Electronic Supplementary Material

Machine learning-based solubility prediction and methodology evaluation of active pharmaceutical ingredients in industrial crystallization

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1. Detail information about the dataset

The name, SMILES format, melting point, solubility at 25 °C, and source literature of the selected APIs in dataset are shown in the table below.

Table S1. Detail information about the dataset

API name	SMILES format	Melting Point/ K	Solubility/ mol/mol	References
Nifedipine	[O+](C(O)=C1C(c2c([N+](=O)[O-])cccc2)=C(C(=O)O[C-])C(=C)NC1=C)=C	447.45	0.003920	[1]
tridecanedioic acid	O=C(O)CCCCCCCCCCCC(=O)O	386.21	0.004410	[2]
eszopiclone	Clc1cnc(N2C(=O)c3nccnc3C2OC(=O)N2CCNCC2)cc1	473.53	0.000360	[3]
L-Norvaline	OC(O)C(N)CCC	582.62	0.000178	[4]
Benzoin	O=C(C(O)c1ccccc1)c1ccccc1	406.55	0.002460	[5]
Pyrimethanil	N(C1NC(C)CC(C)N1)C1CCCCC1	369.29	0.026700	[6]
3,4-Dichloronitrobenzene	Clc1c(Cl)ccc([N+](=O)[O-])c1	316.15	0.099670	[7]
Furan-2-carboxylic acid	O=C(O)c1occc1	403.55	0.208100	[8]
3,5-dichloroaniline	Clc1cc(Cl)cc(N)c1	325.15	0.294700	[9]
aceclofenac	Clc1c(Nc2c(CC(=O)OCC(=O)O)cccc2)c(Cl)ccc1	423.15	0.010603	[10]
Azithromycin Monohydrate	O(C)C1(C)C(OC)C(C)N(C)CC(C)CC(O)(C)C(OC2C(O)C(N(C)C)CC(C)O2)C(C)C(OC2OC(C)C(OC)C(OC)(C)C2)C(C)C(O)(O)OC1CC.O	386.15	0.040600	[11]
2,3,4,5-Tetrabromothiophene	Brc1c(Br)c(Br)sc1Br	391.15	0.002207	[12]
4,4′-Diaminodiphenylmethane	Nc1ccc(Cc2ccc(N)cc2)cc1	363.3	0.046100	[13]
Acetylsalicylic acid	O=C(Oc1c(C(=O)O)cccc1)C	408.65	0.131900	[14]
Acetaminophen	O=C(Nc1ccc(O)cc1)C	442.35	0.053900	[14]
Cimetidine	S(CCNC(=NC#N)NC)Cc1c(C)[nH]cn1	414.15	0.005000	[14]
Famotidine	S(=O)(=O)(N=C(N)CCSCc1nc(N=C(N)N)sc1)N	439.35	0.001700	[14]
isatin	O=C1C(=O)c2c(N1)cccc2	476.15	0.004090	[15]
vanillic acid	O=C(O)c1cc(OC)c(O)cc1	484.9	0.034500	[16]
4-nitrophthalimide	O=[N+]([O-])c1cc2C(=O)NC(=O)c2cc1	474.71	0.002014	[17]

