Computation of Brain−Blood Partitioning of Organic Solutes via Free Energy Calculations

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The ratio of brain−blood partitioning, $\log(C_{brain}/C_{blood})$ (log BB), of a series of compounds that range from simple solutes to histamine H_2 antagonists was correlated with computed solvation free energy in water ($\Delta G°_W$). The free energies were computed with the AMSOL 5.0 program using the AM1-SM2.1 solvation model. From a set of 55 compounds, a function was developed in which log BB was related to the free energy of solvation as follows: log BB = $0.054\Delta G°_W$ + 0.43 (r = 0.82 and standard error = 0.41). This correlation provided successful prediction of brain−blood partitioning for compounds outside the training dataset. Furthermore, for a set of 10 drugs, $\Delta G°_W$ correlated well with literature data for the permeability of endothelial cell monolayers from bovine brain microvessels. In neuroscience drug discovery, the use of computed solvation free energies to predict brain penetration provides a facile method for prioritizing synthetic targets.

Introduction

Optimization of the distribution of therapeutic compounds between brain and blood is an important component in the design of CNS-active drugs.[1,2] The experimental determination of the brain−blood partition ratio is difficult and time-consuming, since it involves the direct measurement of the drug concentration in the brain and blood of laboratory animals, and obviously requires the synthesis of the compounds, often in radiolabeled form.[3−5]

It is desirable to predict the brain−blood distribution ratio of complex molecules from physicochemical parameters or, ideally, from their molecular structures. An estimation method capable of discriminating 5−10-fold differences in brain penetration among compounds would be of utility in prioritizing synthetic targets. Although *in vitro* techniques for the prediction of brain penetration are available,[4] they are experimentally cumbersome; while the determination of physicochemical parameters or partition coefficients is certainly easier than *in vivo* measurements, it still requires the synthesis of the compounds of interest. Additionally, measurement of a partition coefficient may be problematic due to compound instability, assay sensitivity, the presence of confounding impurities, and the wide variation in the lipophilicity of the compounds to be tested. A variety of approaches have been examined which generally rely on fewer experimentally determined parameters, or none at all. Several of the more successful approaches are summarized below.

In their work on a series of 20 structurally diverse histamine H_2 antagonists (Chart 1), Young *et al.*[5] determined a correlation between $\log(C_{brain}/C_{blood})$ and $\Delta\log P$ (octanol−cyclohexane)[6] (r = 0.83; s = 0.44). A significant correlation was also observed using only log $P_{cyclohexane}$, though not with log P_{oct}.

van de Waterbeemd and Kansy[7] examined the same series of 20 compounds and found a significant correlation (r = 0.934; s = 0.290) between log BB and the experimentally determined log $P_{cyclohexane}$ when a calculated volume descriptor was included in the parameterization. They concluded that only one experimental log P value (cyclohexane/water) was necessary to predict the brain uptake of the compounds examined. More importantly, van de Waterbeemd and Kansy demonstrated a significant correlation between log BB and the computed hydrophilic fraction of the van der Waals surface area (r = 0.835), thus eliminating the need to include any experimentally determined partition coefficients.

Abraham *et al.*[8−10] related log BB to the excess molar refraction, solute polarizability, hydrogen bond acidity and basicity, and molecular volume (r = 0.952; s = 0.197). In order to derive a correlation for a more diverse group of compounds than previously reported, Abraham considered data for a set of 65 compounds. For some of these compounds, *in vitro* values were derived from the differences between air−blood and air−brain partition coefficients. In the case of hexane, the difference between the *in vivo* and *in vitro* values was found to be 0.4 log unit (2.5-fold).[8] Due to the experimental difficulties involved in either type of measurement, and the volatility of some of the compounds considered, the agreement is reasonable. Using this expanded set of 57 molecules (8 of the original 65 compounds were excluded as outliers), Abraham obtained an equation that was shown to be useful for the prediction of the brain−blood partitioning of complex molecules using only empirically determined fragment descriptors. While Abraham's descriptors are available for many fragments, care must be exercised when breaking down complex molecules into smaller fragments; the additivity of the descriptors may be difficult to judge, as some fragment values may be inappropriate in differing stereochemical and conformational environments.[11]

The difficulties associated with the experimental determination of partition coefficients and measurements of brain−blood distributions prompted us to explore alternative ways to predict the ratio of brain−blood distribution for complex molecules, ideally from

