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Prediction of Melting Point and Aqueous Solubility of Barbiturates

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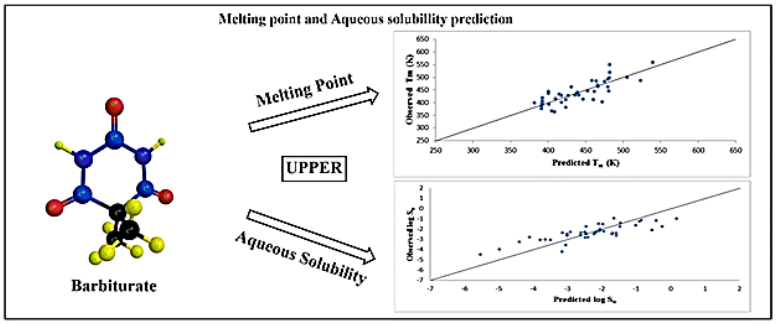
ABSTRACT

*Classical Barbiturates are formed by substituting one or both hydrogen atoms at the 5-position with alkyl, aryl, and/or alicyclic groups. In this study, a previously developed UPPER (**U**nified **P**hysicochemical **P**roperty **E**stimation **R**elationships) approach is applied to predict the melting points and aqueous solubilities of a series of barbiturates. The descriptors from a previously developed UPPER model on hydrocarbons are used to generate new descriptors for barbiturate ring using multiple linear regression analysis. Melting points can be predicted solely from additive enthalpic and non-additive entropic descriptors. These predicted melting points and aqueous activity coefficients are used to predict the aqueous solubilities. Only three new parameters are added to predict the each of above properties. The average absolute errors in prediction of melting points and aqueous solubilities are 20.6°C and 0.57 respectively. This simple and efficient UPPER approach can be useful for predicting melting points and aqueous solubilities of novel barbiturates and other compounds for which the experimental values are unavailable in the literature.*

Graphical Abstract



Keywords: Melting point; Solubility; Prediction; Barbiturate; UPPER; GSE

Abbreviations: UPPER: Unified Physicochemical Property Estimation Relationships; AQUAFAC: Aqueous Functional Group Activity Coefficients; GSE: General Solubility Equation

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INTRODUCTION

Classical barbiturates are malonyl urea derivatives substituted at the five positions with alkyl, aryl and/or alicyclic groups [1] (Figure 1). Since the introduction of barbiturates by Baeyer in 1864, more than 2500 derivatives have been synthesized, and a few of them are still being marketed [2]. The present work focuses on predicting the melting points and aqueous solubilities of the classical barbiturates from their chemical structures. Drug discovery is a very expensive and difficult process. In order to minimize the overall cost and speedup the process, many approaches

have been developed to estimate physicochemical properties of drugs before they are synthesized [3,4]. The UPPER approach developed by Yalkowsky et al. [5] offers a rapid and inexpensive means of calculating melting points, vapor pressures, aqueous solubilities and other biorelevant properties. The melting point has wide application in the field of pharmaceutical, biochemical and environmental sciences because of its relationship with the solubility and vapor pressure [6]. Recently, Lian et al. used the UPPER model to predict the melting point of a large number of hydrocarbons [7]. The aqueous solubility is an important determinant of dissolution rate, absorption, and bioavailability. Poor aqueous solubility is a key problem during formulation development and drug design [8]. The GSE (General Solubility Equation) developed by Jain and Yalkowsky requires the calculated octanol-water partition coefficient and the experimental melting point to predict the aqueous solubility [9]. Yalkowsky and Pinal used the GSE to calculate the aqueous solubility of several barbiturates [10]. In this manuscript, we applied UPPER model only to the classical barbiturates, as besides general ring structure only other substitution at five positions is hydrocarbon moieties (Figure 1). Here, only UPPER is used to predict the melting points while both UPPER and GSE are used to calculate the aqueous solubilities of barbituric acid derivatives.

