS_w$) and calculated ($clogS_w$) aqueous solubility data, deviation values (absolute error [AE] and percentage deviation [PD]) of three different models.

No.	Solute	Ref.	$logS_w$	GSE			LSER			Proposed model		
				$clogS_w$	AE	PD	$clogS_w$	AE	PD	$clogS_w$	AE	PD
1	1-Naphthol	[18]	-1.98	-3.04	1.06	91.3	-2.59	0.61	75.3	-3.37	1.39	95.9
2	2-Amino-5-bromobenzoic acid	[18]	-3.07	-3.72	0.64	77.1	-1.70	1.37	2249.2	-2.94	0.14	36.6
3	4-Iodophenol	[18]	-1.71	-3.11	1.39	95.9	-2.17	0.45	64.6	-3.33	1.61	97.6
4	1,6-Cleve's acid	[16]	-2.35	-**	-	-	-1.50	0.85	606.2	-1.97	0.38	139.3
5	2,2',4,5,5'-PCB	[7]	-6.77	-6.23	0.54	246.7	-7.18	0.41	60.7	-6.04	0.73	432.3
6	2,4,5-Trichlorophenol	[16]	-2.22	-3.56	1.34	95.5	-2.92	0.70	80.0	-3.38	1.16	93.1
7	2,4-DB	[16]	-3.73	-3.74	0.01	1.5	-3.38	0.36	126.7	-3.14	0.59	292.8
8	2-Cyclohexyl-4,6-dinitrophenol	[16]	-4.25	-4.44	0.19	35.7	-4.86	0.61	75.3	-4.09	0.16	43.5
9	2-Ethyl-1-hexanol*	[16]	-2.17	-2.11	0.06	15.0	-2.56	0.39	58.9	-1.80	0.37	136.5
10	3,4-Dinitrobenzoic acid	[16]	-1.50	-2.65	1.15	92.9	-1.83	0.33	53.1	-2.48	0.98	89.4
11	4-Amino-2-sulfobenzoic acid	[16]	-1.85	-**	-	-	0.15	2.00	9852.4	-0.29	1.56	3509.9
12	4-Hydroxybenzoic acid	[18]	-1.46	-2.80	1.33	95.3	-0.49	0.97	836.9	-1.93	0.46	65.6
13	Acequinocyl	[16]	-6.76	-**	-	-	-7.13	0.37	57.6	-6.38	0.38	138.9
14	Acetamide	[16]	1.58	1.00	0.58	73.7	0.86	0.72	81.0	0.17	1.41	96.1
15	Acetamiprid	[16]	-1.72	-1.75	0.02	5.4	-1.94	0.21	38.5	-2.34	0.61	75.7
16	Acetanilide	[16]	-1.32	-1.44	0.12	23.8	-1.27	0.05	13.4	-1.62	0.29	49.2
17	Acetochlor	[16]	-3.08	-4.73	1.64	97.7	-4.21	1.13	92.5	-2.95	0.13	34.8
18	Acetylacetone*	[16]	0.22	0.65	0.43	168.8	-0.34	0.56	72.3	-0.39	0.61	75.4
19	Acibenzolar-S-methyl	[16]	-4.44	-2.63	1.81	6309.0	-2.83	1.60	3899.5	-3.41	1.03	967.4
20	Aconitic acid	[16]	0.46	-**	-	-	0.59	0.13	34.2	0.00	0.46	65.0
21	Acrylamide	[16]	0.95	0.19	0.77	83.0	0.61	0.34	54.6	-0.43	1.39	95.9
22	Acrylonitrile	[16]	0.15	0.15	0.00	0.6	-0.48	0.62	76.3	-0.55	0.70	80.1
23	Adenine	[16]	-2.12	-2.68	0.56	72.6	-0.02	2.09	12334.1	-1.80	0.32	108.0
24	Adipic acid	[16]	-0.75	-0.84	0.09	18.9	-0.29	0.46	188.3	-0.41	0.34	117.1
25	Aldicarb	[16]	-1.50	-1.40	0.10	25.7	-2.09	0.59	74.2	-1.56	0.06	13.5
26	Allidochlor	[16]	-0.95	-**	-	-	-1.99	1.04	90.9	-1.59	0.64	77.2
27	Allobarbital	[16]	-2.06	-2.13	0.07	14.8	-1.17	0.89	680.0	-2.05	0.01	2.1
28	Alochlor	[16]	-3.05	-2.52	0.53	239.6	-4.21	1.16	93.1	-2.95	0.10	25.2
29	Alpha-acetylbutyrolactone*	[16]	0.19	0.22	0.03	6.3	-0.07	0.26	45.3	-0.81	1.01	90.1
30	Alprenolol	[18]	-2.63	-3.27	0.64	76.9	-3.11	0.48	66.6	-3.07	0.44	63.6
31	Amicarbalide	[16]	-1.77	-**	-	-	-3.16	1.39	95.9	-3.46	1.69	97.9
32	Aminopromazine	[16]	-5.75	-**	-	-	-4.92	0.83	580.8	-4.85	0.90	698.8
33	Amitraz	[16]	-5.47	-5.34	0.13	34.1	-6.24	0.78	83.3	-5.13	0.33	115.3
34	Amobarbital	[16]	-2.57	-2.70	0.13	25.1	-1.96	0.61	310.9	-2.22	0.36	128.4
35	Ampicillin	[2]	-1.69	-0.87	0.82	560.7	-2.45	0.76	82.6	-2.64	0.95	88.7
36	Ancymidol	[16]	-2.60	-1.75	0.85	609.2	-2.89	0.29	49.2	-2.75	0.15	29.1
37	Androstanolone	[20]	-4.16	-4.49	0.33	53.2	-5.09	0.93	88.3	-3.64	0.52	227.5
38	Aniline*	[16]	-0.41	-0.64	0.23	40.7	-1.21	0.80	84.1	-1.64	1.23	94.1
39	Anthraquinone	[20]	-5.19	-5.03	0.16	44.5	-3.23	1.96	9111.8	-3.80	1.39	2348.2
40	ANTU	[16]	-2.53	-2.76	0.23	41.4	-3.53	1.00	89.9	-4.01	1.49	96.7
41	Ascorbic acid	[16]	0.28	-1.12	1.40	96.0	1.62	1.34	2106.8	-1.56	1.83	98.5
42	Aspirin	[7]	-1.61	-1.82	0.21	38.3	-1.43	0.18	51.9	-1.66	0.05	11.9
43	Asulam	[16]	-1.66	-0.44	1.22	1571.8	-1.09	0.57	274.6	-1.47	0.19	54.7
44	Atrazine	[7]	-3.55	-3.52	0.03	7.2	-2.74	0.81	538.5	-2.91	0.64	335.9
45	Azidamfenicol	[16]	-1.17	1.18	2.35	22245.6	-1.87	0.70	80.1	-1.15	0.02	5.1
46	Azintamide	[16]	-1.72	-1.68	0.04	8.5	-2.71	1.00	89.9	-2.53	0.82	84.7
47	Azoxystrobin	[16]	-4.61	-3.81	0.80	524.8	-4.58	0.03	6.1	-4.62	0.01	2.4
48	Badische acid	[16]	-2.57	-**	-	-	-1.50	1.07	1085.6	-1.86	0.71	414.9
49	Barban	[16]	-4.37	-3.43	0.94	770.5	-3.68	0.69	390.0	-3.42	0.95	786.1
50	Barbital	[16]	-1.39	-1.80	0.41	60.9	-0.64	0.75	466.9	-1.48	0.09	18.1
51	Bendiocarb	[16]	-2.93	-2.43	0.50	219.0	-2.12	0.82	553.1	-2.36	0.57	274.4
52	Benzidine	[16]	-2.76	-2.20	0.56	263.4	-3.00	0.24	42.7	-3.26	0.50	68.4
53	Benzoic acid	[2]	-1.59	-2.51	0.92	88.1	-1.46	0.13	36.4	-2.18	0.59	74.2
54	Benzylimidazole	[16]	-2.26	-1.73	0.53	237.1	-2.72	0.46	65.3	-2.41	0.15	29.0
55	Betamethasone	[20]	-3.77	-3.35	0.42	163.0	-4.24	0.47	66.1	-3.38	0.39	145.4
56	Bifenox	[16]	-5.93	-4.19	1.74	5410.5	-5.30	0.63	330.3	-4.46	1.47	2841.5
57	Bifentrhin	[16]	-6.63	-6.87	0.24	43.0	-8.59	1.97	98.9	-5.92	0.71	409.4
58	Bifonazole	[19]	-5.59	-5.65	0.06	12.7	-7.11	1.52	97.0	-5.85	0.26	44.7
59	Biotin	[16]	-3.05	-2.81	0.24	72.2	-1.98	1.07	1064.0	-2.24	0.80	533.8
60	Bupivacaine	[18]	-3.22	-4.68	1.45	96.5	-4.80	1.57	97.3	-4.07	0.85	85.9
61	Caffeine	[20]	-0.95	-1.19	0.24	42.5	-0.82	0.13	36.1	-1.38	0.43	62.5
62	Capric acid	[16]	-3.45	-3.06	0.39	143.3	-3.13	0.32	108.6	-2.27	1.18	1402.3
63	Caproic acid*	[16]	-1.05	-1.05	0.00	0.7	-1.29	0.24	42.5	-1.12	0.06	13.8
64	Carbofuran	[16]	-2.84	-2.99	0.15	29.2	-2.89	0.05	10.5	-2.56	0.28	91.0
65	Carbosulfan*	[16]	-6.10	-5.63	0.47	196.8	-5.74	0.36	130.2	-5.46	0.64	336.7

