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# Brain/blood distribution described by a combination of partition coefficient and molecular mass

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**Abstract**

Limited performance of the octanol-water partition coefficient has been known in predicting the brain/blood equilibrium distribution ratio. There have been reports that predictive ability of the in vitro partition parameters increases after the introduction to regression of a correction term reflecting bulkiness of the compounds. Here a rationalization for such observations has been proposed by considering the brain/blood and the octanol-water distribution as composed of a part determined by polarity of a compound and another part determined by its nonspecific, dispersive properties. The model proposed was shown theoretically to apply to the four available representative sets of brain/blood distribution data. Instead of a search for an in vitro partition system precisely mimicking the brain/blood distribution equilibrium a model is recommended by a combination of standard partition parameters with a molecular bulkiness descriptor. Copyright © 1996 Elsevier Science B.V.

*Keywords:* Brain/blood distribution; Bulkiness parameters; Log P; Partition coefficients; Polarity parameters; Quantitative structure-activity relationships (QSAR)

## 1. Introduction

Convenient and reliable methods of prediction of the equilibrium distribution of xenobiotics between blood and brain are highly desired. As yet the attempts to correlate cerebrovascular permeability to the octanol-water partition coefficient ($P$) cannot be called fully successful. Correlation of that kind was graphically presented by Rapoport et al. (1979). The observed marked deviations from the linear regression line have been explained by the authors as effects of size, steric and electronic parameters, and possibly of specific interaction with cell membranes. Better linear correlations (correlation coefficient $r$ ranging from 0.85 to 0.91) were reported by Levin (1980) and by Cornford et al. (1982). Those authors assumed

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that permeability is a function of the diffusion coefficient and that variability in diffusion coefficients of small molecules approximates to the square root of the molecular mass ($M_m$). Thus, Levin (1980) correlated a logarithm of rat brain capillary permeability to a term $\log[P(M_m)^{-1/2}]$ and Cornford et al. (1982) correlated the product of the logarithm of the rat brain uptake index times the square root of $M_m$ to $\log P$.

The observations that $\log P$ alone is unable to account for differences in drugs brain/blood concentration ratios were proved in a careful study by Young et al. (1988). For 20 $H_2$ histamine receptor antagonists the respective correlation was only $r = 0.436$. There was a better correlation ($r = 0.732$) with the logarithm of cyclohexane-water partition coefficient ($\log P_{cyh}$). The correlation further improved (to $r = 0.831$) after applying the $\Delta(\log P_s)$ parameter of Seiler (1974) as a regressor. The $\Delta(\log P_s)$ is defined as the difference between $\log P$ and $\log P_{cyh}$ and is to represent a measure of the hydrogen-bonding ability of a compound. Consequently, Young et al. (1988) suggested that brain penetration might be improved by reducing the overall hydrogen-bonding ability of a drug. A similar conclusion was reached by Abraham et al. (1994) who analyzed brain/blood concentration ratios of xenobiotics in terms of their linear solvation energy relationship (LSER)-derived parameters.

Reanalyzing the data of Young et al. (1988); van de Waterbeemd and Kansy (1992) obtained a surprisingly good two-parameter regression equation ($r = 0.934$) describing the brain uptake in terms of the calculated molar volume of the molecule ($V_M$) and a descriptor derived from the measurements of an alkane-water partition coefficient. As noticed by Abraham et al. (1994) the actual form of the relationship found by van de Waterbeemd and Kansy (1992) is:

$$\log(C_{brain}/C_{blood}) = 1.359 + 0.338 \log P_{cyh} - 0.00618\, V_M \quad (1)$$

where $V_M$ is in cubic centimeters.

In view of the observations of Levin (1980), Cornford et al. (1982) and van de Waterbeemd and Kansy (1992) a question arose whether the analyte bulkiness correction term in equations relating brain/blood ratio to the in vitro partition coefficient was a fortuitous artifact or its presence could be rationalized.