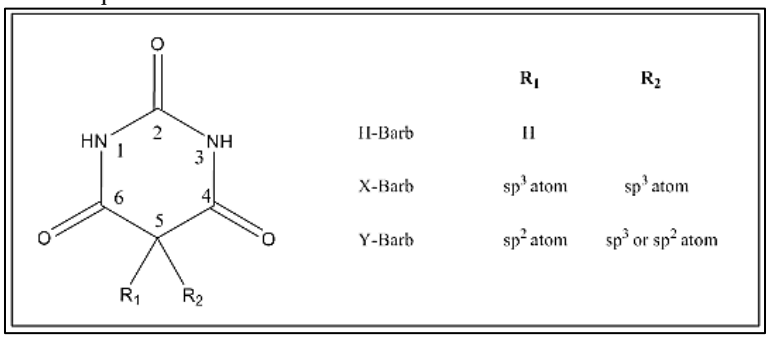

Figure 1: General structure of barbiturate (R_1, R_2 = H, alkyl, aryl, and/or alicyclic)

The Upper Model

Melting point:

Melting points T_m (K) are calculated using equation 1.

$$T_m = \frac{\Delta H_m}{\Delta S_m} \quad (1)$$

Where, ΔH_m is the total enthalpy of melting (kJ/mol), and ΔS_m is the total entropy of melting (J/K · mol) as described below.

Enthalpy of melting:

The enthalpy of melting is defined as the total change in the enthalpy when one mole of crystal is converted into liquid. i.e.,

$$\Delta H_m = H^L - H^C \quad (2)$$

Where, $H^L$is the molar enthalpy of a liquid phase and H^c is the molar enthalpy of a crystal phase.

The enthalpy of melting is an additive property that can be calculated by the sum of constituent group contributions as expressed in equation 3.

$$\Delta H_m = \sum n_i m_i \quad (3)$$

Where, n_i is the number of times that group i appears in the compound, and m_i is the contribution of group i to the total enthalpy of melting.

Entropy of melting:

The entropy of melting is defined as the change in the molar entropy when the crystal converted into the liquid. Hence,

$$\Delta S_m = S^L - S^C \quad (4)$$

Where, S^L is the molar entropy of a liquid phase and S^c is the molar entropy of a crystal phase. Based on the Boltzmann equation, the molar entropy of melting is related to the logarithm of ρ_m, the ratio of the probabilities of existence of the crystal phase to that of the liquid phase. That is

$$\Delta S_m = -R \ln \rho_m \quad (5)$$

Where,

$$\rho_m = \frac{P^C}{P^L} \quad (6)$$

Where, P^C and P^L are the probabilities of achieving the crystal and liquid state, respectively.

The probability of achieving the crystal phase is equal to the number of ways in one mole of molecules can be arranged that conform to the requirements of a crystal, divided by the total number of ways in which all possible phases can exist. In the case of a substance that exists only as a liquid and a solid phase,

$$P^C = \frac{\Omega^C}{(\Omega^C+\Omega^L)} \text{ and } P^L = \frac{\Omega^L}{(\Omega^C+\Omega^L)} \quad (7)$$

Where, the numerators are the number of ways in which the crystal and liquid can be achieved, respectively and the denominator is the total number of ways in which the molecule can exist.

Combining equations 4 thru 7 gives,

$$S^C = -R \ln \frac{\Omega^C}{(\Omega^C+\Omega^L)} \text{ and } S^L = -R \ln \frac{\Omega^L}{(\Omega^C+\Omega^L)} \quad (8)$$

Where, R is the gas constant.

Walden [11] estimated the entropy of melting of a variety of coal tar derivatives as approximately 57 J/K·mol (Walden's Rule). This constant value of the entropy of melting is traditionally use for all organic compounds. However, deviations from Walden's rule are common.

Bondi reported that the total entropy of melting could be explaine as the sum of its rotational (ΔS_m^{rot}), conformational (ΔS_m^{conf}) and expansional (ΔS_m^{expan}) components [12].

$$\Delta S_m = \Delta S_m^{rot} + \Delta S_m^{conf} + \Delta S_m^{expan} \quad (9)$$

Three geometric descriptors; symmetry (σ), flexibility (ϕ) and eccentricity (ε) are used in UPPER to characterize each type of entropic component, respectively.

