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Lipophilicity Screening of Novel Drug-like Compounds and Comparison to cLogP

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Abstract

We determined the distribution coefficients of solutes between a polymer film phase (polyvinyl chloride (PVC) with 67% (w/w) dioctyl sebacate (DOS)) and an aqueous phase in a 96-well format. The parallel measurement approach is efficient and uses very little material. Polymer-water distribution coefficients (D_{pw}) at different pH values yield the pK_a and polymer-water partition coefficient values (P_{pw}) of the solutes. Log P_{pw} of a prominent drug-like compound, 2H-1, 2, 6-thiadiazine, 3-methyl-5-phenyl-, 1, 1-dioxide, is in good agreement with cLogP, while the pK_a value is substantially different from calculated values. This method has been also successfully applied to a library of novel drug-like compounds. Log D_{pw} values (at pH 4.0, 7.0, 10.0) of 24 novel drug-like compounds have been determined with good reproducibility with the 96-well plate approach. Differences between experimental values and a variety of available calculated values are significant. This emphasizes the need for laboratory separations-based measurements of logD.

Keywords

Drug-like compounds; partition coefficient; logP; calculated partition coefficient (cLogP); UHPLC

1. INTRODUCTION

Acid dissociation constants (pK_a s) and the logarithmic value of the 1-octanol/water partition coefficient (log P_{ow}) are important parameters in environmental, medical, toxicological and pharmaceutical studies of novel organic molecules. Sixty-three percent of the molecules listed in the 1999 *World Drug Index* are ionizable between pH 2 and pH 12[1]. Various ionized forms of a compound may differ in physical, chemical, and biological properties, so it is important to predict which ionic form of the molecule is present at the site of action. The partition coefficient is often used in combination with the pK_a value to predict the distribution of a compound in a biological or ecological system. This knowledge can be

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valuable in the estimation of drug absorption, distribution, metabolism, and excretion (ADME), or for the estimation of the distribution of a solute in an ecological system.

Numerous methods exist to measure or estimate the pK_a and $\log P_{ow}$ values. The shake-flask method and RP-HPLC method are the main experimental methods to determine partition coefficients. The shake-flask procedure is a standard method to determine octanol/water partition coefficients in the range of -2 to 4 [2,3]. This method is the most reliable and accurate one, however, it is tedious, time consuming, and requires large amounts of pure material. In addition, octanol/water emulsions can be severe problems, especially for hydrophobic compounds, limiting the upper measurable $\log P_{ow}$ value to 4 [4]. Recently, a micro-volume flow extraction system consuming less than 1 mL of octanol and aqueous sample has been developed[5]. To increase sample throughput, the traditional shake-flask method has been automated and scaled down using 96-well plate technology and a robotic liquid handler[6]. However, the emulsion problem still exists for scaled down shake flask method, especially for hydrophobic compounds.

The RPLC method is an indirect but popular way to measure $\log P_{ow}$ values in the range of 0 – 6 [7]. This method is rapid and reproducible for sets of similar compounds, although impurities may make the interpretation of the results difficult due to uncertainty in peak assignments. However, it is not applicable to strong acids and bases, metal complexes, substances that react with the eluent, or surface-active agents[4]. One further disadvantage with this method is that the reference compounds should be preferably similar to those being studied and difficulties arise if suitable standards are unavailable.

There are some theoretical approaches to predict lipophilicity. Most of them add up the $\log P_{ow}$ contribution from each fragment and then apply structure-based correction factors[3]. There are at least 20 software packages available at present, which provide convenient and fast prediction of lipophilicity for novel compounds. However, studies show calculations are not reliable for $\log P_{ow}$ and pK_a of zwitterionic, tautomeric and charged compounds as well as for strong hydrogen-bonding compounds[8]. It was reported by investigators at Wyeth Research[9] that the average difference between the calculated and measured $\log P_{ow}$ values for 70 commercial drugs is about 1.05 log units.