p-coumaric acid	O=C(O)C=Cc1ccc(O)cc1	494.35	0.045600	[18]
Telmisartan	O=C(O)c1c(-c2ccc(Cn3c(CCC)nc4c(C)cc(-c5n(C)c6c(n5)cccc6)cc34)cc2)cccc1	542.42	0.000063	[19]
erlotinib hydrochloride	O(CCOc1c(OCCOC)cc2ncnc(Nc3cc(C#C)ccc3)c2c1)C	502.1	0.000012	[20]
cefmenoxime hydrochloride	S(CC1=C(C(=O)O)N2C(=O)C(NC(=O)C(=N[O+]=C)c3[nH]c(N)[s+]c3)C2SC1)C=1[N+](=C)N=NN=1	621	0.000032	[21]
thymol	Oc1c(C(C)C)ccc(C)c1	322.65	0.636100	[22]
Flufenamic acid	FC(F)(F)c1cc(Nc2c(C(=O)O)cccc2)ccc1	407.77	0.068100	[23]
2,6-Dihydroxybenzoic Acid	O=C(O)c1c(O)cccc1O	440.2	0.272530	[24]
p-Iodoaniline	Ic1ccc(N)cc1	331.95	0.171015	[25]
o-Iodoaniline	Ic1c(N)cccc1	325.15	0.141338	[25]
azoxystrobin	O=C(OC)C(=COC)c1c(Oc2ncnc(Oc3c(C#N)cccc3)c2)cccc1	387.67	0.001184	[26]
Cytarabine	O=C1N(C2C(O)C(O)C(CO)O2)C=CC(N)N1	486.33	0.000300	[27]
Loratadine	Clc1cc2c(C(=C3CCN(C(=O)OCC)CC3)c3ncccc3CC2)cc1	411.15	0.023190	[28]
4-cyanopyridine	N#Cc1ccncc1	353.15	0.070600	[29]
1-naphthaleneacetic acid	O=C(O)Cc1c2c(ccc1)cccc2	403.06	0.047000	[30]
Theobromine	O=C1N(C)c2ncn(C)c2C(=O)N1	622.03	0.000023	[31]
theophylline	O=C1N(C)C(=O)c2nc[nH]c2N1C	544.43	0.001160	[31]
caffeine	O=C1N(C)C(=O)c2n(C)cnc2N1C	510.75	0.001890	[31]
Lidocaine	O=C(Nc1c(C)cccc1C)CN(CC)CC	342.51	0.470000	[32]
Budesonide	O=C(C=O)C12C3(C)C(C4C(C5(C)C(=CC(=O)C=C5)CC4)C(O)C3)CC1OC(CCC)O2	499.65	0.049100	[33]
1-(3-Nitrophenyl)ethanone	O=[N+]([O-])c1cc(C(=O)C)ccc1	349.68	0.012460	[34]
3-Hydroxy-2-naphthoic acid	O=C(O)c1c(O)cc2c(c1)cccc2	494.4	0.025830	[35]
2-Amino-4,6-dichoropyrimidine	Clc1nc(N)nc(Cl)c1	496.42	0.182600	[36]
levetiracetam	O=C(N)C(CC)N1C(=O)CCC1	389.85	0.064300	[37]
Benzoic Acid	O=C(O)c1ccccc1	395.5	0.178000	[38]
antipyrine	O=C1N(N(C)C(C)=C1)c1ccccc1	385.05	0.190000	[39]
Vinpocetine	O=C(OCC)C=1n2c3c(c4c2C2C(CC)(C=1)CCCN2CC4)cccc3	422.15	0.001013	[40]
Florfenicol	ClC(Cl)C(=O)NC(C(F)F)C(O)c1ccc(S(=O)(=O)C)cc1	425.51	0.003093	[41]
carbendazim	O=C(OC)Nc1[nH]c2c(n1)cccc2	528.15	0.000032	[42]

capecitabine	FC=1C(NC(=O)OCCCCC)NC(=O)N(C2C(O)C(O)C(C)O2)C=1	393.05	0.035300	[43]
5-fluorouracil	FC=1C(=O)NC(=O)NC=1	555.66	0.001670	[44]
1-naphthoic acid	O=C(O)c1c2c(ccc1)cccc2	436.93	0.031090	[45]
lauric acid	O=C(O)CCCCCCCCCCC	317.71	0.232900	[46]
palmitic acid	O=C(O)CCCCCCCCCCCCCCC	336.13	0.019792	[46]
stearic acid	O=C(O)CCCCCCCCCCCCCCCCC	344.08	0.002423	[46]
sulfacetamide	S(=O)(=O)(NC(=O)C)c1ccc(N)cc1	429.75	0.014650	[47]
Probenecid	S(=O)(=O)(N(CCC)CCC)c1ccc(C(=O)O)cc1	472.05	0.009606	[48]
dibenzothiophene	s1c2c(c3c1cccc3)cccc2	370.15	0.006929	[49]
2-Cyanoacetamide	O=C(N)CC#N	392.84	0.012950	[50]
Mifepristone	O=C1C=C2C(=C3C(c4ccc(N(C)C)cc4)CC4(C)C(O)(C#CC)CCC4C3CC2)CC1	465.45	0.000289	[51]
Gatifloxacin	Fc1c(N2CC(C)NCC2)c(OC)c2N(C3CC3)C=C(C(=O)O)C(=O)c2c1	353	0.000698	[52]
3-Nitrophthalonitrile	Clc1c([N+](=O)[O-])cc([N+](=O)[O-])cc1	435.55	0.001942	[53]
2-chloro-5-nitroaniline	Cc1c(C)nc(C)c(C)n1	393.39	0.019800	[54]
Tetramethylpyrazine	S(=O)(=O)(NC(=O)C)c1ccc(N)cc1	358.55	0.161600	[55]
Pentachloropyridine	Clc1c(Cl)c(Cl)nc(Cl)c1Cl	398.15	0.000811	[56]
1,4-Naphthoquinone	O=C1c2c(C(=O)C=C1)cccc2	356.1	0.041799	[57]
1-(4-methyl-1-naphthyl) ethanone	O=C(C)c1c2c(c(C)cc1)cccc2	312	0.002950	[58]
pimelic acid	O=C(O)CCCCCC(=O)O	377.5	0.120800	[59]
mitomycin C	O=C(OCC1C2(OC)N(C=3C(=O)C(C)=C(N)C(=O)C1=3)CC1NC21)N	505.15	0.000818	[60]
Triclosan	Clc1c(Oc2c(O)cc(Cl)cc2)ccc(Cl)c1	331.05	0.423000	[61]
Atrazine	O=C(N)CN1C(=O)CCC1	446	0.003414	[62]
salicylic acid	O=C(O)c1c(O)cccc1	432.15	0.145500	[63]
4,4‘-oxydianiline	O(c1ccc(N)cc1)c1ccc(N)cc1	462.67	0.000890	[64]
tris(3-hydroxypropyl)phosphine oxide	P(=O)(CCCO)(CCCO)CCCO	387.76	0.022620	[65]
xylitol	OC(C(O)CO)C(O)CO	365.15	0.002500	[66]
Tetracycline hydrochloride	O=C(N)C=1C(=O)C2(O)C(O)=C3C(=O)c4c(O)cccc4C(O)(C)C3CC2C(N(C)C)C=1O.Cl	490	0.001043	[67]