## 2. Theoretical

Eq. (1) may be interpreted that for the compounds considered the equilibrium distribution in one system (brain/blood) increases with their equilibrium distribution in another system (cyclohexane/water) and that that increase is opposed by a molecular bulkiness parameter ($V_M$). The same conclusion can be drawn for the relationships reported by Levin (1980) and by Cornford et al. (1982) in which the molecular mass served as a bulkiness descriptor. This observation reminded us of the rationalization previously derived (Kaliszan, 1981, 1987) for several highly significant relationships between gas chromatographic retention indices ($I$) determined on the two stationary phases of different polarities. The reported relationships were of the following form:

$$I\,(\text{polar phase}) = \alpha \times I\,(\text{nonpolar phase}) - \beta \times \text{bulkiness descriptor} + \gamma \quad (2)$$

where $\alpha$, $\beta$ and $\gamma$ were the regression coefficients. As the bulkiness descriptors the molar refractivity (Radecki et al., 1979; Grzybowski et al., 1980; Kaliszan, 1981, 1987; Kaliszan and Höltje, 1982), molecular mass, van der Waals volume (Bermejo and Guillen, 1985; Bermejo et al., 1985) and molecular length (Halkiewicz et al., 1985) were used.

To arrive at Eq. (2) the following argument was proposed (Kaliszan, 1981, 1987). It has generally been assumed that solute distribution between two phases is, to a first approximation, a net effect of two basic kinds of intermolecular interactions between the solute molecule and the molecules forming the phases. One kind of interactions are nonspecific, bulkiness-related, dispersive interactions, and the second kind are more or less intuitively understood structurally specific polar interactions. Regarding the octanol-water par-

tition coefficient that view was first expressed by Dunn and Wold (1978) and than by several other authors. Dunn and Wold (1978) postulated that partitioning in general depends on two main factors, one being a molecular volume effect and the other possibly due to solute/solvent dipolar interactions. Thus, assuming the linear free energy relationships, one can describe the logarithm of the brain/blood distribution ratio, $\log B$, as well as the logarithm of the octanol-water partition coefficient, $\log P$, in terms of polarity, POL, and dispersive, DIS, parameters of compounds:

$$\log B = a_B\text{POL} + b_B\text{DIS} + c_B \quad (3)$$

$$\log P = a_P\text{POL} + b_P\text{DIS} + c_P \quad (4)$$

where $a_B$, $b_B$, $c_B$, $a_P$, $b_P$ and $c_P$ are constants depending of the properties of the individual phase separation systems. The coefficients $a_B$ and $a_P$ can be treated as the net measures of the polarities of the brain/blood and octanol-water phase systems, respectively. Correspondingly, $b_B$ and $b_P$ should reflect net dispersive properties of the two separation systems considered. Whereas DIS can be approximated by a bulkiness descriptor of solutes, the POL is certainly a more complex, multidimensional quantity. The same reasoning concerns the $b_B$ and $b_P$ coefficients in Eqs. (3) and (4), on one hand, which can be related to the size of the molecules forming the phase systems considered, and $a_B$ and $a_P$ coefficients, on the other hand, which are to characterize polarities of the two distribution systems.

From Eq. (4) one obtains:

$$\text{POL} = (\log P - b_P\text{DIS} - c_P)/a_P \quad (5)$$

Now, Eq. (3) can be rewritten as:

$$\log B = a_B(\log P - b_P\text{DIS} - c_P)/a_P + b_B\text{DIS} + c_B \quad (6)$$

Rearranging one obtains:

$$\log B = (a_B/a_P)\log P - [(a_B/a_P)b_P - b_B]\text{DIS} + \text{const} \quad (7)$$

or

$$\log B = k_1 \log P - k_2\text{DIS} + k_3 \quad (8)$$

where $k_1 - k_3$ are new constants produced by the constants of Eq. (7).

## 3. Results and discussion

Rat brain capillary permeability, $P_c$, logarithm of octanol-water partition coefficient, $\log P$, and molecular mass, $M_m$, of drugs considered by Levin (1980) are given in Table 1. Levin (1980) derived the following equation for 22 out of a total of 27 of his drugs:

$$\log P_c = -4.605 + 0.4115 \log[P(M_m)^{-1/2}] \quad (9)$$

Eq. (9) was characterized by the correlation coefficient $r = 0.91$ and a standard error of estimate $s = 0.431$. The outliers excluded from the