Recently, our group has developed a high-throughput phase-distribution method based on partition of the analyte between a polymer phase and an aqueous phase in a 96-well format. The polymer phase is composed of poly (vinyl chloride) (PVC) and dioctyl sebacate (DOS) at the ratio of $1:2$ (w/w). Studies in our group[10] on the correlation of polymer/water partition coefficient $\log P_{pw}$ and standard 1-octanol/water partition coefficient ($\log P_{ow}$) have shown a good linear relationship with the slope of 0.933 and the intercept close to zero, indicating that DOS plasticized PVC had lipophilicity similar to octanol. Therefore, our polymer/water partition coefficient can be used to predict lipophilicity. This method has been applied to screen chiral selectors[11] and to measure binding constants of drug-cyclodextrins inclusion complexes[12].

In this paper, we have first applied our method to determine pK_a and lipophilicity of a drug-like compound 2H-1, 2, 6-thiadiazine, 3-methyl-5-phenyl-, 1, 1-dioxide (Figure 1). Compounds with the 2H-1, 2, 6-thiadiazine-1, 1-dioxide substructure are prominently featured in patent and medicinal chemistry as hepatitis C virus (HCV) polymerase inhibitors[13], non-nucleoside HIV-1 reverse transcriptase inhibitors[14], analgesics[15], and smooth muscle relaxants[16]. We have further used this high-throughput method to screen lipophilicity of a library of twenty-four novel drug-like compounds. Their $\log D_{pw}$ values (at pH 4.0, 7.0, 10.0) can be measured with good reproducibility in a high-throughput

and automated format. We have found that there is a relatively poor correlation between those experimental values and calculated values with various methods.

2. MATERIALS AND METHODS

2.1 Materials

Acetonitrile (HPLC grade), tetrahydrofuran (THF) (HPLC grade) and dimethyl sulfoxide (DMSO) (anhydrous, 99.9%) were purchased from Aldrich (Milwaukee, WI). PVC (high molecular weight) and dioctyl sebacate (DOS) were purchased from Fluka (Ronkonkoma, NY). HPLC grade trisodium phosphate, phosphoric acid, trifluoroacetic acid (TFA) were also purchased from Fluka (Ronkonkoma, NY). Water used in all the experiments was purified with a Milli-Q Synthesis A10 system (Millipore, Bedford, MA). Costar polypropylene 96-well microplates (flat bottom, 330- μ L well volume) were purchased from Fisher Scientific Co. (Pittsburgh, PA). Storage plate cap strips were purchased from Thermo Scientific Co. (Waltham, MA). 2H-1, 2, 6-thiadiazine, 3-methyl-5-phenyl-, 1, 1-dioxide and a library of twenty-four drug-like compounds were synthesized in the University of Pittsburgh Center for Chemical Methodologies and library Development (UPCMLD) (Pittsburgh, PA). See Tables 1 and 2 for structures and PubChem SID numbers.

2.2 Equipment

An UltraSpense 2000 microplate dispenser (KD Scientific, Holliston, MA) was used to prepare polymer films in 96-well plates. A Deep Well Maximizer (or BioShaker) (Model: M-BR-022 UP, made by Taitec, Japan, and distributed by Bionexus, Inc., Oakland, CA) was used to speed up the solute distribution kinetics and control temperature. An HT-4X evaporator (Genevac inc., Gardiner, NY) was used to evaporate organic solvents. An X-LC (Jasco, Inc.) UHPLC system was used to determine the solute concentration with a UHPLC C₁₈ column (1.0 $\times$ 50 mm, particle size: 1.7 μ m, Waters, Milford, MA). UV absorbances of solutes were acquired with a SpectraMax M2 microplate reader (Molecular Devices, Sunnyvale, CA) in UV-transparent microplates.