Table I - The train set of experimental (logS$_w$) and calculated (clogS$_w$) aqueous solubility data, deviation values (absolute error [AE] and percentage deviation [PD]) of three different models (continued).

| No.	Solute	Ref.	logS$_w$	GSE			LSER			Proposed model		
				clogS$_w$	AE	PD	clogS$_w$	AE	PD	clogS$_w$	AE	PD
66	Carboxin	[16]	-1.94	-2.69	1.13	1257.2	-2.59	0.38	140.9	-2.82	0.26	80.4
67	Carfentrazone-ethyl*	[16]	-1.97	-4.67	2.30	19949.4	-1.70	0.39	59.7	-3.07	1.20	1493.7
68	Carisoprodol	[16]	-2.53	-2.86	0.41	156.2	-2.17	0.08	18.9	-2.08	0.86	620.6
69	Carprofen	[18]	-5.06	-4.72	0.36	56.0	-1.50	0.02	4.8	-4.84	0.14	28.0
70	Chlordane	[7]	-5.98	-6.74	0.63	76.6	-7.18	1.39	96.0	-5.64	0.29	49.0
71	Chlorpropamide	[18]	-2.86	-2.72	0.39	144.6	-2.92	0.52	234.6	-3.02	0.23	69.5
72	Chlorprothixene form I	[18]	-5.53	-6.35	1.22	1577.5	-3.38	0.40	149.2	-5.63	1.12	1210.5
73	Chlorpyriphos	[7]	-4.75	-4.36	0.92	731.8	-4.86	1.31	1961.3	-4.81	0.86	632.8
74	Chlorzoxazone	[18]	-3.72	-1.46	1.06	91.3	-2.56	1.19	1459.4	-3.25	0.59	74.6
75	Cholesterol	[20]	-9.23	-9.18	2.62	99.8	-1.83	2.57	99.7	-6.60	0.01	1.4
76	Cimetidine	[2]	-0.97	-1.76	0.46	188.4	0.15	0.33	52.9	-1.94	0.51	68.9
77	Citral*	[20]	-2.54	-3.00	0.48	66.9	-0.49	0.94	88.4	-2.37	0.31	50.6
78	Codeine	[19]	-2.04	-3.28	0.53	70.5	-7.13	1.77	98.3	-3.14	1.63	97.7
79	Corticosterone	[2]	-3.28	-3.91	0.08	16.8	0.86	0.71	80.3	-3.32	0.12	24.2
80	Crotonic acid	[16]	-0.85	-0.17	0.85	85.8	-1.94	0.17	31.8	-0.89	0.89	87.2
81	Cumic acid	[16]	-3.62	-2.53	0.58	73.6	-1.27	0.51	220.3	-2.78	0.26	81.2
82	Cyanazine	[16]	-2.94	-2.71	0.21	61.6	-4.21	0.44	176.4	-2.77	0.38	138.0
83	Cyclizine	[16]	-2.99	-4.32	0.56	72.4	-0.34	1.90	98.7	-3.50	1.07	91.5
84	Cyclobarbital	[16]	-2.94	-2.09	0.77	83.0	-2.83	0.08	20.6	-2.64	0.47	66.3
85	Cycloleucine	[16]	-0.61	0.11	0.20	36.4	0.59	0.52	231.6	0.54	0.95	796.3
86	Cymoxanil	[16]	-0.71	-0.18	1.64	4296.0	0.61	2.17	14677.1	-0.93	1.41	2499.4
87	Cyproconazole	[16]	-3.06	-4.52	0.26	83.7	-0.48	1.20	93.7	-3.78	0.46	65.5
88	Cyprodinil	[16]	-3.25	-4.43	0.99	876.7	-0.02	0.19	35.9	-3.89	0.35	124.9
89	Danazol	[20]	-5.57	-6.28	0.06	12.9	-0.29	0.77	83.0	-4.82	0.69	392.5
90	DDT	[7]	-6.89	-7.48	1.19	1448.8	-2.09	0.60	298.9	-5.88	2.20	15728.1
91	Dehydroacetic acid	[16]	0.37	0.17	2.76	57007.0	-1.99	2.56	35849.2	-0.60	1.79	6050.9
92	Desipramine	[2]	-5.60	-5.11	1.79	98.4	-1.17	1.30	95.0	-4.52	0.71	80.6
93	Dexamethasone	[16]	-3.67	-4.24	0.03	5.6	-4.21	0.59	74.6	-3.38	0.26	84.0
94	Diallate	[16]	-3.35	-3.79	0.93	760.4	-0.07	0.50	214.0	-3.48	0.80	530.7
95	Diazinon	[7]	-4.26	-3.70	0.50	68.4	-3.11	0.06	13.6	-3.74	0.02	5.0
96	Dibucaine	[17]	-4.68	-4.58	0.29	48.7	-3.16	0.19	36.0	-4.71	0.32	52.2
97	Dicamba	[16]	-2.69	-2.47	0.27	45.7	-4.92	0.04	9.8	-2.56	0.14	27.1