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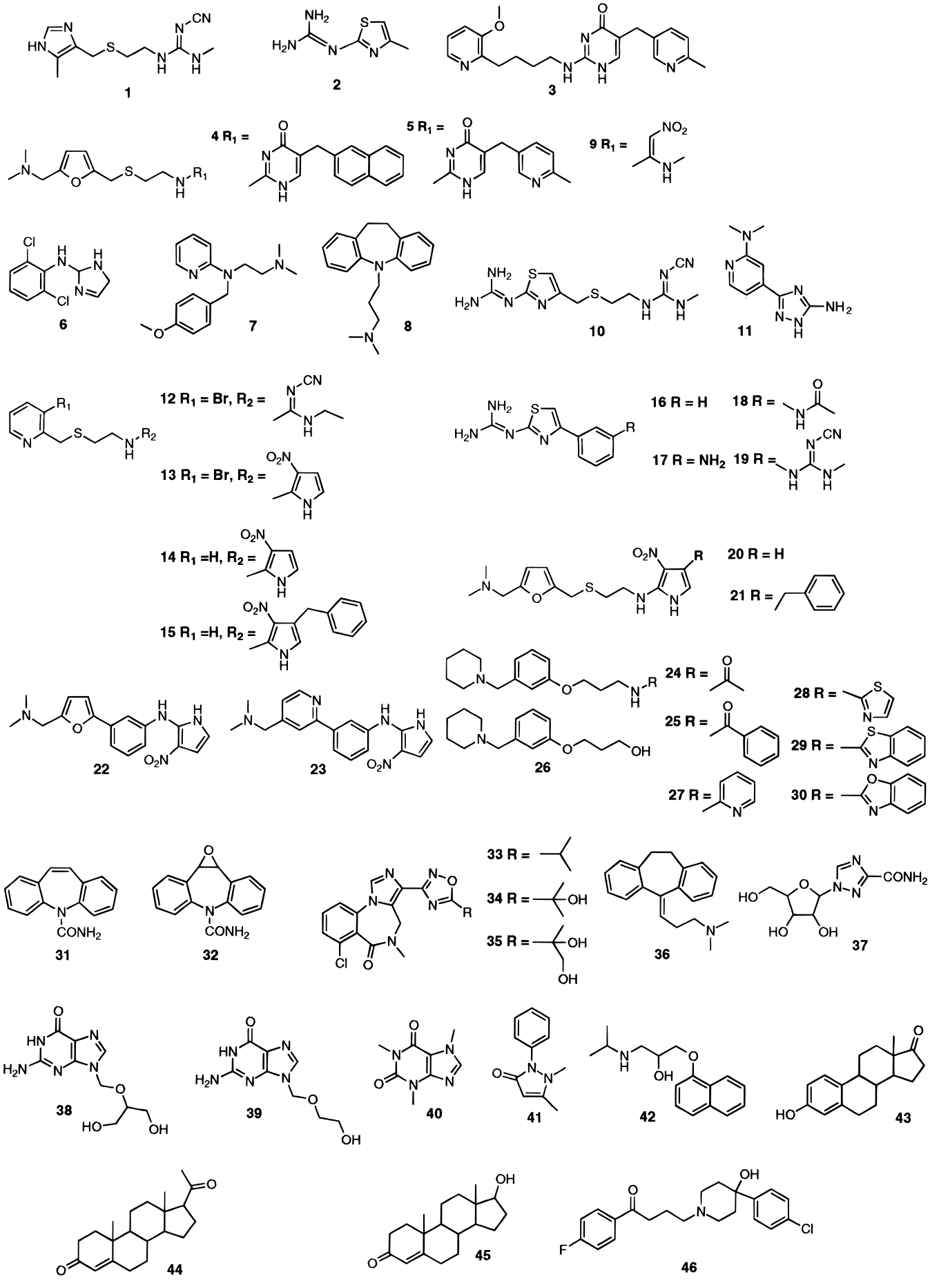
Chart 1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their molecular structures. Alkane−water partition coefficients work reasonably well or in conjunction with octanol−water partition coefficients, and they avoid the use of additive fragments or large numbers of calculated descriptors. Thus, our efforts focused on theoretical methods that would yield these fundamental quantities. By relying on a more theoretical approach, we hope to be able to treat any arbitrary compound and gain an understanding of the molecular basis for the factors affecting brain permeability. Fortunately, Richards,[12] Jorgensen,[13] and Reynolds[14] have shown that free energy simulations and continuum solvation models[15] are capable of yielding a reasonable estimate of log *P*.