2.3 Buffer Preparation

The phosphate-citrate buffer solutions (20 mM, pH 2.7, 2.8, 3.2, 3.9, 4.0, 5.1, 6.1, 7.0, 7.2) were made by mixing appropriate amounts of 20 mM sodium phosphate dibasic solution and 10 mM citric acid solution. The phosphate buffer solutions (20 mM, pH 1.9, 2.5, 9.2, 10.0) were made by mixing appropriate amounts of 20 mM trisodium phosphate solution and 20 mM phosphoric acid solutions. The trifluoroacetic acid (TFA) buffer solutions (pH 0.9, 1.1) were made by preparing 0.2%, 0.1% TFA in water (v/v) respectively.

2.4 Determination of log P_{pw} and pK_a of a solute

2.4.1 Partitioning—Figure 2 gives the sequence of operations for P_{pw} and pK_a determination of a solute. The plasticized PVC films were prepared in polypropylene 96-well microplates. Aliquots of the solute in the aqueous buffers (200 μ L) with different pH values were then manually dispensed over the films with a multichannel pipet. The wells in each plate were covered by storage plate caps and the plate was incubated in a shaker (500 rpm, 25 $^{\circ}$ C). In order to determine the equilibration time, a kinetic study was first performed. The concentration of solute remaining in the aqueous phase was measured as a function of time. All of the other data generated were from systems at equilibrium. To determine the drug concentration, the supernatant from each well was transferred to another plate. Concentrations can be determined either by UHPLC or by measuring the absorbance in a UV plate reader. The distribution coefficient at a specific pH could be calculated as

$$D_{pw}^{pH} = \frac{(C_s - C_E) \cdot \Phi}{C_E} \quad (1)$$

Here D_{pw}^{pH} is the distribution coefficient of the solute in the polymer phase over the aqueous phase at a specific pH value. C_s is the initial solute aqueous concentration, C_E is the solute's aqueous concentration at equilibrium after the extraction, and Φ is the phase ratio (aqueous over polymer).

2.4.2 UHPLC Method to Determine Concentrations of the Solute—A Waters UHPLC C18 column was used for this method. The mobile phase was acetonitrile-ammonium acetate buffer (pH 4.92; 10 mM) (20:80, v/v), with a flow rate of 0.1 mL/min. The back-pressure was approximately 4300 psi. The injection volume was 2 μ L. Detection was by UV absorbance at 343 nm, at which the solute peak had best signal-to-noise ratio. Peak area was used for the calibration and determination of sample concentration. The time per analysis was ~1.3 min.

2.4.3 UV Plate Reader Method to Determine Concentrations of the Solute—UV absorbances of the solute at 343 nm were used for calibration and determination of solute concentrations. They were acquired with a microplate reader in UV-transparent 96-well plates. Absorbances of the buffers were measured as the background and subtracted to get the absorbances of the solute.

2.5 Lipophilicity Screening

Ten nmol of 24 compounds in 20 μ L DMSO were placed in a 96-well microplate according to the experimental design shown in Table 1. The PubChem SID numbers of those compounds are shown in Table 2. According to the experimental design shown in Figure 2, a THF solution of plasticizer and PVC was then dispensed into the plate, which was gently shaken for a few minutes to let the compound and the polymer dissolve in THF/DMSO mixed solvent. An evaporator was then used to evaporate THF and DMSO, leaving homogeneous polymer films with dissolved solutes formed at the bottom of the wells. Aliquots of the aqueous buffer solutions (pH 4.0, 7.0, 10.0) were then dispensed on top of the polymer films in the plate. The plate was covered and incubated in a shaker (500 rpm, 25 $^{\circ}$ C) for 4 hours. To determine the solute concentration, the supernatant from each well was transferred to another UV-transparent plate by a multichannel pipet and put in the plate reader for UV determination at 250 nm, at which sample peaks showed the best signal-to-noise ratios. If all of the solute was extracted into the 100 μ L of aqueous phase, the solute concentration in the aqueous buffer would be 100 μ M.