As described by Lian and Yalkowsky, the rotational symmetry (σ) is defined as the number of positions into which a molecule can be placed that are identical to a reference position [7]. Since highly symmetrical molecules can crystallize more readily, they have lower entropies of melting. If the rotational symmetry number is incorporated as the probability ratio into the Boltzmann equation (equation 5), then

$$\Delta S_m^{rot} = -R \ln \sigma \quad (10)$$

The molecular flexibility number (ϕ) is related to the ratio of the total number of possible conformations of a compound in the crystal to that of the liquid. The conformational component of entropy is related to the molecular flexibility as highly flexible molecules can have many conformations in the liquid and are less likely to be in the single trans-conformation of crystal. Thus, they tend to have higher entropies of melting. By incorporating the flexibility number as the probability ratio into the Boltzmann equation, we get:

$$\Delta S_m^{rot} = -R \ln \phi \quad (11)$$

For a hypothetical long chain normal alkane with completely free bond rotation (assuming equal energies for the trans and two gauche conformations), the probability of being in the all-trans form would be 0.33. According to Wunderlich, the trans conformation is more stable than the gauche conformation by 2.09 KJ/mol, and certain combinations of adjacent gauche conformations would place two atoms in the same place. Correcting for these effects gives the overall probability of a molecule to being in the all transform is

$$\phi = (0.4)^{\Phi} \quad (12)$$

Where, Φ, the effective number of torsional units in the molecule.

In UPPER, this effective number of torsional units is calculated using equation 13.

$$\Phi = \text{LIN} + 0.3\ \text{ROT}^* + 0.5(\text{BR} + \text{SP2} + \text{RING}) - 1 \quad (13)$$

Where, LIN is the sum of all non-ring, non-terminal sp^3 atoms; ROT^* is the sum of all freely rotating linear chain sp^3 atoms less 4 (e.g. Octane has six linear chain sp^3 atoms, so ROT^* value is 2); BR is the sum of all branched, non-ring sp^3 atoms; SP2 is the sum of all non-ring, non-terminal sp^2 atoms; RING is the total number of independent single, fused or conjugated aromatic rings present in the molecule.

Molecular eccentricity (ε) is defined as the total number of atoms in the aromatic and/or aliphatic rings. It is related to the packing efficiency of molecules in the crystal, and thus, to the amount of expansion required for melting. Since highly eccentric molecules are more likely to pack efficiently in the crystal, they need more expansion to from a liquid. This gives them higher entropy of melting. By substituting the probability ratio of the Boltzmann equation with the eccentricity, we get:

$$\Delta S_m^{expan} = R\ ln\ \varepsilon \quad (14)$$

Using equation 9,10,11, and 14, the total entropy of melting can be described as:

$$\Delta S_m = W' - R \ln \sigma - R \ln \phi + R \ln \varepsilon \quad (15)$$

Where, W' is the modified Walden's Rule constant.

In base 10 logarithmic terms it can be represented as,

$$\Delta S_m = W' - 19.1 \log \sigma + 7.6\ \Phi + 19.1 \log \varepsilon \quad (16)$$

As described by Lian and Yalkowsky [7], the deviation form ideal entropy of melting is common, the entropy of melting for hydrocarbons can be well described by the following empirical equation:

$$\Delta S_m = 43.54 - 8.95 \log \sigma + 7.93\ \Phi + 9.16 \log \varepsilon_{ar} + 9.43 \log \varepsilon_{al} \quad (17)$$

Where, ε_{ar} and ε_{al} are the molecular eccentricity contribution for the aromatic and the aliphatic rings respectively. The lower coefficients in equation 17 reflect the facts that the crystal is not a perfect crystal and the liquid is not a perfect liquid.

Ideal solubility:

The ideal solubility of a crystalline solute, X_i^C, is its solubility in a hypothetical perfect solvent, i.e., one in which the solute-solvent interactions are exactly equal to the sum of the solute-solute and solvent-solvent interactions. It is entirely dependent on the crystallinity of the solute and independent of the solvent. The ideal solubility can be thought of as the ratio of the solubility of a crystal in any solvent to the solubility of its hypothetical supercooled liquid in the same solvent. The ideal solubility is approximated from the Clausius-Clapeyron equation or the Van't Hoff equation, both of which can be expressed as equation 18 [9],

$$\log X_i^C = -\Delta S_m \frac{(T_m - T)}{2.303\, R\, T} \quad (18)$$

Where, T and T_m are the room temperature and melting point in Kelvin and R is the gas constant.