The partition coefficient of a solute in two immiscible phases is related to the solvation free energies of the solute in the two phases.[16,17] Since solvation free energy models for water[18] and for a variety of alkanes[17] have become available, we set out to explore their application to the estimation of brain−blood partitioning of various solutes. log *P* data encompasses both polarity and volume terms,[7,19,20] and a solvation model that incorporates these same factors should be suitable for correlating experimental brain−blood partition data with a calculated log *P*, expressed in terms of solvation free energies.

Computational Methods

The calculation of solvation free energies for a series of solutes (Chart 1) were performed using the AMSOL 5.0 program[21] on a Silicon Graphics Iris. Since many of the molecules used in this study are quite flexible, the initial conformations of the solutes were generated by carrying out a Monte Carlo conformational search with MacroModel v5.5 employing the MM2 force field with the GB/SA continuum solvation model.[22] In each Monte Carlo search, 2000 possible conformers were generated. Full geometry optimizations were then carried out with AMSOL on the 25 lowest energy conformations for each compound using the AM1 Hamiltonian and no symmetry constraints. All compounds were optimized in the un-ionized state in the gas phase. The solvation free energies in water and *n*-hexadecane[23] were computed with the AM1-SM2.1[18] and AM1-SM4[17] solvation models, respectively. The wave functions were recomputed in the presence of each solvent using the previously determined gas-phase geometries. Full relaxation of the geometry in the presence of the solvent is expected to have only a minor influence on the geometry and energetics at considerable computational cost. The solvation free energies were then recorded for the conformer with the lowest combined heat of formation and solvation free energy (Table 1).

Results and Discussion

Brain−Blood Partitioning. Table 1 presents computed free energies of solvation in water ($\Delta G°_W$) and hexadecane ($\Delta G°_{HD}$) for the 57 compounds used in this study. This set consists of the compounds reported by Young *et al.*[5] (**1**−**30** in Chart 1) and the solutes reported by Abraham.[8] It should be mentioned that it is difficult to determine accurate C_{brain}/C_{blood} ratios even for nonvolatile, metabolically stable compounds. It is not uncommon to encounter data with standard deviations almost as large as the mean value, even with a reasonable number of replicate experiments. For example, Lin *et al.*[24] report C_{brain}/C_{blood} for L-663,581 of 0.50 ± 0.30, which represents a 4-fold variation (one standard deviation).

Two outliers (**3**, **12**) were removed from the 57 compound set in Table 1 to form a training set of 55 compounds. These two outliers were also among the eight compounds removed by Abraham *et al.*[8] to arrive at their relationship. As shown in Table 1, these two compounds gave predicted log BB values that differed from the measured values by greater than 1.3 log units. Inspection of structures **3** and **12** does not reveal any peculiarity that would result in an erroneous calculation of solvation free energy. As with all compounds in Table 1, the possibility exists that the measured log BB is influenced by metabolic factors and other experimental difficulties such as extraction from complex biological matrices.

The relationship between log BB and the computed solvation free energy is given by eq 1 and illustrated in Figure 1

$$\log BB = 0.054(0.005)\Delta G°_W + 0.43(0.07) \quad (1)$$

$$n = 55, \quad r = 0.82, \quad s = 0.41, \quad F = 108.3$$

where *n* is the number of compounds in the dataset, *r* is the correlation coefficient, *s* is the standard error, and *F* is the Fisher test for significance. The standard errors of the regression coefficients are given in parentheses. In determining eq 1, a variety of additional parameters were considered during the multivariate analysis, such as molecular weight, molecular volume, or surface area of each compound. For the experimental data considered, these additional terms were not statistically significant and were subsequently dropped from further consideration. This is not surprising since the computed $\Delta G°_W$ encompasses terms for the creation of a molecular-shaped cavity, solvent-accessible surface area, and polarization effects, which are discussed in detail elsewhere.[17] Additionally, $\Delta G°_W$ should reflect many of the properties contained within the parameters Abraham used, such as dipolarity/polarizability, hydrogen bond acidity and basicity, and a molecular volume descriptor. Our initial efforts also considered inclusion of $\Delta G°_{HD}$ in the correlation. It was hoped that this term might be more representative of the environment that a compound would encounter while crossing various membranes. However, inclusion of this term did not lead to a significant improvement in the correlation over $\Delta G°_W$ alone. Since the sign of the coefficient for the free energy of solvation in water is positive, eq 1 offers a physically reasonable model for brain−blood partitioning. A polar compound, well solvated in water, would have a relatively large negative value for $\Delta G°_W$, consistent with low partitioning into the brain. Conversely, a relatively nonpolar compound would yield a more positive value for $\Delta G°_W$, which is consistent with higher brain partitioning. This is in agreement with the positive sign for the coefficient of log $P_{cyclohexane}$ in the Young *et al.* equation,[5] the negative coefficients for the hydrogen bond donor and acceptor and dipolarity/polarizability term in Abraham's equation,[8,9] and the generally accepted notion that lipophilic compounds partition well into the brain,[1,2] suggesting that solute hydrogen-bonding ability has a large negative effect on brain partitioning.