3. RESULTS AND DISCUSSION

3.1 Determining Partition Coefficient and pK_a of a Solute Simultaneously

2H-1, 2, 6-thiadiazine, 3-methyl-5-phenyl-, 1, 1-dioxide is a weakly acidic sulfonamide. It will be largely ionized in an environment having pH greater than its pK_a . In practice not only neutral molecules but also ion pairs may partition. The distribution of the neutral and ionized forms between the polymer film phase and the aqueous phase is determined by the distribution coefficient D_{pw} :

$$D_{pw} = \frac{[S^-]_{film} + [HS]_{film}}{[S^-] + [HS]} \quad (2)$$

where $[HS]$ and $[HS]_{film}$ are the drug concentrations in the aqueous phase and film phase, respectively; $[S^-]$ and $[S^-]_{film}$ are the concentrations of the ionized drug and its ion pair in the aqueous phase and film phase. The partition coefficient for the neutral drug is defined as:

$$P_{pw} = \frac{[HS]_{film}}{[HS]} \quad (3)$$

The conditional partition coefficient for the anionic drug in the presence of a particular set of counterions at certain concentrations is defined as:

$$P_{pw}^- = \frac{[S^-]_{film}}{[S^-]} \quad (4)$$

It is known that the equilibrium equation for acid dissociation constant K_a is

$$K_a = \frac{[S^-][H^+]}{[HS]} \quad (5)$$

Inserting Equation (3), Equation (4) and Equation (5) into Equation (2):

$$D_{pw} = \frac{P_{pw} + P_{pw}^- \cdot \frac{[S^-]}{[HS]}}{1 + \frac{[S^-]}{[HS]}} = \frac{P_{pw} + P_{pw}^- \cdot \frac{K_a}{[H^+]}}{1 + \frac{K_a}{[H^+]}} = P_{pw}^- + \frac{P_{pw} - P_{pw}^-}{1 + 10^{pH - pK_a}} \quad (6)$$

By plotting D_{pw} versus pH, the P_{pw} , P_{pw}^- and pK_a values of the solute can be obtained by applying a nonlinear least-squares curve fitting according to Equation (6).

3.2 Determination of $\log P_{pw}$ and pK_a of a solute in a 96-well format

A kinetic study was first performed to determine the time needed for the phase distribution of the solute to reach equilibrium. The results show that two hours were enough for the distribution experiments to reach equilibrium. Based on the kinetic data, all other distribution experiments were performed for four hours.

Distribution coefficients of the compound, 2H-1, 2, 6-thiadiazine, 3-methyl-5-phenyl-, 1, 1-dioxide were determined at various pH values, analyzed by both UHPLC and UV plate reader. The results obtained by UHPLC and plate reader are shown in Figure 3 and 4 respectively. Each measurement was repeated twice and the corresponding error bars indicate the standard error of the mean (SEM). The SEM values were then used in error propagations to determine the errors of the calculated distribution coefficients. It is shown that distribution coefficient of the compound decreases with increasing pH of the buffer, indicating more ionic form existing in the higher pH range, which is consistent with the fact 2H-1, 2, 6-thiadiazine, 3-methyl-5-phenyl-, 1, 1-dioxide is an acidic amide. Applying nonlinear least-squares curve fitting based on Equation (6), the P_{pw} , P_{pw}^- and pK_a values of the solute were obtained. The pK_a values of the solute are 2.94 ± 0.10 and 2.52 ± 0.17 , determined by HPLC and plate reader measurements of the equilibrium concentration of the solute in the aqueous phase respectively. The $\log P_{pw}$ values are 1.04 ± 0.02 and 1.10 ± 0.03 respectively. Both of the P_{pw}^- values are statistically zero ($p > 0.05$), indicating most of the ionized solute stays in the aqueous phase rather than the polymer film phase.