98	Dichlobenil	[16]	-3.36	-3.20	0.55	257.7	-6.24	0.71	408.2	-2.71	1.20	1496.7
99	Dichlofenthion	[16]	-**	-4.68	-	-	-1.96	1.43	2580.7	-4.66	1.45	2733.6
100	Diclofop-methyl	[16]	-4.01	-5.31	1.62	4059.1	-2.45	0.32	108.3	-4.38	1.25	1675.3
101	Difenoconazole	[16]	-3.90	-6.16	0.53	240.3	-2.89	1.73	98.1	-5.17	0.73	81.5
102	Digallic acid	[16]	-3.75	-2.59	0.94	88.5	-5.09	0.22	65.9	-3.60	0.79	83.7
103	Digitoxin	[20]	-4.39	-9.98	0.89	676.2	-1.21	4.70	100.0	-5.39	0.11	22.9
104	Dimethenamid*	[16]	-1.14	-4.05	1.22	1565.7	-3.23	1.69	97.9	-2.17	0.19	54.7
105	Dimethirimol	[16]	-1.70	-1.70	0.54	248.1	-3.53	0.55	251.5	-1.94	0.31	102.6
106	Dimethomorph	[16]	-5.34	-5.13	1.02	90.5	1.62	0.81	84.5	-5.14	0.82	85.0
107	Dimorpholamine	[16]	-1.74	-4.30	1.83	98.5	-1.43	4.40	100.0	-2.77	2.87	99.9
108	Diniconazole	[16]	-**	-5.49	-	-	-1.09	0.58	73.8	-3.91	1.00	897.8
109	Diphenhydramine	[18]	-4.16	-4.64	1.21	93.9	-2.74	1.69	98.0	-3.45	0.50	68.5
110	Diphenylhydantoin	[18]	-4.07	-3.20	0.21	38.9	-1.87	0.65	348.3	-3.33	0.52	234.8
111	Diuron	[7]	-3.58	-2.87	0.18	51.4	-2.71	0.89	683.3	-3.05	0.71	408.7
112	Enrofloxacin	[18]	-1.46	-3.52	1.72	5161.5	-4.58	0.34	53.9	-2.51	0.67	371.1
113	EPTC*	[16]	-2.67	-2.79	0.03	7.9	-1.50	0.09	18.7	-2.64	0.06	14.6
114	Equilin	[16]	-5.04	-4.26	0.24	73.3	-3.68	1.02	937.5	-4.24	1.04	997.4
115	Estrone	[20]	-5.31	-4.44	1.36	95.6	-0.64	0.49	67.9	-4.13	0.18	33.9
116	Ethinamate	[16]	-1.58	-2.13	0.25	75.9	-2.12	0.30	50.4	-1.72	0.10	27.0
117	Ethirimol	[16]	-2.77	-4.32	0.25	77.7	-3.00	1.30	95.0	-2.26	0.76	472.4
118	Ethofumesate	[16]	-2.14	-2.61	1.62	4048.5	-1.46	1.15	1310.0	-2.45	1.31	1926.3
119	Ethohexadiol	[16]	-0.78	-1.74	0.24	42.2	-2.72	1.19	93.6	-1.23	0.69	79.7
120	Ethoprop*	[16]	-2.74	-3.04	0.23	41.2	-4.24	0.53	70.4	-2.91	0.40	60.1
121	Ethyl-p-hydroxybenzoate	[19]	-2.49	-1.54	0.14	27.6	-5.30	0.81	546.1	-2.21	0.14	36.9
122	Fenbufen	[16]	-4.10	-4.20	0.96	814.8	-8.59	0.86	626.5	-3.78	1.28	1804.7
123	Fenoprofen*	[18]	-2.54	-3.82	1.16	1339.5	-7.11	0.12	25.0	-3.37	0.33	114.6
124	Fenoxaprop-ethyl	[16]	-4.50	-4.89	1.10	1171.9	-1.98	0.72	419.9	-4.97	0.64	335.3
125	Fenpiclonil	[16]	-4.91	-4.14	0.22	39.3	-4.80	0.55	254.4	-4.49	0.20	59.9
126	Fludrocortisone	[16]	-**	-4.02	-	-	-0.82	0.58	73.8	-3.32	0.12	31.3
127	Flufenacet	[16]	-4.02	-3.85	0.21	38.0	-3.13	0.04	8.9	-3.80	0.01	2.1
128	Flufenamic acid	[16]	-5.07	-4.06	0.57	73.4	-1.29	0.43	170.2	-4.08	0.41	154.3
129	Flumioxazin	[16]	-2.87	-3.19	2.43	26903.2	-2.89	2.11	12691.3	-3.53	1.76	5709.9
130	Flurbiprofen	[2]	-3.90	-4.21	0.47	191.7	-5.74	0.15	40.4	-3.72	0.64	334.8

Table I - The train set of experimental ($logS_w$) and calculated ($clogS_w$) aqueous solubility data, deviation values (absolute error [AE] and percentage deviation [PD]) of three different models (continued).