trans-Cinnamic Acid	O=C(O)C=Cc1ccccc1	406.15	0.073300	[68]
Antioxidant 626	O(P1OCC2(CO1)COP(Oc1c(C(C)(C)C)cc(C(C)(C)C)cc1)OC2)c1c(C(C)(C)C)cc(C(C)(C)C)cc1	448.15	0.015011	[69]
N-acetyl-L-glutamine	O=C(O)C(NC(=O)C)CCC(=O)N	472.2	0.000580	[70]
Vortioxetine Hydrobromide	S(c1c(C)cc(C)cc1)c1c(N2CCNCC2)cccc1.Br	504	0.001623	[71]
iodopropynyl butylcarbamate	IC#CCOC(=O)NCCCC	341.41	0.215000	[61]
itraconazole	Clc1c(C2(Cn3ncnc3)OC(COc3ccc(N4CCN(c5ccc(N6C(=O)N(C(CC)C)N=C6)cc5)CC4)cc3)CO2)ccc(Cl)c1	442.15	0.000016	[72]
Glibenclamide	Clc1cc(C(O)NCCc2ccc(S(=O)(=O)NC(=O)NC3CCCCC3)cc2)c(OC)cc1	446.98	0.000249	[73]
dapsone	S(=O)(=O)(c1ccc(N)cc1)c1ccc(N)cc1	454.41	0.004774	[74]
dipyridamole	OCCN(CCO)c1nc(N2CCCCC2)c2nc(N(CCO)CCO)nc(N3CCCCC3)c2n1	398.15	0.003932	[75]
Imatinib Mesylate	S(=O)(=O)(O)C.O=C(Nc1cc(Nc2nc(-c3cnccc3)ccn2)c(C)cc1)c1ccc(CN2CCN(C)CC2)cc1	488.32	0.000320	[76]
Tetrabromo bisphenol A	Brc1c(O)c(Br)cc(C(C)(C)c2cc(Br)c(O)c(Br)c2)c1	454.02	0.051070	[77]
Diphenhydramine hydrochloride	O(C(c1ccccc1)c1ccccc1)CCN(C)C.Cl	442.3	0.063300	[78]
Isoniazid	O=C(NN)c1ccncc1	446.04	0.004647	[79]
4-Aminobenzamide	O=C(N)c1ccc(N)cc1	453.4	0.007771	[80]
Nicotinamide	O=C(N)c1cnccc1	401.6	0.046000	[81]
erythritol	OC(C(O)CO)CO	391.2	0.003520	[82]
Thymoquinone	O=C1C(C(C)C)=CC(=O)C(C)=C1	318.52	0.017900	[83]
1,9-Nonanedioic acid	O=C(O)CCCCCCCC(=O)O	379.28	0.054600	[84]
Lidocaine hydrochloride	O=C(Nc1c(C)cccc1C)CN(CC)CC.Cl	353.68	0.160000	[85]
Benzophenone	O=C(c1ccccc1)c1ccccc1	323.4	0.138900	[86]
Benzotriazole	[nH]1nnc2c1cccc2	369.26	0.367900	[87]
Raspberry Ketone	O=C(CCc1ccc(O)cc1)C	357.58	0.213700	[88]
1-Hydroxybenzotriazole	On1nnc2c1cccc2	424.26	0.052810	[89]
formononetin	O(C)c1ccc(C=2C(=O)c3c(OC=2)cc(O)cc3)cc1	526.85	0.000278	[90]
daidzein	O=C1C(c2ccc(O)cc2)=COc2c1ccc(O)c2	605.78	0.000418	[90]
1,3-dimethylurea	O=C(NC)NC	379.4	0.396000	[91]
β-Alanine	O=C(O)CCN	450.27	0.131200	[92]
griseofulvin	Clc1c(OC)cc(OC)c2C(=O)C3(C(OC)=CC(=O)CC3C)Oc12	491.61	0.000433	[93]