To our knowledge, there have been no reported experimental log P and pK_a values for 2H-1, 2, 6-thiadiazine, 3-methyl-5-phenyl-, 1, 1-dioxide. Compared to the calculated log P_{ow} (1.10 ± 0.75) using ACD software (Advanced Chemistry Development inc., Toronto, Canada), our results are consistent and showed better precision. The calculated pK_a value from ACD software and ADMET Predictor™ software (Simulations Plus inc., Lancaster, CA) are 5.13 and 0.25 respectively, which are quite different from each other, while our results are in the middle. 2H-1, 2, 6-thiadiazine, 3-methyl-5-phenyl-, 1, 1-dioxide is a tautomeric and ionisable compound with both acidic and basic centers. It is known that predictions are not particularly good for partition coefficients and pK_a values of zwitterionic, tautomeric and charged compounds[8]. The UHPLC method gives better sensitivity than the optical absorbance measurements[10]. Unlike the plate reader method, it does not suffer from the potential for interfering compounds biasing the result. The higher sensitivity translates into the method's capability to measure a wider dynamic range of log P_{pw} values in comparison to the optical absorbance approach [10]. On the other hand, compared to the plate reader, the UHPLC measurement generates lower throughput due to method development time. Thus both approaches have strengths. For detailed analysis of a single compound, the UHPLC method may be better, but for screening large numbers of dissimilar compounds, the optical absorbance method is preferred unless the molar absorptivities of the solutes are too low.

3.3 Optical Absorbance-based Lipophilicity Screening of a Library of Drug-like Compounds

The experimental log D results (pH 4.0, pH 7.0, and pH 10.0) of all of these compounds have been successfully obtained. As shown in Figure 5, good linearity was found for a plot of log D for each compound in separate runs with a correlation coefficient of 0.97. A slope of 1.00 ± 0.05 and an intercept of -0.04 ± 0.10 ($p > 0.05$, statistically zero) was found, showing good reproducibility of our method. The experimental log D_{pH7.0} results are located in the range of 0.68 to 3.12. According to Lipinski[17,18] drug-like molecules should have log D values less than five for reasonable absorption and permeation. These compounds have appropriate log D values to be considered as drug-like compounds. Errors in the quantitative determination of solute concentrations contributed to the limits for the applicable log D range of our method. For example, if the log D value is equal to -1 at the phase ratio equal to 16, the final concentration after the extraction would be 99.4% of the initial concentration calculated from Equation (1), meaning the error could not be higher than ±0.3%, which is not easy to achieve with optical absorbance. Therefore, the measurable log D range of our method is three units at one fixed phase ratio. Of course, it is easy to alter the phase ratio by changing the volume of the aqueous phase and the polymer phase. For example, this method successfully measured the lipophilicity of the hydrophobic drug econazole (log P = 4.83)[10]. This is a challenge for the shake-flask method.

Compared to other experimental methods, this method shows several advantages. The technique is faster, more automated, and compatible with microplates unlike the standard shake-flask method. This method also demonstrates capability of determining log D for charged compounds which is a challenge for the RPLC method.

Our experimental results and calculated log D values by MarvinView software (ChemAxon Ltd., Budapest, Hungary) and the correlation are represented in Table 3 and Figure 6 respectively. There were rather poor correlations between measured (y) and calculated (x) log D values with $y = 1.86 + 0.08 \cdot x$ ($r = 0.16$), $y = 1.64 + 0.19 \cdot x$ ($r = 0.50$), $y = 1.79 + 0.11 \cdot x$ ($r = 0.37$), for pH 4.0, 7.0, and 10.0 respectively. The average difference between the calculated and measured values is 1.04 log units, which is similar to the reported difference (1.05 log units) for 70 commercial drugs[9]. Computational approaches will always be approximate because new compounds may contain substructures that are not covered by the software. Therefore, an accurate contribution of each substructure of the new compounds

may not exist. Moreover, it is known that theoretical predictions are not reliable for distribution coefficients and pK_a values of zwitterionic, tautomeric and charged compounds[8], like most of the compounds in this library.