| No.	Solute	Ref.	$logS_w$	GSE			LSER			Proposed model		
				$clogS_w$	AE	PD	$clogS_w$	AE	PD	$clogS_w$	AE	PD
131	Fluspirilene	[16]	-4.68	-**	-	-	-7.41	2.73	99.8	-6.92	2.24	99.4
132	Fluthiacet-methyl	[16]	-5.68	-**	-	-	-3.96	1.72	5122.7	-4.94	0.73	441.8
133	Folic acid	[16]	-5.44	-1.39	4.05	1121490.4	-3.95	1.49	2978.1	-3.39	2.05	11187.4
134	Fumaric acid	[16]	-1.22	-1.94	0.72	81.0	0.78	2.00	10003.3	-0.45	0.77	490.9
135	Furametpyr	[16]	-3.17	-**	-	-	-4.86	1.69	97.9	-4.25	1.08	91.7
136	Furazolidone	[16]	-3.75	-2.91	0.84	591.0	-1.83	1.92	8174.5	-2.12	1.63	4145.0
137	Ganciclovir	[16]	-1.77	0.25	2.02	10466.6	0.78	2.56	35887.9	-1.17	0.60	301.2
138	Glipizide	[18]	-5.49	-3.97	1.52	3235.5	-5.15	0.34	118.9	-4.38	1.11	1189.9
139	Gluconolactone	[16]	0.52	-**	-	-	1.71	1.19	1460.7	-0.08	0.60	74.9
140	Glyburide	[20]	-5.09	-4.96	0.13	34.9	-6.56	1.47	96.6	-5.34	0.25	44.2
141	Heptabarbital	[16]	-3.00	-3.34	0.34	54.2	-2.56	0.44	177.4	-2.88	0.12	33.3
142	Hexazinone	[16]	-0.88	-1.46	0.58	73.5	-1.46	0.58	73.5	-2.09	1.20	93.7
143	Hexobarbital	[18]	-2.67	-2.72	0.04	9.2	-2.00	0.68	375.4	-2.68	0.00	0.7
144	Hydrocortisone	[16]	-3.05	-3.05	0.00	1.0	-4.00	0.94	88.6	-3.23	0.17	32.8
145	Hydroflumethiazide	[16]	-3.04	-1.86	1.19	1442.5	-1.05	1.99	9694.3	-1.83	1.21	1532.0
146	Hydroxyphenamate	[16]	-0.92	-1.23	0.31	50.6	-1.75	0.82	85.0	-2.17	1.25	94.3
147	Hydroxyproline	[16]	0.44	0.01	0.43	62.8	0.99	0.55	257.1	0.34	0.10	20.1
148	Hymexazol	[16]	-0.07	-0.38	0.31	50.8	-0.19	0.12	24.4	-1.02	0.96	88.9
149	Idoxuridine	[16]	-2.25	-0.89	1.36	2181.0	-0.85	1.40	2419.6	-1.90	0.35	124.0
150	Imazapyr	[16]	-1.36	-3.01	1.65	97.7	-1.85	0.49	67.6	-2.96	1.60	97.5
151	Imazaquin	[16]	-3.54	-4.76	1.22	94.0	-3.53	0.00	1.0	-4.51	0.97	89.4
152	Imazethapyr	[16]	-2.32	-3.93	1.61	97.6	-2.84	0.52	69.9	-3.54	1.22	94.0
153	Imipramine	[18]	-4.11	-5.58	1.47	96.6	-5.73	1.62	97.6	-4.76	0.65	77.7
154	Indoprofen	[19]	-4.82	-3.45	1.37	2249.8	-3.87	0.95	793.5	-3.38	1.44	2654.6
155	Isoflurophate*	[16]	-1.08	-1.31	0.23	41.4	-0.69	0.38	142.5	-1.24	0.16	31.1
156	Isoleucine	[16]	-0.58	-0.34	0.25	76.5	0.02	0.61	303.8	0.63	1.21	1515.8
157	Isophorone*	[16]	-1.06	-1.41	0.35	55.2	-2.54	1.48	96.7	-1.74	0.68	79.3
158	Ketanserin	[16]	-4.60	-3.70	0.90	689.0	-4.85	0.25	44.2	-4.04	0.56	261.0
159	Khellin	[16]	-2.40	-3.05	0.65	77.4	-3.00	0.60	74.9	-3.34	0.94	88.5
160	Lenacil	[16]	-4.59	-4.84	0.25	43.7	-3.12	1.47	2858.1	-2.89	1.70	4920.2
161	Lidocaine	[20]	-1.76	-3.00	1.24	94.2	-3.16	1.40	96.0	-3.06	1.30	94.9
162	Linalool*	[18]	-1.99	-2.38	0.39	59.3	-2.96	0.97	89.3	-2.21	0.22	40.4
163	Linuron	[16]	-3.52	-3.18	0.34	119.0	-2.43	1.09	1117.6	-3.25	0.27	84.8
164	Lomefloxacin	[18]	-2.33	-0.55	1.78	5965.0	-3.03	0.70	79.9	-1.42	0.91	717.1
165	Lorazepam	[20]	-3.60	-3.82	0.22	39.7	-4.03	0.43	63.1	-4.37	0.77	83.1
166	Malathion	[7]	-3.36	-1.92	1.44	2654.2	-3.13	0.23	68.6	-2.61	0.75	467.5
167	Medrogestone	[20]	-5.27	-5.21	0.06	14.8	-6.25	0.98	89.5	-4.60	0.67	367.2
168	Methomyl	[16]	-0.45	-0.78	0.33	53.5	-1.20	0.75	82.4	-1.31	0.86	86.1
169	Metoprolol	[2]	-1.20	-2.17	0.97	89.3	-2.43	1.23	94.1	-2.14	0.94	88.6
170	Morphine	[19]	-3.15	-2.58	0.57	271.5	-3.32	0.17	31.8	-2.95	0.20	59.6
171	Nadolol	[2]	-1.57	-1.09	0.48	202.0	-2.32	0.75	82.4	-2.15	0.58	73.5
172	Nalidixic acid	[18]	-3.61	-2.32	1.30	1873.0	-1.78	1.83	6646.6	-2.27	1.34	2069.4
173	Naphthoic acid	[17]	-3.77	-4.15	0.38	57.9	-2.83	0.94	779.3	-3.61	0.17	47.5
174	Naproxen	[2]	-4.21	-3.79	0.42	163.0	-3.71	0.50	216.3	-3.62	0.59	293.1
175	Nicotinic acid	[20]	-0.84	-2.46	1.62	97.6	-0.23	0.61	307.3	-1.38	0.54	71.3
176	Niflumic acid	[18]	-4.58	-5.20	0.62	76.1	-3.49	1.09	1141.3	-3.83	0.75	464.8
177	Ofloxacin	[18]	-1.27	-1.55	0.28	48.1	-2.86	1.60	97.5	-2.37	1.10	92.1
178	Oxazepam	[20]	-3.95	-3.63	0.32	108.9	-3.52	0.43	171.0	-3.87	0.08	20.4
179	Parathion*	[7]	-4.29	-3.30	0.99	877.2	-3.78	0.51	222.2	-3.89	0.40	152.0
180	Perphenazine	[19]	-4.59	-4.63	0.04	9.8	-5.73	1.15	92.9	-5.83	1.25	94.4
181	p-Fluorobenzoic acid	[16]	-2.07	-3.26	1.19	93.6	-1.08	0.99	873.1	-2.04	0.03	6.8
182	Phenacetin	[20]	-2.35	-2.28	0.07	17.5	-1.84	0.51	221.4	-2.07	0.28	88.9
183	Phenol	[20]	-0.06	-1.25	1.19	93.5	-0.95	0.89	87.1	-1.82	1.76	98.3
184	Phenolphthalein	[7]	-2.90	-5.01	2.11	99.2	-4.80	1.90	98.8	-4.62	1.72	98.1
185	Phenylbutazone	[18]	-4.39	-3.51	0.88	659.9	-3.67	0.72	425.6	-4.31	0.08	19.5
186	Phthalazine	[16]	-0.42	-1.05	0.63	76.5	-2.13	1.71	98.1	-2.05	1.63	97.7
187	Phthalic acid	[16]	-1.37	-2.87	1.50	96.8	-0.72	0.65	350.2	-1.84	0.46	65.4
188	Phthalimide	[16]	-2.61	-2.85	0.24	42.2	-0.95	1.66	4513.0	-2.11	0.50	217.7
189	p-Hydroxybenzoicacid	[16]	-1.44	-2.80	1.35	95.6	-0.49	0.95	788.2	-1.93	0.49	67.4
190	Picloram	[16]	-2.75	-3.56	0.81	84.3	-1.55	1.20	1467.0	-2.88	0.13	26.3
191	Picric acid	[16]	-1.26	-2.38	1.12	92.4	-3.07	1.81	98.5	-2.73	1.47	96.6
192	Pirimicarb	[16]	-1.95	-2.01	0.06	12.7	-2.45	0.51	68.8	-2.46	0.52	69.7
193	Prednisolone	[20]	-3.21	-3.22	0.01	2.3	-3.78	0.57	72.9	-3.37	0.16	30.8
194	Pregnenolone	[20]	-4.65	-1.17	3.48	299816.3	-5.75	1.10	92.1	-1.75	2.90	78516.4
195	Primidone	[20]	-2.64	-3.06	0.42	62.0	-1.26	1.38	2290.3	-2.28	0.36	130.1