Table 1
Rat brain capillary permeability ($P_c$), logarithm of octanol-water partition coefficient ($\log P$) and molecular mass ($M_m$) of a series of drugs according to Levin (1980)

| Compound | $P_c \times 10^{-6}$ cm s$^{-1}$ | $\log P$ | $M_m$ |
|---|---|---|---|
| $^3H_2O$ | 200 | −1.15 | 18 |
| $^{24}$NaCl | 0.4 | −2.95 | 58 |
| [$^{14}$C]urea | 0.82 | −2.80 | 60 |
| [$^3$H]glycerol | 12 | −1.75 | 92 |
| [$^{14}$C]creatinine | 0.28 | −1.77 | 113 |
| 5-fluoro[$^{14}$C]uracil | 1.7 | −0.95 | 130 |
| [$^{14}$C]dianhydrogalacitol | 2.5 | −1.29 | 150 |
| [$^{14}$C]metronidazole | 14 | −0.16 | 171 |
| [$^{14}$C]ascorbate | 1.3 | −4.04 | 176 |
| [$^3$H]galacitol | 0.39 | −3.10 | 182 |
| [$^{14}$C]misonidazole | 10 | −0.37 | 185 |
| [$^{14}$C]ftorafur | 6.4 | −0.48 | 200 |
| [$^{14}$C]BCNU | 154 | 1.54 | 214 |
| [$^{14}$C]procarbazine | 19 | 0.06 | 221 |
| [$^{14}$C]CCNU | 100 | 2.83 | 234 |
| [$^{14}$C]pyrimethamine | 120 | 2.69 | 249 |
| [$^{14}$C]PCNU | 11 | 0.37 | 263 |
| DDMP | 150 | 2.82 | 269 |
| [$^{14}$C]DDEP | 110 | 3.19 | 284 |
| [$^{14}$C]dibromodulcitol | 1.9 | −0.29 | 308 |
| [$^{14}$C]spirohydantoin mustard | 29 | 2.47 | 315 |
| [$^{14}$C]sucrose | 0.12 | −3.67 | 342 |
| Baker's [$^{14}$C]antifol | 0.18 | −2.46 | 398 |
| [$^{14}$C]adriamycin | <0.014 | −0.10 | 543 |
| [$^3$H]epipodophylotoxin | 0.20 | 2.80 | 657 |
| [$^3$H]vincristine | 0.64 | 2.80 | 825 |
| bleomycin | <0.014 | −3.30 | 1400 |

Table 2
Brain uptake indices (BUI) in newborn rabbit after Cornford et al. (1982), logarithms of octanol-water partition coefficient, log $P$ (Hansch and Leo, 1979) and molecular mass of a series of compounds, $M_m$

| Compound | BUI | log $P$ | $M_m$ |
|---|---|---|---|
| Cytosine | 1.2 | −1.72 | 243.22 |
| Urea | 1.4 | −1.52 | 60.06 |
| Mannitol | 2.0 | −2.11 | 182.17 |
| Thiourea | 5.0 | −0.96 | 76.12 |
| Ethylene glycol | 18 | −1.30 | 62.07 |
| Acetamide | 23 | −1.10 | 59.07 |
| Methanol | 103 | −0.52 | 32.04 |
| Propylene glycol | 27 | −0.92 | 76.10 |
| Ethanol | 107 | −0.18 | 46.07 |
| Butanol | 117 | 0.93 | 74.12 |
| Benzyl alcohol | 94 | 1.10 | 108.14 |
| Phenobarbital | 56 | 1.42 | 232.24 |
| Antipyrine | 83 | 0.38 | 188.23 |
| Caffeine | 103 | 0.02 | 194.19 |
| Dilantin | 71 | 2.40 | 252.27 |
| Estradiol | 94 | 2.61 | 272.39 |
| Testosterone | 85 | 3.28 | 288.43 |
| Diacetyl morphine | 87 | 1.14 | 369.42 |

regression were water, creatinine, adriamycin, epipodophylotoxin and bleomycin. (Levin (1980) had mistakingly written that vincristine was excluded instead of creatinine.) For the same series of 22 drugs we obtained the following relationship:

$$\log P_c = -3.288(\pm 0.157) + 0.431(\pm 0.037)\log P - 0.0035(\pm 0.00055)M_m \quad (10)$$

where $n$ (the number of observations) = 22; $r$ (the multiple correlation coefficient) = 0.939; $s$ (the standard error of estimate) = 0.359; $F$ (the value of the $F$-test) = 70.4; and $P$ (the significance level) $< 10^{-4}$ and where numbers in parentheses are the standard errors of the regression coefficients; the $t$-test values for the first, second and third coefficient of Eq. (10) are −20.9, 11.8 and −6.4, respectively, and each coefficient is significant at at least $10^{-4}$ significance level. Eq. (10) is simpler and more predictive than Eq. (9).