We then compared experimental logP values and clogP for only the neutral compounds in the library by four different software packages, ACD, Marvin, QikProp (Schrodinger, Portland, OR), and Sybyl (Tripos Inc., St. Louis, MO). As summarized in Table 4, a total average logP difference of 0.58 log units are shown for neutral compounds, smaller than that for ionisable compounds. Better correlations between measured (y) and calculated (x) logP values were shown with $y=0.91+0.52*x$ ($r=0.91$), $y=1.31+0.31*x$ ($r=0.43$), $y=0.96+0.46*x$ ($r=0.45$), $y=0.92+0.47*x$ ($r=0.82$) for ACD, QikProp, Marvin, and Sybyl respectively. We note, however, that even for neutral compounds the range of clogP values yielded by the different programs is often significant.

Our choice of buffer components was made based on the range of pH values and the compatibility with the analytical methods used. We also wanted to minimize the number of buffer components use across the total range of pH values. Ultimately, we chose phosphate and phosphate/citrate which are adequate for the entire pH range investigated except near pH 10. We determined that the poor buffer capacity of phosphate at pH 10 was not a limitation. From Table 3, the lowest clog D_{pH10} is about -2. Using Eqn.1, the aqueous concentration for this solute would be 100 μ M at equilibrium (phase ratio = 20). The phosphate buffer concentration is 20 mM. So the solute concentration is at most 0.5% of the buffer concentration. The pK_a values of phosphoric acid are 2.1, 7.2, and 12.2. At pH 10, $[HPO_4^{2-}]/[PO_4^{3-}]=158$. From the structures shown in Table 1, most of our solutes in the library are amines. If the solute has the same basic strength as NaOH, which is the worst case, 0.5% of the acidic ion will be neutralized, $pH=12.2-\log(157.2/1.8)=10.26$. The small change of pH will not influence the measured distribution coefficient unless the pK_a of the solute is around 10. In that case, only about half of the solute can neutralize the acidic ion in the buffer (0.25%), $pH=12.2-\log(157.6/1.4)=10.15$. In conclusion, despite the phosphate buffer's low strength at pH 10.0 distribution coefficients will be measured accurately in our experiment because of the solute and buffer concentrations used.

4. CONCLUSIONS

We have successfully developed a phase-distribution method to measure simultaneously pK_a and lipophilicity of drug-like compounds using well-plate technologies. This method has been applied successfully to measure pK_a and log P_{pw} values of a drug-like compound, 2H-1, 2, 6-thiadiazine, 3-methyl-5-phenyl-, 1, 1-dioxide. Moreover, the distribution coefficients of a library of novel drug-like compounds were determined by this approach. This method is fast, requires only a small amount of material, has great flexibility, and has the potential to be fully automated; thus showing great potential in the pharmaceutical and environmental fields.

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***Highlights (for review)**

Determined log P (or log D) by 96-well plate technology.

The method uses UHPLC or optical concentration measurements

Investigated 25 novel organic compounds.

Compared log P or log D to commercial software.

None of four programs is very accurate, but all are better for neutral than for ions

Figure 1.
Chemical structure of 2H-1, 2, 6-thiadiazine, 3-methyl-5-phenyl-, 1, 1-dioxide.

Add polymer/plasticizer in THF

Evaporate organic solvents

Add aqueous buffer solution

Equilibrate (const. T)

Transfer the aqueous phase
Measure solute concentration
by HPLC/plate reader

Figure 2. Schematic of the preparation and use of polymer films in 96-well plates for Log D_{pw} determination.

Figure 3. Distribution coefficients of 2H-1, 2, 6-thiadiazine, 3-methyl-5-phenyl-, 1, 1-dioxide at various pH values analyzed by UHPLC.

Figure 4. Distribution coefficients of 2H-1, 2, 6-thiadiazine, 3-methyl-5-phenyl-, 1, 1-dioxide at various pH values determined by plate reader.