Table I - The train set of experimental (logS$_w$) and calculated (clogS$_w$) aqueous solubility data, deviation values (absolute error [AE] and percentage deviation [PD]) of three different models (continued).

No.	Solute	Ref.	logS$_w$	GSE			LSER			Proposed model		
				clogS$_w$	AE	PD	clogS$_w$	AE	PD	clog-S$_w$	AE	PD
196	Promazine*	[19]	-4.30	-4.08	0.22	66.4	-5.24	0.93	88.4	-5.11	0.81	84.5
197	Promethazine	[2]	-4.39	-4.08	0.31	104.2	-4.88	0.49	67.5	-4.97	0.58	73.6
198	Propranolol	[2]	-3.62	-3.93	0.31	50.5	-3.66	0.04	9.2	-3.74	0.12	25.0
199	Pyrimethamine	[17]	-4.11	-4.10	0.01	3.0	-3.87	0.23	71.3	-4.02	0.09	23.4
200	Ranitidine	[18]	-2.50	-0.08	2.43	26559.8	-2.20	0.30	100.3	-1.79	0.71	413.5
201	Salbutamol	[20]	-1.22	-1.91	0.69	79.6	-1.56	0.34	54.1	-1.73	0.51	68.9
202	Santonin	[20]	-3.09	-2.02	1.07	1074.9	-3.15	0.06	13.1	-2.04	1.05	1032.2
203	Sulfadiazine	[20]	-3.51	-1.71	1.80	6209.6	-1.91	1.60	3865.7	-2.27	1.24	1657.8
204	Sulfamerazine	[20]	-3.12	-1.94	1.18	1413.6	-2.39	0.73	435.5	-2.53	0.59	286.5
205	Sulfamethizole	[20]	-2.41	-1.86	0.55	254.8	-2.57	0.16	30.1	-2.73	0.32	52.2
206	Sulfamethoxazole	[20]	-2.62	-1.78	0.84	591.8	-2.41	0.21	62.0	-2.73	0.11	22.0
207	Sulfamethoxypyridazine	[20]	-3.28	-1.68	1.60	3881.1	-2.06	1.22	1565.9	-2.76	0.52	234.0
208	Sulfisomidine	[20]	-2.24	-1.84	0.40	151.2	-2.81	0.57	72.8	-2.81	0.57	73.3
209	Sulindac	[18]	-4.50	-4.75	0.25	44.3	-4.89	0.40	59.9	-4.71	0.22	39.1
210	Tetracycline	[18]	-2.93	-0.64	2.29	19444.9	-3.78	0.86	86.1	-3.53	0.61	75.3
211	Thionazin*	[16]	-2.34	-2.05	0.29	94.0	-1.93	0.41	156.6	-2.92	0.58	73.7
212	Thymol	[18]	-2.19	-2.92	0.73	81.3	-2.84	0.65	77.6	-2.82	0.64	76.8
213	Tolmetin	[18]	-4.09	-3.73	0.36	130.1	-3.67	0.42	164.7	-3.46	0.63	326.9
214	Triamcinolone	[20]	-3.69	-2.68	1.01	923.3	-3.48	0.21	62.8	-2.82	0.87	635.0
215	Triazolam	[20]	-4.08	-5.66	1.58	97.4	-6.62	2.54	99.7	-5.48	1.40	96.1
216	Trichloromethiazide	[18]	-3.53	-2.48	1.05	1019.3	-2.46	1.07	1080.0	-2.96	0.56	267.2
217	Trifluoperazine*	[19]	-4.52	-4.65	0.13	25.4	-6.11	1.59	97.4	-5.50	0.98	89.4
218	Triflupromazine*	[19]	-5.30	-5.04	0.26	82.4	-6.02	0.72	80.9	-5.31	0.01	1.8
219	Trimipramine	[18]	-4.79	-4.54	0.25	77.4	-6.11	1.32	95.3	-4.92	0.13	26.5
220	Tryptamine	[18]	-3.30	-1.92	1.38	2274.7	-1.89	1.41	2463.8	-2.49	0.80	533.6