Approximate ideal solubility:

Incorporating Walden's Rule (ΔS_m=57 J/K mol) into the above equation gives,

$$\log X_i^C = -0.01\,(T_m - T) \quad (19)$$

Which can be written in celsius as

$$\log X_i^C = -0.01\,(MP - 25) \quad (20)$$

Aqueous activity coefficient:

The logarithm of the aqueous activity coefficient log γ_w (like the enthalpy of melting) is a group additive property. Myrdal and Yalkowsky developed the AQUAFAC (AQUeous Functional group Activity Coefficients) model to calculate the total logarithmic aqueous activity coefficient by adding all group contribution as expressed in equation 21 [13].

$$\log \gamma_w = \sum n_i q_i \quad (21)$$

Where, n_i is the number of times that group i appears in a compound and q_i is the contribution of group i to the total logarithmic aqueous activity coefficient.

Aqueous solubility:

The molar aqueous solubility (S_w) is the ratio of the ideal solubility of a solute to its aqueous activity coefficient [14]. In logarithmic terms it is,

$$\log S_w = log\ X_i^c - log\ \gamma_w \quad (22)$$

Where, $log\ X_i^c$ is obtained by equation 18 and $log\ \gamma_w$ by equation 21.

EXPERIMENTAL

Data

The reported experimental melting point and aqueous intrinsic solubility values of 44 5-substituted barbiturates were collected from Prankerd and McKeown [15], Pinal and Yalkowsky [10], Hughes et al. [16], and the Merck Index [17] are listed in Table 1. This table includes the melting points (Range between 364 K to 561 K) and aqueous molar intrinsic solubilities (which range between 3.45 E-5 M to 0.12 M). The partition Coefficient (log P) values were obtained from Advanced Chemistry Development Software V11.02 [18].