Figure 5.
Correlation of distribution coefficients between different runs.

Figure 6.
Correlation of distribution coefficients between our experimental values and calculated values.

Table 1

Experimental Design of 24 compounds in a 96-well microplate

	Wells 1-4	Wells 5-8	Wells 9-12
A
B
C
D
E
F
G
H

Table 2

PubChem SID of 24 compounds in a 96-well microplate

	Wells 1–4	Wells 5–8	Wells 9–12
A	26696971	26681202	17390303
B	26696976	26683722	26696997
C	26696951	26683740	26681305
D	26696995	8142836	26681407
E	26696950	8142904	26681268
F	87341695	26696959	26681269
G	26696948	8143072	26681280
H	26697001	8143105	8143071

Table 3
Experimental and calculated log D results for 24 compounds at pH 4.0, 7.0, 10.0

Wells	pH 4.0		pH 7.0		pH 10.0	
	Measured	Calculated	Measured	Calculated	Measured	Calculated
A 1-4	1.87	1.82	1.62	0.28	1.80	-0.55
B 1-4	3.04	3.34	2.79	3.34	2.75	1.10
C 1-4	2.47	3.38	0.93	0.87	0.99	-0.21
D 1-4	2.21	2.39	2.22	2.39	2.21	2.39
E 1-4	1.40	1.55	1.78	-0.16	1.88	-1.47
F 1-4	2.00	2.56	2.01	2.72	1.96	2.72
G 1-4	2.54	2.91	2.57	2.91	2.58	2.91
H 1-4	2.40	2.55	2.12	2.55	2.26	2.55
A 5-8	2.22	3.00	2.16	3.00	1.90	3.00
B 5-8	1.60	2.89	1.94	2.89	1.75	2.89
C 5-8	2.45	2.78	2.22	2.80	2.08	2.80
D 5-8	1.38	1.78	1.37	1.83	1.40	1.83
E 5-8	2.18	-0.84	2.14	1.82	2.20	2.09
F 5-8	1.75	2.03	1.94	2.41	1.89	2.41
G 5-8	1.69	2.72	1.19	0.01	1.16	-0.41
H 5-8	1.94	1.33	1.92	-1.40	1.76	-1.91
A 9-12	3.18	2.41	3.12	2.41	3.02	2.41
B 9-12	1.76	1.29	2.01	0.75	2.01	-1.98
C 9-12	1.99	1.16	2.02	1.22	1.89	1.22
D 9-12	2.06	2.97	2.10	2.97	2.01	2.97
E 9-12	2.00	-1.15	2.05	-1.15	2.09	-1.15
F 9-12	2.14	0.62	2.09	0.62	2.08	0.62
G 9-12	1.59	1.59	1.45	1.59	1.49	1.59
H 9-12	0.56	2.72	0.68	0.01	0.77	-0.41

Table 4

Experimental and calculated log P results for 10 neutral compounds in the library.

Wells	Experimental logP	ACD	QikProp	Marvin	Sybyl	RSD% of calculated logP	Average Difference
D 1-4	2.21	2.74	3.25	2.39	2.76	13%	0.57
G 1-4	2.56	3.20	3.59	2.91	3.25	9%	0.67
H 1-4	2.26	2.53	3.03	2.55	2.83	9%	0.47
A 5-8	2.09	2.35	2.72	3.00	2.11	15%	0.45
B 5-8	1.76	2.24	2.75	2.89	2.83	11%	0.91
C 5-8	2.25	1.99	2.77	2.80	3.20	19%	0.57
D 5-8	1.38	1.58	2.33	1.81	1.92	16%	0.53
A 9-12	3.11	3.96	2.26	2.41	3.84	29%	0.78
D 9-12	2.06	2.05	2.20	2.97	1.97	20%	0.29
G 9-12	1.51	0.73	1.09	1.59	0.77	38%	0.51