*Melting point is less than 25 °C. **Melting point has not been reported in the literature.
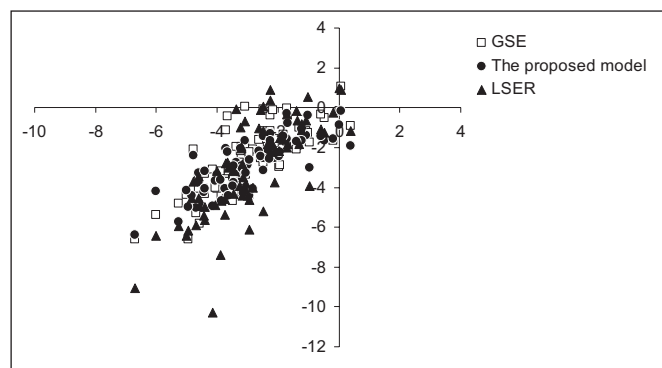
Figure 3 - The correlation between experimental values versus predicted value using GSE (R^2 = 0.62), LSER (R^2 = 0.57) and the proposed (*Equation 12*) (R^2 = 0.66) models for test set.
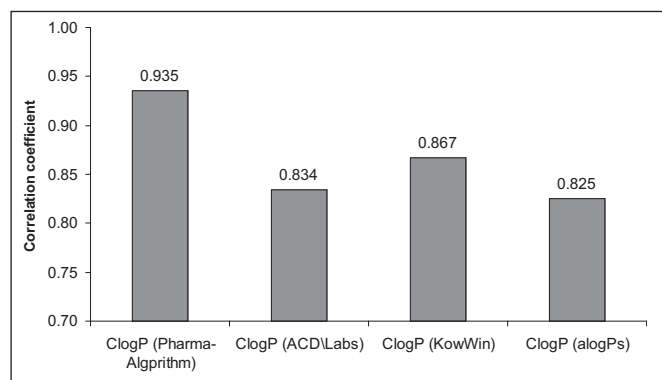
Figure 4 - Correlation between experimental *logP* (*ElogP*) and different calculated logPs (*ClogP*) for the test set.

and the obtained AAE values are listed in *Table V*. These results show there is good correlation between *ElogP* and *ClogP* values. The best correlation is observed for the *ClogP* of the Pharma-Algorithms and there are no significant differences between AAE values of aqueous solubilities computed using *ElogP* and *ClogP* values (p > 0.05). Also using *ElogP* and different *ClogPs*, the proposed model has lower deviation when compared with that of GSE.

The validity of the proposed model was investigated by cross-validation method. The cross-validation results of the model are investigated and the obtained QSPR models, R^2, Q^2 (for F_1, F_2, F_3) and AAE of 2, 4 and 10-folds of the cross validations are listed in *Table VI*. The coefficients of QSPRs models are not significantly changed in different cross-validation methods. The R^2 values of all models varied between 0.92-0.94 and different Q^2 values are greater than 0.6. The overall AAE for 2-fold, 4-fold and 10-fold are 0.709, 0.714 and 0.707, so the evidence shows that *Equation 12* is a robust model.

Table II lists details of the proposed test set to compare the accuracies of the aqueous solubility prediction models, experimental and predicted values of solubilities and the references. Normal distribution of this data set was investigated by the Kolmogorov-Smirnov and Shapiro-Wilk tests and the results indicated that the experimental solubility, *logP* and *E* of 75 official drugs are normally distributed with the significance level of less than 0.05. The range of the logarithm of the molar solubility is from -6.69 to 0.39, *logP* from -2.00 to 5.90, *E* from 0.17 to 3.67 and *mp* from -118 to 360 ºC.

External validation using the test set was performed according to the above mentioned criteria. The R^2, Q^2, $[(R^2 - R_0^2)/R^2]$ and k values are 0.66, 0.65, 0.09 and 0.936, respectively, which are in good agreement with the critical values and show the validity of the proposed model.

The results presented in this study show that *E* and the experimental or calculated *logP* are effective descriptors in predicting the aqueous

Table II - The proposed test set of experimental (logS$_w$) and calculated (clogS$_w$) aqueous solubility data, deviation values (absolute error [AE] and percentage deviation [PD]) of three different models.