Table 1: Experimental and predicted melting point and aqueous solubility

No	Name of Barbiturate	Exp. MP (K)	Pred. MP (K)	Residual	Exp. log S_w	GSE log S_w	Residual	UPPER log S_w	Residual
1	5,5-Diethylbarbiturate	463	431	32	-1.4	-1.95	-0.56	-1.47	-0.07
2	5,5-Di-i-propylbarbiturate	501	505	4	-2.77	-3.04	-0.27	-2.41	0.36
3	5,5-Dimethylbarbiturate	551	482	69	-1.74	-1.82	-0.07	-0.26	1.48
4	5,5-Diphenylbarbiturate	561	539	22	-4.2	-2.38	1.81	-3.18	1.02
5	5,5-Dipropylbarbiturate	420	392	27	-2.47	-2.54	-0.07	-2.46	0.01
6	5-Allyl-5-neopentylbarbituric acid	429	426	3	-2.80[p]	-3.01	-0.22	-2.5	0.3
7	5-Allyl-5-phenylbarbiturate	432	436	4	-2.37	-1.84	0.53	-1.7	0.67
8	5-Ethyl-5-(1-ethylbutyl)barbituric acid	395	400	5	-3.06[p]	-3.16	-0.1	-3.51	-0.45
9	5-Ethyl-5-(3-methylbut-2-enyl)barbiturate	431	441	9	-2.25	-2.69	-0.44	-2.18	0.07
10	5-Ethyl-5-allylbarbiturate	435	415	20	-1.61	-1.8	-0.18	-1.02	0.59
11	5-Ethyl-5-heptylbarbiturate	391	391	0	-3.22	-3.78	-0.56	-4.42	-1.2
12	5-Ethyl-5-nonylbarbiturate	378	391	13	-4.46	-4.66	-0.2	-5.54	-1.08
13	5-Ethyl-5-octylbarbiturate	386	391	5	-3.94	-4.21	-0.27	-5	-1.06
14	5-Ethyl-5-pentylbarbiturate	408	392	16	-2.34	-2.93	-0.59	-3.15	-0.81
15	5-Ethyl-5-propylbarbiturate	417	409	8	-1.49	-2	-0.51	-1.98	-0.49
16	5-Ethyl-barbiturate	464	479	15	-0.92	-1.07	-0.15	-1.66	-0.73
17	5-i-Propyl-5-(3-methylbut-2-enyl)barbiturate	404	472	68	-2.59	-2.77	-0.18	-2.63	-0.04
18	5-Methyl-5-(3-methylbut-2-enyl) barbiturate	466	466	0	-2.6	-2.53	0.08	-1.59	1.01
19	5-Methyl-5-allylbarbiturate	440	438	2	-1.16	-1.34	-0.18	-0.43	0.73
20	5-Methyl-5-ethylbarbiturate	489	458	31	-1.23	-1.7	-0.48	-0.91	0.31
21	5-Methylbarbiturate	493	479	14	-1.13	-0.85	0.27	-0.86	0.27
22	5-t-Butyl-5-(3-methylbut-2-enyl) barbiturate	485	475	10	-3.55	-3.99	-0.44	-3.07	0.48
23	Allobarbital	445	400	45	-2.08	-1.89	0.19	-0.55	1.53
24	Amobarbital	430	417	13	-2.62	-3	-0.38	-3.02	-0.4
25	Aprobarbital	415	446	31	-1.71	-1.95	-0.23	-1.48	0.24
26	Barbituric acid	521	482	39	-0.96	-0.6	0.36	0.17	1.12
27	Butalbital	413	423	10	-2.12	-2.44	-0.32	-2.07	0.05
28	Butethal	398	392	6	-1.75	-2.32	-0.58	-2.46	-0.72
29	Cyclobarbital	446	461	15	-2.27	-2.48	-0.21	-2.93	-0.65
30	Cyclopentobarbital	413	460	47	-2.46[p]	-1.64	0.82	-1.71	0.74
31	Heptabarbital	448	480	32	-3	-3.03	-0.03	-3.66	-0.66
32	Heptobarbital	499	481	18	-2.38	-1.53	0.85	-1.59	0.79
33	Hexethal	398	391	7	-3.05	-3.34	-0.29	-3.8	-0.75
34	Idobutal	401	381	20	-2.17	-2.48	-0.3	-2.09	0.08
35	Isopropylbarbiturate	489	523	34	-1.46	-1.68	-0.22	-2.11	-0.65
36	Pentobarbital	402	417	16	-2.45	-2.71	-0.26	-3.02	-0.57
37	Phenobarbital	448	452	4	-2.31	-1.53	0.78	-2.18	0.13
38	Probarbital	471	465	6	-2.19	-2.39	-0.2	-1.95	0.23
39	Reposal	486	463	23	-2.77	-3.48	-0.71	-4.11	-1.34
40	Secbutabarbital	441	439	2	-2.26	-2.6	-0.33	-2.51	-0.24
41	Secobarbital	368	404	36	-2.33	-2.5	-0.17	-2.62	-0.29
42	Talbutal	382	423	41	-2.02	-2.13	-0.11	-2.07	-0.05
43	Vinbarbital	438	400	38	-2.46	-2.14	0.32	-2.23	0.23
44	Vinylbital	364	408	44	-2.32[p]	-1.34	0.98	-2.49	-0.17

Note: [p] Values obtained from ACD/Lab Software V11.02

In Tables 2 and 3, the first column shows the atomic composition of the groups considered and the first row gives the following the environmental descriptors.

X: the group is bonded only to sp^3 hybrid atoms;
Y: the group is singly bonded to sp^2 hybrid atom;
RG: the group is within an aliphatic ring;
AR: the group is within aromatic ring;
FU: the group is a bridgehead in an aliphatic ring system;
H: the group is bonded to H atom
Barb: the value for whole barbituric acid ring

Table 2: Group contribution coefficients (J/mol) for the calculation of total enthalpy of melting

Group	X	Y	RG	AR	FU	H
0	1183	1785	-	-	-	-
0	1906	684	1319	-	-	-
*-CH₂**	4000	-	-	-	-	-
-CH	1047	-1545	836	1387	1127	-
-C	-85	-2246	-519	1219	1152	-
0	1371	-	-	-	-	-
#NAME?	1667	1399	973	-	-	-
=C	1296	-1005	531	-	-	-
-Barb	***20859***	***18578***	**-**	**-**	**-**	***23207***

Table 3: Group contribution coefficients for the calculation of total logarithm aqueous activity