Based on the brain uptake indicies (BUI) in newborn rabbit given numerically for 18 agents by Cornford et al. (1982) (Table 2) we derived the following relationship:

$$\log \text{BUI} = 1.844(\pm 0.278) + 0.417(\pm 0.086)\log P - 0.00273(\pm 0.00133)M_m \quad (11)$$

where $n = 18$; $r = 0.788$; $s = 0.458$; $F = 12.2$; $P \leq 0.0007$ and the $t$-test values for the first, second and third coefficient of Eq. (11) are 8.1, 4.9 and −2.1, respectively, and the corresponding significance levels are $< 10^{-4}$, $\leq 0.0002$ and $< 0.06$, respectively. Correlation improves if urea is excluded as an outlier:

$$\log \text{BUI} = 1.952(\pm 0.203) + 0.387(\pm 0.076)\log P - 0.00302(\pm 0.00116)M_m \quad (12)$$

where $n = 17$; $r = 0.808$; $s = 0.399$; $F = 13.2$; $P \leq 0.0006$ and the $t$-test values for the first, second and third coefficient of Eq. (12) are 9.6, 5.1 and −2.6, respectively, and the corresponding significance levels are $< 10^{-4}$, $\leq 0.0002$ and $\leq 0.02$, respectively.

Correlations expressed by Eqs. (11) and (12) appear slightly weaker than that reported by Cornford et al. (1982) between the product (log BUI) × $(M_m)^{1/2}$ and log $P$ ($r = 0.859$). However it is not quite clear which log BUI and log $P$ data have actually been used by the original authors.

Structure of 20 histamine receptor $H_2$ antagonists studied by Young et al. (1988) is given in Fig. 1. The rat $\log(C_{brain}/C_{blood})$ data, log $P$ and log $P_{cyh}$ determined by Young et al. (1988) are collected in Table 3 along with molecular mass ($M_m$) and water accesible volume ($V_{wav}$) calculated by a program ChemPlus, extension for HyperChem (Hypercube, Canada).

The brain/blood concentration ratio describes the following equation involving the log $P$ and $M_m$ terms:

$$\log(C_{brain}/C_{blood}) = 0.476(\pm 0.454) + 0.541(\pm 0.106)\log P - 0.00794(\pm 0.00172)M_m \quad (13)$$

where $n = 20$; $r = 0.801$; $s = 0.486$; $F = 15.2$; $P \leq 0.0002$ and the $t$-test values for the first, second and third coefficient of Eq. (13) are 1.0, 5.1 and −4.2, respectively, and the corresponding significance levels are $< 0.32$, $\leq 0.0001$ and $\leq 0.0002$, respectively.