No.	Solute	Ref.	logS$_w$	GSE			LSER			Proposed model		
				clogS$_w$	AE	PD	clogS$_w$	AE	PD	clogS$_w$	AE	PD
1	Acetaminophen	[18]	-1.06	-1.18	0.116	23.5	-0.63	0.430	169.3	-1.39	0.328	53.0
2	Acetazolamide	[30]	-2.49	-1.180	1.315	1965.4	0.06	2.546	35080.2	-1.43	1.061	1049.5
3	Acyclovir	[2]	-2.24	-0.37	1.870	7313.1	0.91	3.145	139693.2	-1.26	0.981	856.2
4	Allopurinol	[20]	-2.26	-2.19	0.070	17.5	0.38	2.639	43483.5	-1.30	0.960	812.5
5	Amiloride	[2]	-3.36	-1.96	1.400	2411.9	-0.07	3.292	195775.4	-2.74	0.621	317.6
6	Amoxicilin	[2]	-2.17	-0.11	2.060	11381.5	-1.90	0.275	88.2	-2.38	0.207	37.9
7	Antipyrine	[7]	0.39	-0.9	1.290	94.9	-1.16	1.553	97.2	-1.91	2.304	99.5
8	Atenolol	[2]	-1.30	-0.98	0.320	108.9	-1.85	0.545	71.5	-1.81	0.513	69.3
9	Atropine	[20]	-2.12	-1.77	0.355	126.5	-3.77	1.653	97.8	-2.43	0.312	51.2
10	Azathioprine	[18]	-3.21	-1.98	1.233	1609.4	-1.95	1.263	1731.2	-3.16	0.044	10.6
11	Baclofen	[31]	-1.67	-0.53	1.142	1286.2	-1.84	0.167	31.9	-0.76	0.913	718.5
12	Benzocaine	[17]	-2.33	-1.98	0.346	121.8	-1.82	0.510	223.4	-2.14	0.189	54.5
13	Celecoxib	[30]	-3.74	-3.73	0.011	2.6	-5.38	1.646	97.7	-4.55	0.812	84.6
14	Chloramphenicol*	[31]	-2.11	-1.57	0.543	248.8	-2.16	0.052	11.3	-2.55	0.439	63.6
15	Chlorpromazine	[2]	-5.27	-4.82	0.450	181.8	-5.97	0.696	79.9	-5.72	0.448	64.3
16	Ciprofloxacin	[2]	-3.73	-1.11	2.620	41586.9	-2.78	0.954	800.4	-2.04	1.685	4745.1
17	Colchicine	[31]	-0.96	-1.76	0.797	84.0	-3.93	2.964	99.9	-3.00	2.036	99.1
18	Cortisone	[2]	-3.00	-2.72	0.285	92.8	-4.43	1.427	96.3	-2.88	0.117	31.0
19	Dapsone	[31]	-3.19	-2.43	0.766	483.2	-2.05	1.136	1268.5	-2.94	0.246	76.1
20	Diazepam	[33]	-3.76	-3.34	0.420	163.0	-4.58	0.818	84.8	-4.06	0.304	50.4
21	Diethylstilbestrol	[17]	-4.57	-5.81	1.239	94.2	-4.94	0.376	57.9	-4.82	0.254	44.3
22	Digoxin	[20]	-4.16	-3.12	1.040	996.5	-10.31	6.150	100.0	-4.94	0.777	83.3
23	Diltiazem	[2]	-2.95	-4.39	1.440	96.4	-4.64	1.694	98.0	-4.41	1.456	96.5
24	Ephedrine	[20]	-0.47	-0.52	0.050	10.9	-1.28	0.810	84.5	-1.65	1.185	93.5
25	Estradiol	[20]	-4.84	-4.95	0.110	22.4	-4.53	0.306	102.3	-4.43	0.408	155.8
26	Famotidine	[2]	-2.48	-0.09	2.395	24731.3	-1.18	1.297	1882.7	-2.53	0.054	11.6
27	Fluorouracil	[31]	-1.03	-1.24	0.212	38.7	0.55	1.578	3685.9	-0.38	0.645	342.0
28	Gemfibrozil	[7]	-3.16	-4.26	1.100	92.1	-4.44	1.276	94.7	-3.54	0.377	58.0
29	Griseofulvin	[7]	-4.61	-3.45	1.160	1345.4	-3.47	1.140	1279.3	-3.28	1.329	2032.1
30	Guaifenesin	[16]	-0.60	-0.36	0.244	75.4	-1.10	0.503	68.6	-1.45	0.847	85.8
31	Haloperidol*	[16]	-4.43	-4.08	0.353	125.4	-5.44	1.013	90.3	-4.22	0.205	60.5
32	Halothane*	[20]	-1.71	-1.68	0.030	7.2	-1.99	0.285	48.1	-1.56	0.147	40.1
33	Hydrochlorothiazide	[2]	-2.63	-1.61	1.020	947.1	-1.04	1.590	3786.2	-2.18	0.450	181.6
34	Hydroquinone	[16]	-0.18	-1.66	1.478	96.7	-0.23	0.046	10.0	-1.56	1.371	95.7
35	Isoniazid	[16]	0.01	-0.15	0.163	31.3	0.97	0.961	814.7	-0.85	0.856	86.1
36	Ketoprofen	[2]	-3.25	-2.73	0.520	231.1	-3.95	0.700	80.0	-3.27	0.019	4.2
37	Labetalol	[2]	-3.45	-3.44	0.010	2.3	-4.32	0.871	86.5	-3.75	0.300	49.9
38	Lamotrigine	[33]	-3.14	-4.05	0.913	87.8	-3.48	0.339	54.2	-4.26	1.127	92.5
39	Levodopa	[31]	-1.72	-0.02	1.697	4881.7	-0.35	1.370	2244.1	-0.29	1.426	2565.5
40	Lindane	[7]	-4.60	-4.08	0.520	231.1	-4.53	0.070	17.4	-3.76	0.838	588.8
41	Lovastatin	[31]	-6.01	-5.40	0.610	307.4	-6.42	0.416	61.7	-4.18	1.824	6565.0
42	Manitol	[7]	0.06	1.08	1.020	947.1	0.89	0.832	578.5	-0.18	0.240	42.4
43	Maprotiline	[18]	-4.69	-5.28	0.589	74.2	-5.91	1.218	93.9	-5.03	0.335	53.7
44	Meprobamate	[31]	-1.82	-1.36	0.460	188.7	-1.62	0.202	59.3	-1.44	0.384	142.3
45	Mercaptopurine	[31]	-3.09	-1.84	1.249	1674.0	-0.70	2.389	24381.6	-1.66	1.430	2591.6
46	Metoclopramide	[34]	-3.18	-2.99	0.184	52.6	-2.85	0.330	113.6	-3.04	0.136	36.9
47	Metronidazole	[18]	-1.22	-0.59	0.636	332.9	-1.14	0.086	21.9	-1.09	0.129	34.5
48	Minoxidil	[20]	-1.98	-2.97	0.990	89.8	-2.19	0.209	38.1	-2.46	0.483	67.1
49	Mitomycin C	[31]	-2.56	-2.53	0.034	8.1	-0.12	2.444	27710.1	-2.46	0.101	26.2
50	Mycophenolic acid	[31]	-4.39	-3.30	1.092	1135.1	-4.99	0.602	75.0	-3.19	1.203	1494.9
51	Nifedipine	[31]	-4.78	-2.10	2.676	47332.0	-3.71	1.069	1071.5	-2.42	2.358	22703.0
52	Nitrofurantoin	[19]	-3.24	-2.19	1.048	1018.2	-0.98	2.254	17859.9	-2.03	1.205	1502.5
53	Nitroglycerin*	[31]	-2.26	-1.19	1.069	1073.1	-2.22	0.039	9.4	-1.66	0.597	295.7
54	Omeprazole	[35]	-3.62	-3.21	0.413	158.8	-3.00	0.621	317.7	-4.43	0.805	84.3
55	Oxytetracycline	[18]	-3.09	0.07	3.153	142171.5	-4.04	0.950	88.8	-3.30	0.215	39.1
56	PABA	[16]	-1.37	-1.93	0.557	72.3	-0.65	0.713	416.7	-1.65	0.281	47.6
57	Papaverine	[18]	-3.87	-4.43	0.558	72.3	-4.66	0.791	83.8	-4.67	0.802	84.2
58	Phenobarbital	[18]	-2.29	-2.39	0.096	19.9	-1.90	0.390	145.6	-2.59	0.292	49.0
59	Phenytoin	[20]	-3.99	-4.07	0.080	16.8	-3.20	0.785	510.2	-3.35	0.643	339.7
60	Progesterone	[2]	-4.40	-4.35	0.050	12.2	-5.64	1.242	94.3	-4.08	0.323	110.2
61	Propofol*	[36]	-3.05	-3.38	0.333	53.6	-3.82	0.776	83.3	-3.28	0.229	41.0
62	Propoxyphene	[2]	-5.01	-4.38	0.635	331.5	-6.45	1.441	96.4	-4.14	0.869	639.9
63	Prostaglandin–E2	[7]	-2.47	-2.73	0.260	45.1	-5.22	2.753	99.8	-3.16	0.692	79.7
64	Quinine	[2]	-2.82	-2.11	0.710	412.9	-4.01	1.195	93.6	-4.06	1.240	94.2
65	Riboflavin	[31]	-3.65	-0.43	3.218	165026.8	-2.77	0.881	659.9	-2.21	1.441	2662.5

Table II - The proposed test set of experimental ($logS_w$) and calculated ($clogS_w$) aqueous solubility data, deviation values (absolute error [AE] and percentage deviation [PD]) of three different models (continued).