Group	*X*	*Y*	*RG*	*AR*	*FU*	*H*
0	0.958	0.711	-	-	-	-
0	0.687	0.334	0.52	-	-	-
$(-CH_2)^2$	-0.018	-	-	-	-	-
-CH	-0.1	-0.342	0.254	0.312	0.513	-
-C	-0.662	-0.89	-0.291	0.112	-	-
0	0.627	-	-	-	-	-
#NAME?	0.284	0.29	0.269	-	-	-
=C	-0.044	-0.23	0.087	-	-	-
-Barb	***-3.212***	***-2.901***	**-**	**-**	**-**	***-1.716***

Each compound was broken down into the groups using the same molecular fragmentation scheme described by Lian and Yalkowsky. Microsoft Excel 2012 was used to perform all calculations for group counts, enthalpies of melting, entropies of melting, and aqueous activity coefficients. The barbiturate compounds are subdivided into three different groups based on whether they contain hydrogen, only sp3 atoms or at least one sp2 atoms at 5-position. These are designated as H-Barb, X-Barb, and Y-Barb, respectively (Figure 1). The mi and qi contributions of the barbiturate rings to the of enthalpy of melting and the aqueous activity coefficient were generated by subtracting the hydrocarbon group values in Tables 2 and 3 from the observed values.

Calculation of Melting Point by Upper

For each compound the total entropy of melting (ΔS_m) was estimated by equation 17. The total enthalpy of melting (ΔH_m) for each barbiturate compound was calculated by multiplying the experimental melting point (T_m^{Obs}) by the calculated entropy of melting. The enthalpy of hydrocarbon groups ($\sum n_i m_i$) were obtained from Lian and Yalkowsky [7]. The mean enthalpy m_i^{barb} values for H-Barb, X-Barb, and Y-Barb (Table 2) were obtained from the difference between the calculated total enthalpy and the sum of the hydrocarbon values. Finally, the total enthalpies for predicting melting point were obtained by adding the calculated m_i^{barb} value to the hydrocarbon group values. These calculated enthalpy and entropy values were used to calculate melting point T_m^{Calc} via equation 23.

$$T_m^{Calc} = \frac{\Delta H_m}{\Delta S_m} = \frac{\sum n_i m_i + m_i^{barb}}{43.54 - 8.95 \log \sigma + 7.93\ \Phi + 9.16 \log \varepsilon_{ar} + 9.43 \log \varepsilon_{al}} \quad (23)$$

Where, m_i^{barb} is the group contribution value for one of the three above mentioned barbituric acid rings to the total enthalpy of melting.

Calculation of Solubility by Upper

The effect of solute crystallinity is determined by incorporating the calculated entropy of melting and the calculated melting point into equation 18. The aqueous activity coefficient for each compound was calculated by adding the q_i^{barb} value for the ring to the sum of the hydrocarbon group values. These equations are combined to give:

$$\log S_w^{Calc} = -\frac{(43.54 - 8.95 \log \sigma + 7.93\ \Phi + 9.16 \log \varepsilon_{ar} + 9.43 \log \varepsilon_{al})\,(T_m^{Calc} - T)}{2.303\ RT} - (\sum n_i q_i + q_i^{barb}) \quad (24)$$

The total aqueous activity coefficient for each barbiturate compound was calculated using equation 21. The aqueous activity coefficients of the hydrocarbon groups ($\sum q_i m_i$) were calculated by adding group q_i values from Lian and Yalkowsky [7]. The aqueous activity coefficients q_i^{barb} values for H-Barb, X-Barb, and Y-Barb (Table 3) were obtained from the difference between calculated total aqueous activity coefficient and the sum of the hydrocarbon values. As shown in equation 24, the final calculated log γ_w for predicting solubility was obtained by adding the q_i^{barb} values and other substituted group values and these values were used to calculate log S_w^{Calc}.

Calculation of solubility by the GSE

The General Solubility Equation (GSE) of Yalkowsky provides a simple means of estimating the aqueous solubility of nonelectrolytes in which the logarithm of the octanol-water partition coefficient is used to represent the aqueous activity coefficient and equation 20 is used as the ideal solubility. Thus

$\log S_w = 0.5 - \log P - 0.01\,(MP - 25)$ (25)

Where, P is the octanol-water partition coefficient.