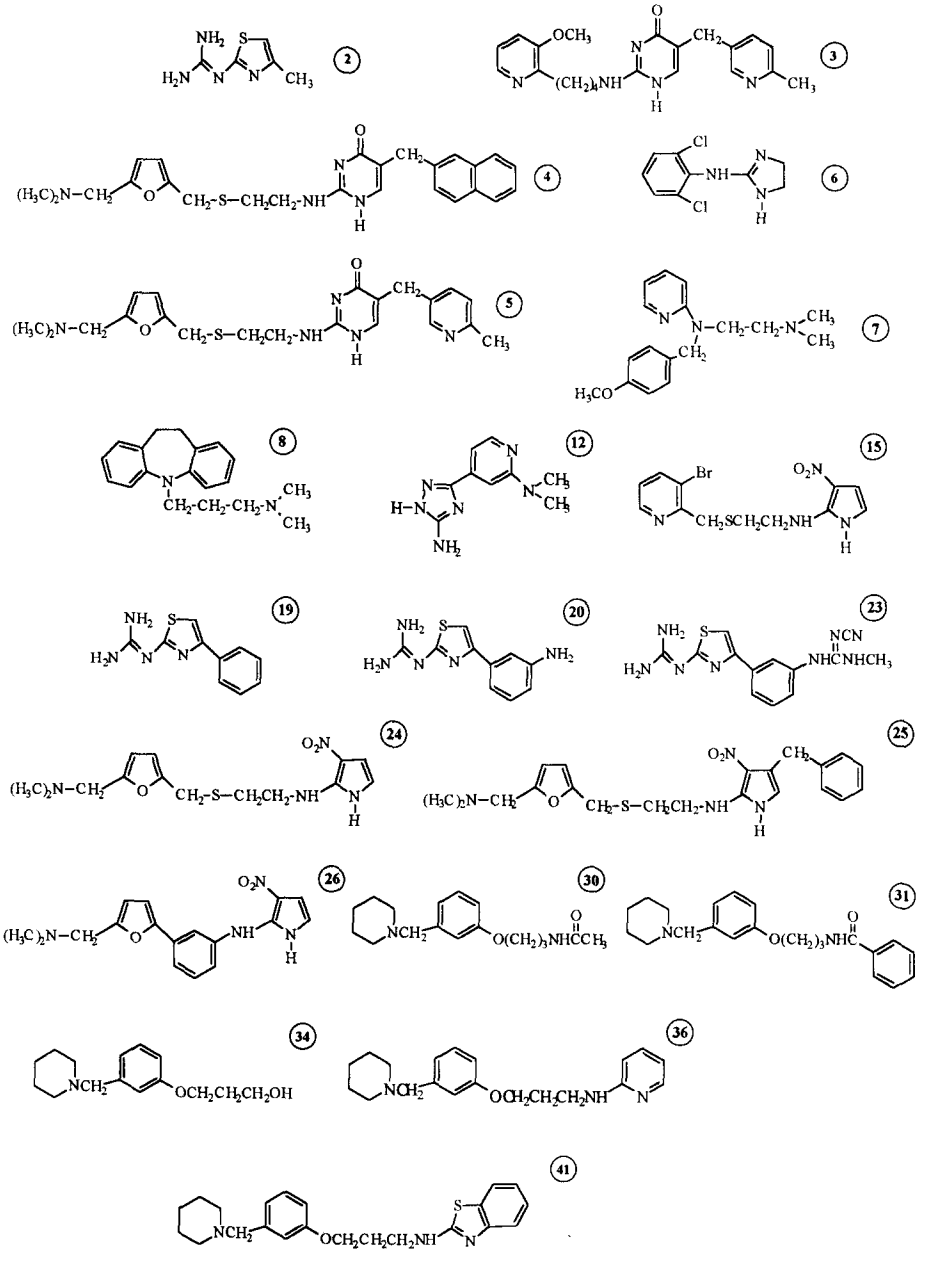

Fig. 1. Structure of histamine receptor $H_2$ antagonists studied by Young et al. (1988).

Evidently a better regression equation is obtained if log $P$ is replaced with the logarithm of cyclohexane-water partition coefficient, log $P_{cyh}$:

$$\log(C_{brain}/C_{blood}) = 1.296(\pm 0.313) + 0.309(\pm 0.034)\log P_{cyh} - 0.00570(\pm 0.00098)M_m \quad (14)$$

where $n = 20$; $r = 0.919$; $s = 0.321$; $F = 46.0$; $P \leq 10^{-4}$ and the $t$-test values for the first, second and

Table 3
Logarithms of the rat brain/blood concentration ratio, log $C_{brain}/C_{blood}$, of octanol-water partition coefficient, log $P$, of cyclohexane-water partition coefficient, log $P_{cyh}$, after Young et al. (1988) and molecular mass, $M_m$, and water accessible volume, $V_{wav}$, for compounds given in Fig. 1