Dimethyl sulfone	S(=O)(=O)(C)C	381.92	0.008440	94
praziquantel	O=C(N1CC(=O)N2C(c3c(cccc3)CC2)C1)C1CCCCC1	411.51	0.010015	95
alpha-(trichloromethyl) benzyl acetat	ClC(Cl)(Cl)C(OC(=O)C)c1ccccc1	360.59	0.013400	96
cyhalothric acid	ClC(C(F)(F)F)=CC1C(C)(C)C1C(=O)O	383.27	0.081260	97
5,5-Dimethylhydantoin	O=C1C(C)(C)NC(=O)N1	448.93	0.059240	98
Trifloxystrobin	FC(F)(F)c1cc(C(NOCc2c(C(=NOC)C(=O)O)cccc2)=C)ccc1	345.67	0.007900	99
Indomethacin	Clc1ccc(C(=O)n2c(C)c(CC(=O)O)c3c2ccc(OC)c3)cc1	433	0.004170	100
Carvedilol	O(CCNCC(O)COc1c2c([nH]c3c2cccc3)ccc1)c1c(OC)cccc1	398.68	0.001060	101
Methyl gallate	O=C(OC)c1cc(O)c(O)c(O)c1	477.1	0.075800	102
p-toluenesulfonamide	S(=O)(=O)(N)c1ccc(C)cc1	410.25	0.036120	103
Musk ketone	O=[N+]([O-])c1c(C(C)(C)C)c([N+](=O)[O-])c(C)c(C(=O)C)c1C	407.65	0.004351	104
2-phenylacetamide	O=C(N)Cc1ccccc1	431.35	0.021385	105
Benzamide	O=C(N)c1ccccc1	401.1	0.064820	106
Marbofloxacin	Fc1c(N2CCN(C)CC2)c2OCN(C)N3c2c(C(=O)C(C(=O)O)=C3)c1	559.15	0.000117	107
2,6-Dichloro-4-nitroaniline	Clc1c(N)c(Cl)cc([N+](=O)[O-])c1	467.2	0.001831	108
o-Toluenesulfonamide	S(=O)(=O)(N)c1c(C)cccc1	427.35	0.019570	109
1,3,5-Trifluoro-2,4,6-triiodobenzene	Ic1c(F)c(I)c(F)c(I)c1F	424.01	0.000874	110
Dimethyl Terephthalate	O=C(OC)c1ccc(C(=O)OC)cc1	413.88	0.002123	111

2. Comparison Between the ANN Model and RDF Model.

Because of the large diversity of crystal structures and compound categories, it is unsurprisingly foreseen that a small percentage of datasets showed poorly performance (significant deviations between predicted and experimental values). In consideration of the comprehensiveness of the dataset, the difference between the maximum and minimum values of the collected raw datasets is over 10^3 times (mole fraction). Such an overly scattered dataset might trigger the occurrence of the prediction bias. Compare the prediction accuracy of the dataset after removing the outliers (stage 2) with the original dataset (stage 1), and the statistical result shows in Table S1. Clearly, removing outliers from the model can help improve accuracy. The appearance of outliers in our model is directly related to the amount of data, regardless of the type and physical properties of the APIs. Outliers tend to be more likely to appear when the number of training sets is insufficient. Partially underrepresented compounds make it difficult to calculate the contribution of descriptors to machine learning models. We attempted to eliminate a small fraction of compounds that were not in the above range from the model to significantly improve the prediction of compounds in independent test sets.