The predictive ability of eq 1 was assessed for a series of six compounds outside the training set (Table 2). The computed C_{brain}/C_{blood} for these compounds agrees well with the values reported by van Belle *et al.*[25] for carbamazepine (**31**) and carbamazepine 10,11-epoxide

Table 1. Computed $\Delta G°_W$ and $\Delta G°_{HD}$ and log BB Obtained from Eq 1[a]

compound	$\Delta G°_W$	$\Delta G°_{HD}$	log BB[b]	computed log BB	difference
1	−22.48	−15.43	−1.42	−0.78	−0.64
2	−23.16	−11.79	−0.04	−0.82	0.78
3	−20.66	−24.65	−2.00	−0.68	−1.32
4	−20.30	−26.19	−1.30	−0.66	−0.64
5	−22.87	−24.47	−1.06	−0.80	−0.26
6	−10.02	−11.57	0.11	−0.11	0.22
7	−8.30	−14.37	0.49	−0.02	0.51
8	−3.45	−13.37	0.83	0.24	0.59
9	−17.15	−12.27	−1.23	−0.49	−0.74
10	−36.72	−19.38	−0.82	−1.55	0.73
11	−22.37	−14.08	−1.17	−0.78	−0.39
12	−17.39	−16.16	−2.15	−0.51	−1.64
13	−18.39	−12.26	−0.67	−0.56	−0.11
14	−17.41	−10.99	−0.66	−0.51	−0.15
15	−12.98	−15.57	−0.12	−0.27	0.15
16	−25.31	−15.42	−0.18	−0.93	0.75
17	−29.56	−16.19	−1.15	−1.16	0.01
18	−31.41	−18.65	−1.57	−1.26	−0.31
19	−36.05	−21.33	−1.54	−1.51	−0.03
20	−17.98	−13.24	−1.12	−0.54	−0.58
21	−16.01	−16.37	−0.73	−0.43	−0.30
22	−14.36	−14.99	−0.27	−0.34	0.07
23	−14.22	−14.79	−0.28	−0.34	0.06
24	−9.39	−12.84	−0.46	−0.08	−0.38
25	−9.24	−15.89	−0.24	−0.07	−0.17
26	−7.31	−12.46	−0.02	0.03	−0.05
27	−7.91	−16.66	0.69	0.00	0.69
28	−15.01	−14.10	0.44	−0.38	0.82
29	−14.51	−19.33	0.14	−0.35	0.49
30	−10.38	−16.70	0.22	−0.13	0.35
31	−10.46	−12.80	0.00	−0.14	0.14
32	−13.15	−13.56	−0.34	−0.28	−0.06
33	−16.46	−16.32	−0.30	−0.46	0.16
34	−19.88	−17.28	−1.34	−0.64	−0.70
35	−23.05	−18.04	−1.82	−0.81	−1.01
36[c]	−2.96	−13.32		0.27	
butanone	−3.16	−3.37	−0.08	0.26	−0.34
benzene	−0.69	−4.45	0.37	0.39	−0.02
3-methylpentane	2.01	−3.25	1.01	0.54	0.47
3-methylhexane	2.28	−3.95	0.90	0.55	0.35
2-propanol	−4.13	−2.33	−0.15	0.21	−0.36
2-methylpropanol	−4.10	−2.82	−0.17	0.21	−0.38
2-methylpentane	2.03	−3.34	0.97	0.54	0.43
2,2-dimethylbutane	1.95	−3.14	1.04	0.53	0.51
1,1,1-trifluro-2-chloroethane	0.68	−1.37	0.08	0.46	−0.38
1,1,1-trichloroethane	−0.95	−4.05	0.40	0.38	0.02
diethyl ether	−0.33	−3.30	0.00	0.41	−0.41
enflurane	0.74	−2.34	0.24	0.47	−0.23
ethanol	−5.00	−1.74	−0.16	0.16	−0.32
fluroxene	−0.09	−3.22	0.13	0.42	−0.29
halothane	0.48	−2.64	0.35	0.45	−0.10
heptane	2.34	−4.16	0.81	0.55	0.26
hexane	2.08	−3.45	0.80	0.54	0.26
isoflurane	0.60	−2.19	0.42	0.46	−0.04
methane	0.93	0.13	0.04	0.48	−0.44
methylcyclopentane	1.68	−2.86	0.93	0.52	0.41
nitrogen	−4.82	3.15	0.03	0.17	−0.14
pentane	1.83	−2.74	0.76	0.53	0.23
propanol	−4.69	−2.41	−0.16	0.18	−0.34
propanone	−4.03	−2.75	−0.15	0.21	−0.36
teflurane	1.33	−1.40	0.27	0.50	−0.23
toluene	−0.45	−5.03	0.37	0.40	−0.03
trichloroethene	−0.91	−3.99	0.34	0.38	−0.04