No.	Solute	Ref.	$logS_w$	GSE			LSER			Proposed model		
				$clogS_w$	AE	PD	$clogS_w$	AE	PD	$clogS_w$	AE	PD
66	Salicylic acid	[17]	-1.93	-2.87	0.939	88.5	-1.53	0.401	152.0	-2.24	0.310	51.1
67	Sertraline	[14]	-4.94	-6.59	4.650	97.8	-6.17	1.231	94.1	-4.98	0.045	9.80
68	Sulfacetamide	[20]	-1.23	-0.99	0.240	73.8	-0.83	0.402	152.4	-1.64	0.407	60.9
69	Terfenadine	[2]	-6.69	-6.63	0.065	16.1	-9.05	2.365	99.6	-6.39	0.300	99.5
70	Testosterone	[2]	-4.06	-4.02	0.040	9.7	-4.89	0.833	85.3	-3.66	0.395	148.4
71	Theophylline	[2]	-1.38	-2.09	0.710	80.5	-0.18	1.196	1470.4	-1.71	0.327	52.9
72	Thiabendazole	[17]	-3.48	-4.68	1.196	93.6	-3.21	0.279	90.1	-3.94	0.458	65.1
73	Tolbutamide	[17]	-3.46	-2.93	0.533	241.5	-3.13	0.334	116.0	-2.93	0.536	243.8
74	Trimethoprim	[18]	-2.95	-2.22	0.731	438.4	-6.11	3.163	99.9	-2.61	0.338	117.6
75	Warfarin	[29]	-3.89	-3.19	0.700	401.2	-7.40	3.510	100.0	-3.61	0.277	89.1

*Melting point is less than 25 °C.

Table III - Comparison of AAE and MPD for three studied predictive models using train set.

	GSE	LSER	Proposed model
AAE (± SD)	0.767± 0.683 (N = 205)	0.875 ± 0.690 (N = 220)	0.707 ± 0.540 (N = 220)
MPD (± SD)	8300.3 ± 81043.1 (N = 205)	1117.7 ± 3980.7 (N = 220)	849.9 ± 5476.9 (N = 220)
AAE (excluded 10 % maximum and 10 % minimum values for each model)	0.676 ± 0.441 (N = 163)	0.792 ± 0.415 (N = 176)	0.649 ± 0.344 (N = 176)
MPD (excluded 10 % maximum and 10 % minimum values for each model)	270.2 ± 439.6 (N = 163)	257.4 ± 370.2 (N = 176)	195.8 ± 248.6 (N = 176)

[a]Deviations are calculated for 205 compounds because melting points are not reported for 15 compounds.

Table IV - Comparison of three studied predictive models using test set of 75 drugs.

	GSE	LSER	Proposed model
AAE (± SD)	0.822 ± 0.834	1.179 ± 1.048	0.670 ± 0.545
MPD (± SD)	6234.9 ± 25823.1	6813.2 ± 28287.2	758.4 ± 2779.0
AAE (excluded 10 % maximum and 10 % minimum values for each model)	0.706 ± 0.424	1.016 ± 0.591	0.594 ± 0.356
MPD (excluded 10 % maximum and 10 % minimum values for each model)	391.9 ± 547.2	390.4 ± 666.9	192.3 ± 282.6

Table V - The AAEs of GSE and the proposed model using various logP values for test set of 75 drugs.

	ElogP	ClogP (Pharma-Algorithms)	ClogP (ACD/Labs)	ClogP (KowWin)	ClogP (aLogPs)
GSE	0.882	0.822	0.821	0.903	0.813
Prop. model	0.717	0.710	0.670	0.753	0.755

Table VI - Cross-validation data to investigate the validity of the proposed model.

	QSPR model	R^2	Q^2F_1	Q^2F_2	Q^2F_3	AAE
	2-fold					
1	$logS_w$ = -1.167E-0.585 ClogP	0.943	0.684	0.684	0.680	0.746
2	$logS_w$ = -1.072E-0.614 ClogP	0.926	0.761	0.761	0.763	0.672
	Mean	0.935	0.723	0.723	0.722	0.709
	4-fold					
1	$logS_w$ = -1.149E-0.574 ClogP	0.931	0.751	0.750	0.724	0.687
2	$logS_w$ = -1.064E-0.624 ClogP	0.933	0.720	0.720	0.732	0.728
3	$logS_w$ = -1.122E-0.614 ClogP	0.942	0.607	0.607	0.624	0.811
4	$logS_w$ = -1.144E-0.585 ClogP	0.929	0.795	0.794	0.789	0.631
	Mean	0.934	0.718	0.718	0.717	0.714
	10-fold					
1	$logS_w$ = -1.128E-0.600 ClogP	0.935	0.686	0.681	0.636	0.740
2	$logS_w$ = -1.118E-0.599 ClogP	0.932	0.778	0.777	0.786	0.662
3	$logS_w$ = -1.111E-0.618 ClogP	0.931	0.810	0.809	0.814	0.560
4	$logS_w$ = -1.101E-0.612 ClogP	0.934	0.717	0.717	0.722	0.723
5	$logS_w$ = -1.110E-0.602 ClogP	0.938	0.552	0.551	0.562	0.886
6	$logS_w$ = -1.114E-0.598 ClogP	0.930	0.865	0.865	0.867	0.492
7	$logS_w$ = -1.150E-0.584 ClogP	0.934	0.712	0.711	0.733	0.730
8	$logS_w$ = -1.141E-0.590 ClogP	0.935	0.665	0.664	0.676	0.809
9	$logS_w$ = -1.108E-0.606 ClogP	0.936	0.669	0.667	0.670	0.801
10	$logS_w$ = -1.150E-0.600 ClogP	0.933	0.789	0.785	0.773	0.663
	Mean	0.934	0.724	0.723	0.724	0.707

solubility of pharmaceutical compounds. The GSE is very robust model to predict the aqueous solubility using only two parameters, but the experimental melting point is required. The LSER model also can predict the aqueous solubility of drugs using five Abraham solute parameters. The results revealed that the proposed QSPR model is more accurate than GSE and LSER models and can be used to estimate aqueous solubility of drugs/drug candidates in discovery and development investigations. The proposed test set of aqueous solubility of 75 pharmaceutically interested compounds could be recommended for comparison of the aqueous solubility prediction methods.

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SUPPORTING INFORMATION

The used descriptors for each solute in train and test sets are available from the corresponding author on request.

ACKNOWLEDGEMENT

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