Table S2. Statistical results of the RDF and ANN models using molar solubility

Times	Method	Standard Error of Prediction (SEP)	Pearson Correlation Coefficient (PCC)
Stage 1	RDF	0.022	0.978
	ANN	0.018	0.998
Stage 2	RDF	0.104	0.979
	ANN	0.011	0.999

[a] Stage 1 represents the statistical results of the original data set; The statistical results in Stage 2 are derived from the data set of partial data (The APIs which mole fraction solubility is greater than 0.2, less than 0.001 are removed).

The culled sample is derived from the poorly predicting data set of the RDF model in Stage 1. It is supposed

that the modified RDF model would have a good performance in all datasets. While the TIC and SEP of processed data set are 0.143 and 0.104 for RDF, respectively. Compared to Stage 1, the accuracy of Stage 2 (Table S1) has decreased for nearly one third. The attenuation in SEP is due to the contribution of the more compact dataset. This unexpected situation occurs mainly owing to the reduction of the number of data. Although a small percentage of outliers were deleted, and the decision tree was also pruned, fewer branches result in new "outliers". The TIC and SEP of the processed datasets are 0.028 and 0.011 for ANN, respectively. The accuracy of the ANN model has been greatly improved, and the PCC has reached 0.999, which indicates that the ANN has a more positive response trend to the seven descriptors prediction model we built.

3. Comparing ANN and RDF Models with the Modified Solubility Equations (MSEs) and the QSPR model

Table S3. Relative importance of descriptors as Described by normalization of equation coefficients for Models 01−03

Models	Coefficient	Values	Std. Error	Normalized Values
Model 01	Constant	-0.582	0.177	0.643
	Melting Point	-0.011	0.001	0.503
Model 02	Constant	-2.839	0.189	0.945
	Melting Point	-0.005	0.001	0.501
	Mixing Enthalpy	0.885	0.063	0.708
Model 03	Constant	-2.084	0.222	0.889
	Melting Point	-0.004	0.001	0.501
	Mixing Enthalpy	0.767	0.060	0.685
	Melting Enthalpy	-0.021	0.004	0.505

Table S4. Eigenvalue, Percentage of Variance and Cumulative of ANN-QSPR model with 7 principal components after PCA

Principal Component Number	Eigenvalue	Percentage of Variance (%)	Cumulative (%)
1	88.45876	41.92358	41.92358
2	32.98397	15.63221	57.55579
3	15.17442	7.19167	64.74746
4	10.67798	5.06066	69.80812
5	9.37188	4.44165	74.24977
6	6.5758	3.11649	77.36626

7	5.83496	2.76538	80.13164

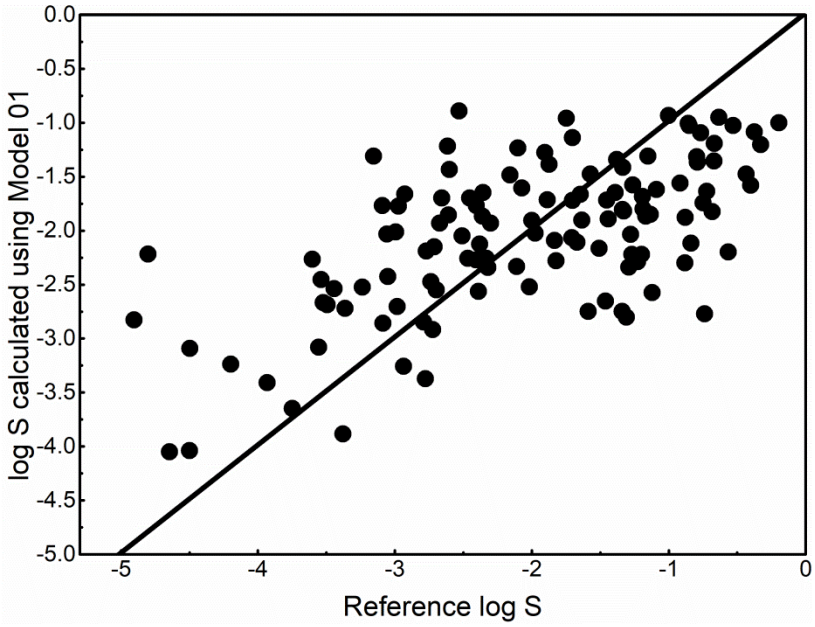

Figure S1. Correlation of predicted versus reference solubilities (log S) after applying MSE 01