[a] All free energies are in kcal/mol. [b] Experimental values taken from refs 8 and 24−27. [c] See Table 2 for range of experimental values.

(**32**). Lin *et al.*[24] reported C_{brain}/C_{blood} for the benzodiazepine receptor agonist L-663,581 (**33**) and its monohydroxylated and bishydroxylated metabolites L-663,581M1 (**34**) and L-663,581M2 (**35**), respectively. As reported in Table 2, eq 1 approximates the experimental values of C_{brain}/C_{blood} reasonably well. While the computed C_{brain}/C_{blood} only approximates the measured C_{brain}/C_{blood} for the two metabolites, the computed and measured values are within 1 log unit of each other. Furthermore, the computed rank order for compounds **33**, **34**, and **35** is correct. Table 2 also illustrates that eq 1 predicts correctly C_{brain}/C_{blood} for amitriptyline (**36**).[26]

Barrier Permeability. Effective delivery of a drug to the brain is a function of both the brain−blood barrier permeability and the relative affinity of the drug for the brain and blood compartments. This relative affinity is reflected in log BB and has been shown above to be

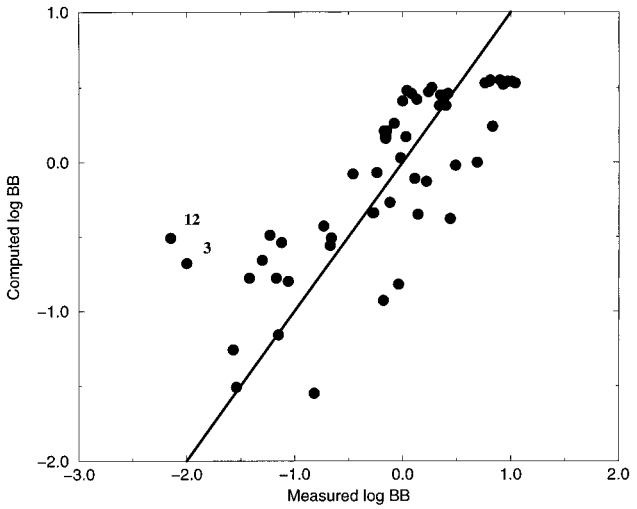

Figure 1. Relationship between experimental log BB values and those computed with eq 1. The two outliers (**3** and **12**) removed from the study are also shown for comparison.

Table 2. Reported Values of C_{brain}/C_{blood} and Predicted C_{brain}/C_{blood} Computed from Eq 1

compound	computed C_{brain}/C_{blood}	reported C_{brain}/C_{blood}	ref
carbamazepine (**31**)	0.73	1.0(0.2)	25
carbamazepine epoxide (**32**)	0.53	0.46(0.08)	25
L-663,581(**33**)	0.35	0.50(0.30)	24
L-663,581M1(**34**)	0.23	0.046(0.02)	24
L-663,581M2(**35**)	0.15	0.015(0.001)	24
Amitriptyline (**36**)	1.9	5.8−9.6	26

[a] Numbers in parentheses correspond to reported standard errors.