| Compound | log $C_{brain}/C_{blood}$ | log $P$ | log $P_{cyh}$ | $M_m$ | $V_{wav}$ |
|---|---|---|---|---|---|
| 2 | −0.04 | 1.24 | −2.79 | 156.21 | 483.24 |
| 3 | −2.00 | 2.58 | −2.60 | 379.46 | 1017.32 |
| 4 | −1.30 | 4.57 | 0.47 | 448.58 | 1185.05 |
| 5 | −1.06 | 2.33 | −1.48 | 413.54 | 1114.31 |
| 6 | 0.11 | 1.59 | −0.85 | 230.10 | 617.12 |
| 7 | 0.49 | 3.30 | 2.59 | 285.39 | 903.62 |
| 8 | 0.83 | 4.42 | 3.57 | 280.41 | 912.28 |
| 12 | −1.17 | 1.19[a] | −2.05[a] | 204.23 | 631.87 |
| 15 | −0.67 | 1.75 | −1.34 | 357.22 | 834.79 |
| 19 | −0.18 | 2.64 | −1.28 | 218.28 | 644.86 |
| 20 | −1.15 | 1.41 | −3.19 | 233.29 | 680.16 |
| 23 | −1.54 | 1.60 | −2.66 | 314.37 | 858.20 |
| 24 | −1.12 | 1.64 | −1.48 | 324.40 | 903.28 |
| 25 | −0.73 | 3.65 | 1.11 | 414.52 | 1094.64 |
| 26 | −0.27 | 3.10 | 0.22 | 326.35 | 907.10 |
| 30 | −0.46 | 2.15 | 0.22 | 290.41 | 957.33 |
| 31 | −0.24 | 3.97 | 2.18 | 352.48 | 1117.36 |
| 34 | −0.02 | 2.78 | 1.31 | 249.35 | 834.32 |
| 36 | 0.69 | 4.29 | 3.23 | 325.45 | 986.18 |
| 41 | 0.14 | 5.41 | 3.72 | 382.54 | 1081.28 |

[a] Obtained after correction for ionization.

third coefficient of Eq. (14) are 4.1, 9.0 and −5.8, respectively, and the corresponding significance levels are $<0.0007$, $\leq 10^{-4}$ and $\leq 10^{-4}$, respectively.

Statistical quality of regression can be increased by replacing $M_m$ in Eq. (14) with other bulkiness-related parameters of the $H_2$ histamine receptor antagonists, e.g., polarizability, refractivity. The 'best' equation obtained is:

$$\log(C_{brain}/C_{blood}) = 1.979(\pm 0.339) + 0.373(\pm 0.032)\log P_{cyh} - 0.00275(\pm 0.00037)V_{wav} \quad (15)$$

where $n = 20$; $r = 0.943$; $s = 0.271$; $F = 67.9$; $P \leq 10^{-4}$ and the $t$-test values for the first, second and third coefficient of Eq. (15) are 5.8, 11.5 and −7.4, respectively, and all the corresponding significance levels are $\leq 10^{-4}$.

Eq. (15) is statistically more significant than the correlation reported by van de Waterbeemd and Kansy (1992) in spite of including an evident outlier (see Compound 12 in Table 3) which log $P_{cyh}$ value appears disputable.

Abraham and co-workers (Abraham et al., 1985, 1994) assembled a larger set of indirectly determined brain/blood concentration ratios, log BB. This was done through results on air-blood (log $L_{blood}$) and on air-brain (log $L_{brain}$) partitions. The log BB was defined as the difference between log $L_{brain}$ and log $L_{blood}$. The log BB data (Abraham et al., 1985, 1994) along with the available log $P$ data (Hansch and Leo, 1979; El Tayar et al., 1991; Leahy et al., 1992) and molecular mass, $M_m$, are collected in Table 4. Regression equation relating log BB to a combination of log $P$ and $M_m$ has the form:

$$\log BB = -0.088(\pm 0.051) + 0.272(\pm 0.017)\log P - 0.00116(\pm 0.00049)M_m \quad (16)$$

where $n = 33$; $r = 0.947$; $s = 0.126$; $F = 131.1$; $P \leq 10^{-4}$ and the $t$-test values for the first, second and third coefficient of Eq. (16) are −1.7, 15.8 and

$-2.4$, respectively, and the corresponding significance levels are $<0.1$, $\leq 10^{-4}$ and $<0.025$, respectively.

Once more molecular bulkiness, $M_m$, provided a significant (97.5% significance level) and negative correction to the prediction of brain penetration by means of the standard hydrophobicity parameter, log $P$.

In all the regression equations derived in this work the brain/blood equilibrium distribution ratios increased with increasing log $P$ (or log $P_{cyh}$). In Eqs. (10)–(16) the regression coefficient at log $P$ or log $P_{cyh}$ are less than one and range from 0.272 to 0.541. According to Eqs. (7) and (8), these coefficients mean polarity ratio of the two distribution systems considered. As values of second coefficient in Eqs. (10)–(16) are below unity it would mean that the net polarity of the brain/blood system is lower than that of the octanol-water system. This would explain why decreasing polarity of drugs by reducing their overall hydrogen-bonding ability might improve the brain penetration as suggested by Young et al. (1988).