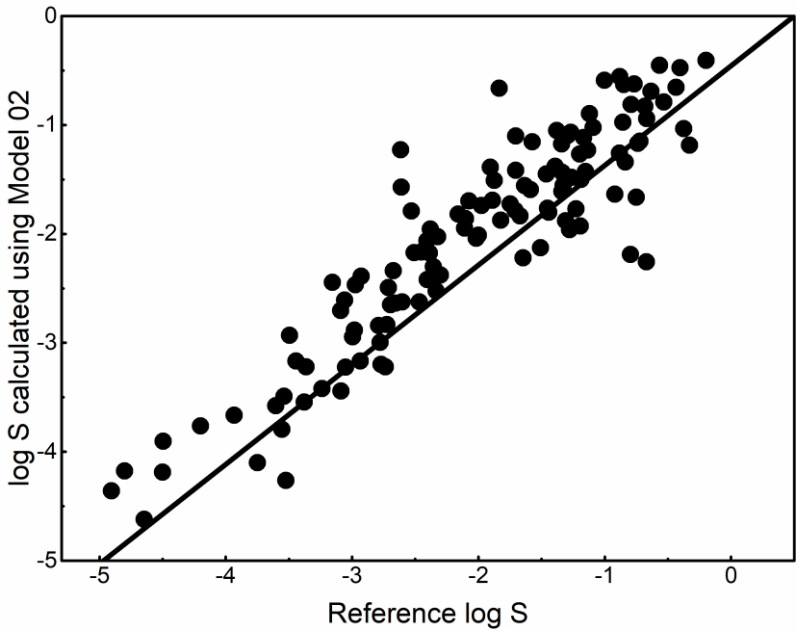

Figure S2. Correlation of predicted versus reference solubilities (log S) after applying MSE 02

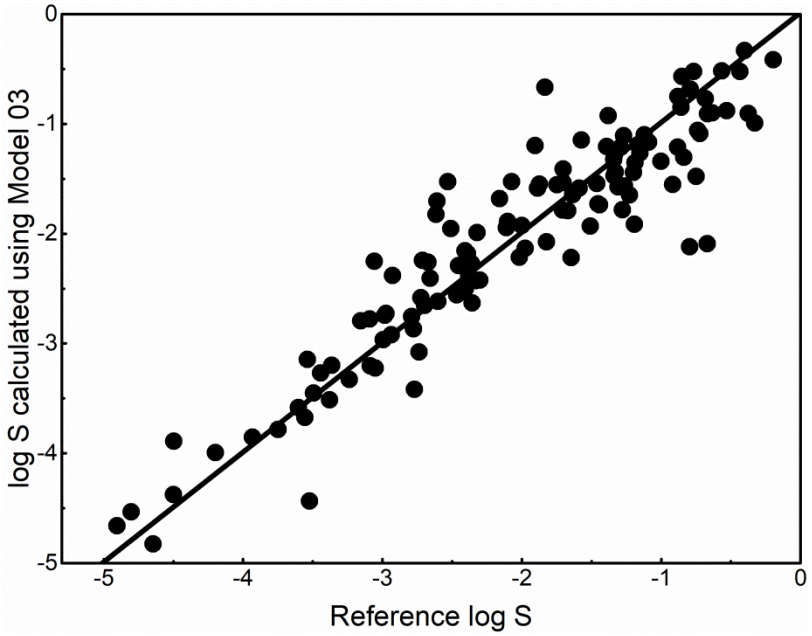

Figure S3. Correlation of predicted versus reference solubilities (log S) after applying MSE 03

4. Modified Solubility Equation (MSE) and the derivation of modified Apelblat equation.

According to the Gibbs–Helmholz equation simplified by Yalkowsky, when a crystalline solute dissolve at thermodynamics equilibrium in an ideal solution (i.e. similar polarity), we get:

$$\frac{\partial R \ln X_{API}^{ideal}}{\partial X_u} = \frac{\Delta H_m}{T^2} \qquad \text{(s1)}$$

Where ΔH_m is the heat of melting and X_{API}^{ideal} is the mole fractional solubility of the solute in an ideal solution. According to Kirchoffs law, the energy of an irreversible process is equal to the energy of a series of reversible processes between the same endpoints. Thus, the irreversible enthalpy of melting at the setting temperature can be described as the sum of three reversible processes: heating of the solid to its melting point, Tm; melting the solid at the melting point; and finally cooling the liquid back to the setting temperature.

$$\Delta H_m = \Delta H_m^{m.p.} + C_P^L \left(T_m - T\right) - C_P^C \left(T_m - T\right) \qquad \text{(s2)}$$