Table 3. Computed $\Delta G°_W$ and $\Delta G°_{HD}$ and Permeability Coefficients from Eq 2[a]

compound	$\Delta G°_W$	$\Delta G°_{HD}$	computed permeability coefficient	measured permeability coefficient[b]
ribavirin (**37**)	−28.28	−12.38	6.18	4.10
ganciclovir (**38**)	−30.30	−15.67	−0.55	4.88
acyclovir (**39**)	−28.72	−14.52	4.71	6.21
caffeine (**40**)	−15.27	−9.31	49.5	40.3
antipyrine (**41**)	−7.99	−10.33	73.74	43.6
propranolol (**42**)	−7.52	−13.15	75.31	68.7
estrone (**43**)	−7.61	−11.26	75.01	81.2
progesterone (**44**)	−4.88	−11.32	84.10	88.5
testosterone (**45**)	−6.18	−10.0	79.77	89.2
haloperidol (**46**)	−7.31	−16.06	76.01	97.0

[a] All free energies are in kcal/mol. [b] Permeability coefficient × 10^4 cm/s (ref 27).

predictable via the free energy of solvation in water. Shah *et al.*[27] studied the permeabilities of a series of compounds by using monolayers of endothelial cells from bovine brain microvessels as a model of the brain−blood barrier. These authors demonstrated that the monolayer permeability was correlated with the log of the octanol/water partition coefficient divided by the square root of the molecular weight [log (P_{oct}/(MW)$^{1/2}$)].

Table 3 presents computed $\Delta G°_W$ and $\Delta G°_{HD}$ values for 10 drugs studied by Shah *et al.*[27] As described in the preceding section, we found $\Delta G°_W$ to be the only significant parameter in the correlation

$$PC = 3.33(0.46)\Delta G°_W + 100.4(8.0) \qquad (2)$$

$$n = 10, \quad r = 0.93, \quad s = 14.4, \quad F = 53.1$$

The computed permeability coefficient (PC) from eq 2 is also reported. Figure 2 illustrates the correlation between the computed $\Delta G°_W$ and the endothelial cell permeability coefficient of Shah *et al.*[27] An excellent correlation is obtained, with $r = 0.93$. As above, we considered inclusion of other factors, none of which improved the correlation significantly.

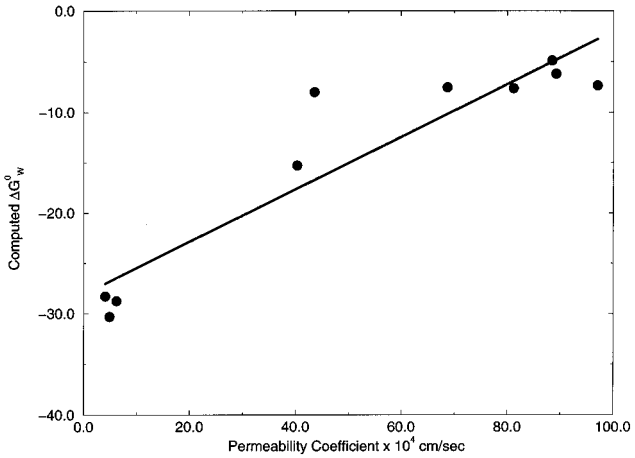

Figure 2. Relationship between the computed $\Delta G°_W$ and the permeability coefficient determined in endothelial cell monolayers.[27]

It is well-known that solute permeability through lipid bilayers decreases with increasing solute molecular weight. While $\Delta G°_W$ does include a cavitation term, this factor would not be expected to reflect the displacement of phospholipid head groups and acyl chains required for a solute to cross an endothelial cell membrane. Thus, for now the correlations of solvation free energy with log BB and with the permeability coefficient from cell monolayers should be limited to the molecular weight ranges of the training sets, 16−413 ($n = 55$) and 188−376 ($n = 10$), respectively.

Conclusion

Brain−blood barrier permeability and solute brain−blood partitioning are both generally believed to be favored by increased solute lipophilicity and decreased hydrogen bond potential.[4] The present work has demonstrated that the computed free energy of solvation in water correlates well with both brain partitioning and permeability. *In vivo*, the brain−blood barrier is structurally complex and poorly understood. It is likely that cell membrane bilayers are involved in this barrier, and it would be naive to assume that solvation in hexadecane mechanistically models this nonisotropic structured barrier.

The power of the present work is in its practical application in the discovery of therapeutic agents that penetrate the brain. In spite of tremendous advances in the understanding of neuropharmacology, and the ability to design and synthesize highly specific receptor antagonists and agonists, discovery of orally active centrally acting agents remains largely a trial and error process. This situation exists because of the complexity of developing predictive structure−activity relationships for dissolution, absorption, first-pass metabolism, brain partitioning, brain metabolism, and pharmacological activity and combining these predictive relationships to design an effective therapeutic agent. The solvation free energy approach described herein can serve as a powerful tool for rank-ordering compounds prior to synthesis.

It is hoped that this will result in a more direct path to discovery of therapeutic agents.

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