Table 4
Logarithms of the indirectly determined rat brain/blood concentration ratio, log BB, after Abraham et al. (1985, 1994) and of octanol-water partition coefficient, log $P$, from literature (Hansch and Leo, 1979; Leahy et al., 1992) and $M_m$ is the molecular mass

| Compound | log BB | log $P$ | $M_m$ |
|---|---|---|---|
| Neon | 0.200 | 0.28 | 20.18 |
| Argon | 0.030 | 0.74 | 39.95 |
| Xenon | 0.030 | 1.28 | 131.30 |
| Nitrogen | 0.030 | 0.67 | 28.01 |
| Nitrous oxide | 0.030 | 0.40 | 44.01 |
| Methane | 0.040 | 1.09 | 16.04 |
| *n*-Pentane | 0.760 | 3.39 | 72.15 |
| *n*-Hexane | 0.800 | 3.90 | 86.18 |
| 2-Methylpentane | 0.970 | 3.60 | 86.18 |
| 3-Methylpentane | 1.010 | 3.60 | 86.18 |
| 2,2-Dimethylbutane | 1.040 | 3.82 | 86.18 |
| *n*-Heptane | 0.810 | 4.50 | 100.20 |
| 3-Methylhexane | 0.900 | 4.50 | 100.20 |
| Methylcyclopentane | 0.930 | 3.37 | 84.16 |
| Trichloromethane | 0.290 | 1.97 | 119.38 |
| 1,1,1-Trichloroethane | 0.400 | 2.49 | 133.40 |
| Trichloroethene | 0.340 | 2.42 | 131.39 |
| Halothane | 0.350 | 2.30 | 197.38 |
| Teflurane | 0.270 | 2.01 | 180.93 |
| Diethyl ether | 0.000 | 0.89 | 74.12 |
| Methoxyflurane | 0.250 | 2.21 | 164.97 |
| Isoflurane | 0.420 | 2.06 | 184.49 |
| Enflurane | 0.240 | 2.10 | 184.49 |
| Fluroxene | 0.130 | 1.77 | 58.08 |
| Propanone | −0.150 | −0.24 | 72.11 |
| Butanone | −0.080 | 0.29 | 46.07 |
| Ethanol | −0.160 | −0.30 | 60.10 |
| Propan-1-ol | −0.160 | 0.25 | 58.08 |
| Propan-2-ol | −0.150 | 0.05 | 74.12 |
| 2-Methylpropan-1-ol | −0.170 | 0.76 | 146.05 |
| Sulphur hexafluoride | 0.360 | 1.68 | 126.08 |
| Benzene | 0.370 | 2.13 | 78.11 |
| Toluene | 0.370 | 2.73 | 92.14 |

In all the regression equations derived in this work, a molecular bulkiness descriptor $M_m$ (or $V_{wav}$) provided a statistically significant negative input to the predicted brain/blood equilibrium distribution ratios. Negative coefficient $k_2$ in equations of the form of Eq. (8), in situation when the $a_B/a_P$ ratio is less than one, means that $b_P$ is appropriately larger than $b_B$. In other words, the net dispersive attraction ability of the octanol-water distribution system is stronger than in the case of the brain/blood system. Thus, the bulkiness parameter in equations relating brain penetration to the standard hydrophobicity parameters plays a role of a correction factor for the dispersive attraction overmanifested in the chemical in vitro system with regards to the biological brain/blood system.

Derived here are relationships for four representative sets of brain/blood distribution data supported by theoretical analysis suggest that two research strategies can be proposed to predict brain penetration of potential drugs. One, more apparent but evidently difficult to realize in practice, would be to identify a model partition system mimicking the brain/blood partition. The octanol-water partition systems does not appear reliable enough for it. The other strategy would be to test various phase distribution systems not necessarily similar to the brain/blood distribution system and use for predictions the data from such systems in combination with some easily calculable drug structure descriptor. A combination of partition parameters from a hydrocarbon/water system

with molecular bulkiness descriptors can be considered. As pointed out by Abraham et al. (1994) the determinations of $\log P_{cyh}$ are much more difficult than determinations of $\log P$ and in such a situation their advantage could be more apparent than a real one. Instead of troublesome determinations of $\log P_{cyh}$ the reversed-phase HPLC can be recommended, especially employing the modern stationary phases which can be operated at a wide pH range and yield partition parameters for nonionized forms of chemically diverse structures (Kaliszan, 1992).

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