Where C_P^L and C_P^C are the heat capacities of the liquid and the solid, respectively. Substituting eq. into eq. and making a rearrangement, we get:

$$R\ln X_{API}^{ideal} = -\Delta H_m \frac{(T_m - T)}{T_m \cdot T} - C_P^C \frac{(T_m - T)}{T} + C_P^C \ln \frac{T_m}{T} + C_P^L \frac{(T_m - T)}{T} - C_P^L \ln \frac{T_m}{T} \quad \text{(s3)}$$

$$R\ln X_{API}^{ideal} = -\frac{\Delta H_m}{T_m} \cdot \frac{(T_m - T)}{T} + \Delta C_{Pm}\left(\frac{(T_m - T)}{T} - \ln \frac{T_m}{T}\right) \quad \text{(s4)}$$

Based on the assumption, the second term on the right side of the equation can be ignored. Using the Gibbs relationship, $\Delta H_m / T_m$ can be substituted by ΔS_m, which is the entropy of melting. Then we get:

$$R\ln X_{API}^{ideal} = -\Delta S_m \cdot \frac{(T_m - T)}{T} \quad \text{(s5)}$$

Which can be simplified to:

$$\log X_{API}^{ideal} = -u \cdot (T_m - 298) = -u \cdot (m.p. - 25) \quad \text{(s6)}$$

Where m.p. is the melting point in degrees Celsius, and u is a constant. However, calculation of the solubility in ethanol of APIs requires further consideration. In order to eliminate the limitation of the polarity requirements, and to supplement the contribution of solute-solute, solute-solvent, and solvent-solvent interactions to solubility values, the MSE equation can be expressed as:

$$\log S_{ethanol} = -u \cdot (m.p. - 25) + \sum_i^n \alpha_i \cdot F_i + c \quad \text{(s7)}$$

Which gives the general form MSE at room temperature. The equation s3 can also be written as:

$$\ln X_{API}^{ideal} = -\frac{\Delta H_m}{R \cdot T_m} \cdot \left(\frac{T_m}{T} - 1\right) - \frac{\Delta C_{Pm}}{R}\left(\ln \frac{T}{T_m} - \frac{T_m}{T} + 1\right) \quad \text{(s8)}$$

According to solid-liquid phase equilibrium theory, activity coefficient (γ_i) of the solute in the studied twelve neat solvents would be deduced by:

$$\gamma_i = \frac{x_{API}^{ideal}}{x_i} \quad \text{(s9)}$$

For correlated the ideal solubilities with real ones, combined equation s9 with $\lambda - h$ model, then we got:

$$\ln \gamma_i = a + \frac{b}{T} \tag{s10}$$

Where a and b are the empirical parameters, and thus the solubility value of APIs in solvents can be expressed by modified Apelblat equation:

$$\ln x_i = \left[\frac{\Delta H_{fus}}{RT_m} + \frac{\Delta c_{p.m}}{R} \cdot (1 + \ln T_m) - a \right] - \frac{T_m \cdot (\frac{\Delta H_{fus}}{RT_m} + \frac{\Delta c_{p.m}}{R}) + b}{T} - \frac{\Delta c_{p.m}}{R} \cdot \ln T \tag{s11}$$