RESULTS AND DISCUSSION

Melting Point

The observed and predicted melting points of the barbiturates are shown in Figure 2. Note that the negative and positive residual values of Table 1 correspond to underestimates and overestimates in the prediction respectively. In order to calculate the total enthalpy of classical barbiturates, we need to calculate enthalpic group contribution of barbiturate ring as the UPPER model of hydrocarbons does not account for the non-hydrocarbon moiety. The melting points were generated by incorporating the group m_i values of Lian and Yalkowsky along with the appropriate barbituric acid ring coefficient. Note that these three m_i^{barb} values are the only regression generated enthalpic parameters used to predict melting points. The average absolute error (AAE) in the prediction of melting points is 20.6° for 44 barbiturates.

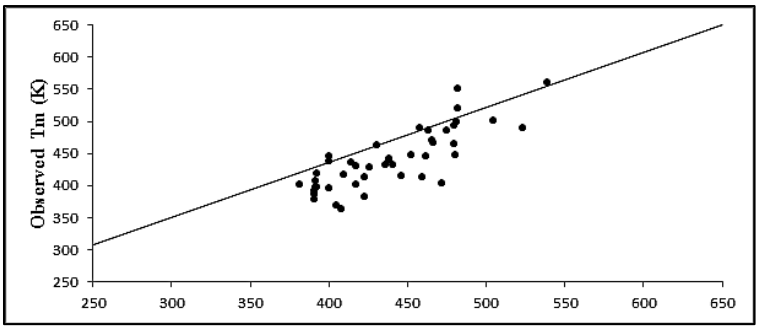

Figure 2: Observed vs. predicted melting point (K). (•) all barbiturates compounds used in the training dataset to generate m_i^{barb} values and (-) the line of identity

Aqueous Solubility

The observed and predicted logarithms of aqueous solubility by the UPPER model are shown in the Figure 3. Again, the new entropic descriptors and only one of the three fitted q_i^{barb} values are used to predict solubility of each compound. The average absolute error for predicting aqueous solubility using the UPPER and GSE models is 0.57 and 0.38 respectively. As shown in Figure 3 these predicted solubility values are in a good agreement with the experimental values. As expected, the GSE model can predict the solubility of barbiturates more accurately, as it uses observed melting point, which might not be available for all compounds in the early stages of drug discovery. UPPER, on the other hand, requires no experimental data and thus can be used in drug design.

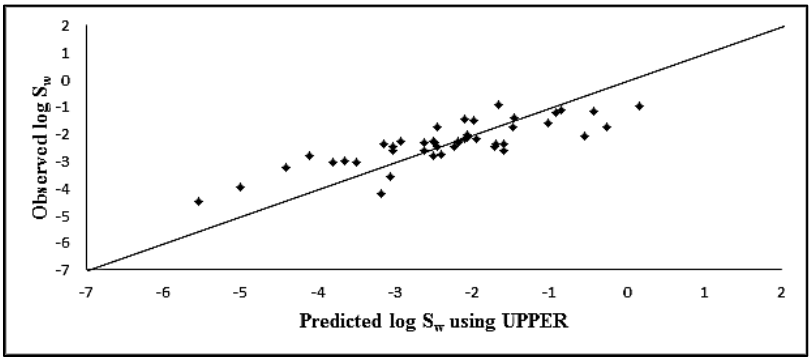

Figure 3: Observed vs. predicted logarithm aqueous solubility using upper. (♦) All barbiturates compounds used in the training dataset to generate q_i^{barb} values and (-) the line of identity

Table 4: Statistical results for melting point and aqueous solubility

Properties	Average Absolute error
T_m^{Calc}	20.6
log byS_w^{Calc} UPPER	0.57
log S_w^{Calc} by GSE	0.38

CONCLUSION

The UPPER model, which is developed on simple hydrocarbons, is applied to barbiturates. The prediction of properties is directly based on the chemical structure and well-known thermodynamic relationships. It is clear from the results listed in Table 4. There is a good agreement between the predicted and observed values. Thus, this simple and efficient approach could be useful for predicting melting points and aqueous solubility of novel barbiturates and other compounds for which the experimental values are unavailable.

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