$$\ln x_i = A + \frac{B}{T} + C \cdot \ln T \tag{s12}$$

5. Evaluation of the seven descriptors.

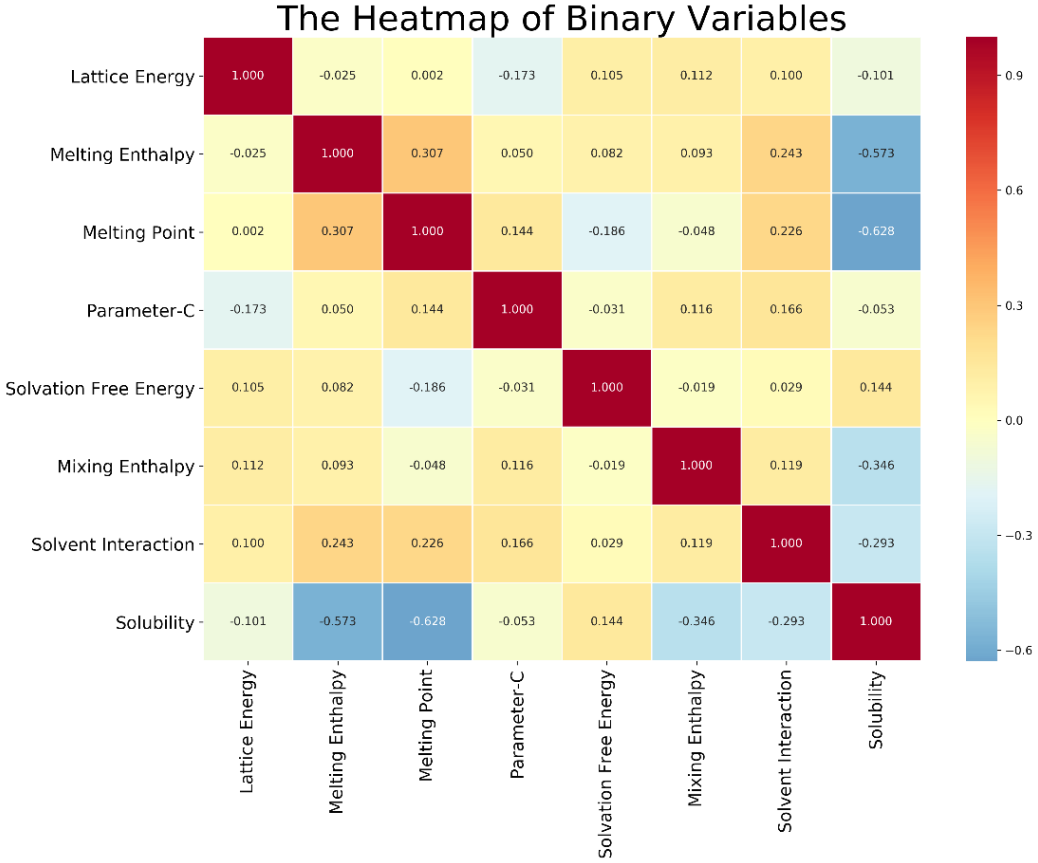

Figure S4. The heatmap between binary variables under log S

5. Key descriptors affecting solubility values

The model parameters and parameter errors for Multiple Linear Regression and Stepwise Regression are listed in Table S6. Statistics of the prediction accuracy of multiple linear regression and stepwise regression

are shown in Table S7.

Table S5. The model parameters and parameter errors for Multiple Linear Regression and Stepwise Regression

Multiple Linear Regression					Stepwise Regression				
Items	B	Std. Error	Beta	Normalization for Beta	Items	B	Std. Error	Beta	Normalization for Beta
Lattice Energy	-0.230	0.089	-0.166	0.339	Lattice Energy	-0.228	0.085	-0.165	0.335
Melting Enthalpy	-0.473	0.097	-0.328	0.671	Melting Enthalpy	-0.476	0.092	-0.331	0.673
Melting Point	-0.641	0.087	-0.489	1.000	Melting Point	-0.645	0.083	-0.492	1.000
Parameter-C	-0.003	0.474	0.000	0.000	Parameter-C	0.000	0.000	0.000	0.000
Solvation Free Energy	0.026	0.078	0.021	0.043	Solvation Free Energy	0.000	0.000	0.000	0.000
Mixing Enthalpy	-1.998	0.467	-0.284	0.581	Mixing Enthalpy	-1.983	0.440	-0.282	0.573
Solvent Interaction	-0.018	0.122	-0.010	0.020	Solvent Interaction	0.000	0.01502	0.000	0.000

Table S6. Statistics of the prediction accuracy of multiple linear regression and stepwise regression

Models	R	r square	Adjust R square	Standard error of skewness
Multiple Linear Regression	0.75	0.56177334	0.53462655	0.741661864
Stepwise Regression	0.749	0.5612561	0.546127	0.732440451

6. Factors Affecting the Accuracy of the ANN and RDF Models.

Table S7. Eigenvalue, Percentage of Variance and Cumulative of the established ML models with 7 principal components after PCA

Principal Component Number	Eigenvalue	Percentage of Variance (%)	Cumulative (%)
1	1.59311	22.75869	22.75869
2	1.41421	20.20306	42.96175
3	1.04707	14.95808	57.91983
4	0.88332	12.61891	70.53874
5	0.81471	11.63877	82.1775
6	0.69723	9.9604	92.13791
7	0.55035	7.86209	100

Table S8. Statistics of the prediction accuracy of the ANN models using 4-6 principal components

Numbers of principal components	r^2	RMSE	MAE	SEP
6 principal components	0.8505078	0.374306	0.2320158	0.374306
5 principal components	0.8314847	0.3974087	0.2557314	0.3974087
4 principal components	0.8429936	0.3835979	0.2380022	0.3835979

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