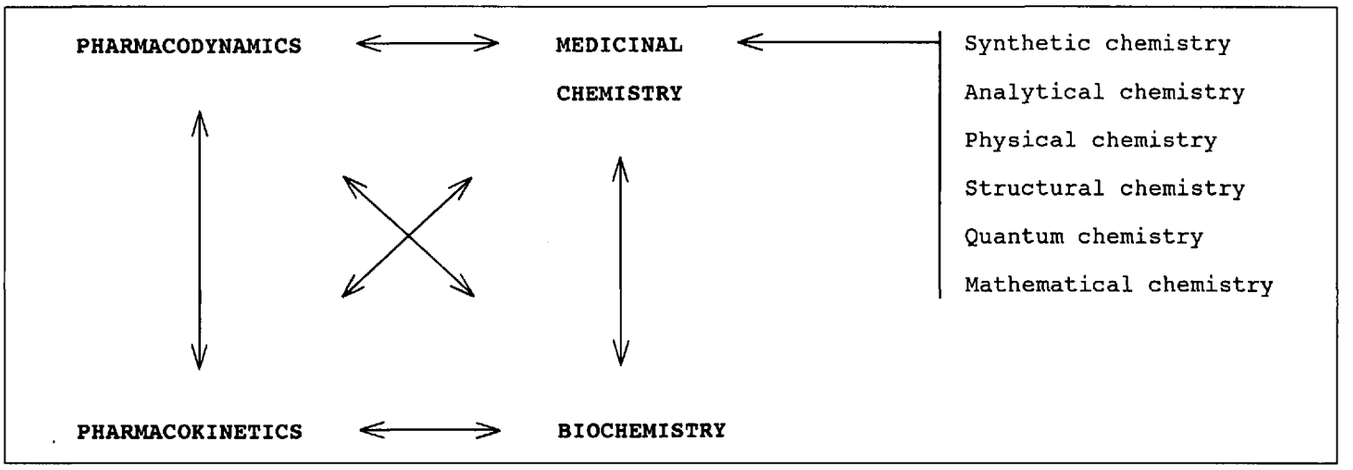


Figure. *The relation of medicinal chemistry with connected disciplines*

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*Molecular biology* is having a major impact on molecular pharmacology and enzymology, and this in turn has begun to deeply affect the thinking and work of medicinal chemists. For example, the cloning of new receptor subtypes and of mutant receptors and enzymes obtained by site-directed mutagenesis has brought us closer to understanding the structure and functioning of these macromolecules. The impact on molecular-graphics studies and on lead generation and optimization is overwhelming.

It is not in the least fortuitous that the development of medicinal chemistry should parallel advances in *mathematical and computational sciences* and their applications. These theoretical advances, coupled to the fast technological evolution of computing machines, will continue to offer to pharmacochemists tools of ever increasing sophistication and efficiency.

In the longer run, however, the molecular level of conceptualization may reveal its limits. At this point, continued progress in medicinal chemistry may call for input from *systemic pharmacology*, in other words from a highly integrated and organismic pharmacology which may well be the clinical pharmacology of the future. In such a perspective, medicinal chemistry would become more 'therapeutic', thus providing a belated vindication of the French label 'chimie thérapeutique'.

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## 1. Brain Uptake and Physicochemical Properties

### 1.1. *The Δlog P Concept*

Numerous QSAR studies on CNS drugs have demonstrated that besides p*K*a and molecular size, lipophilicity is a highly significant contributor to brain penetration [1][2]. Partition coefficients measured in the octan-1-ol/$H_2O$ system are mostly used as experimental assessment of the lipophilicity of a compound. However, it has been observed that neither octan-1-ol/$H_2O$ (log $P_{oct}$) nor cyclohexane/$H_2O$ (log $P_{chex}$) partition coefficients are predictive for brain penetration of $H_2$-

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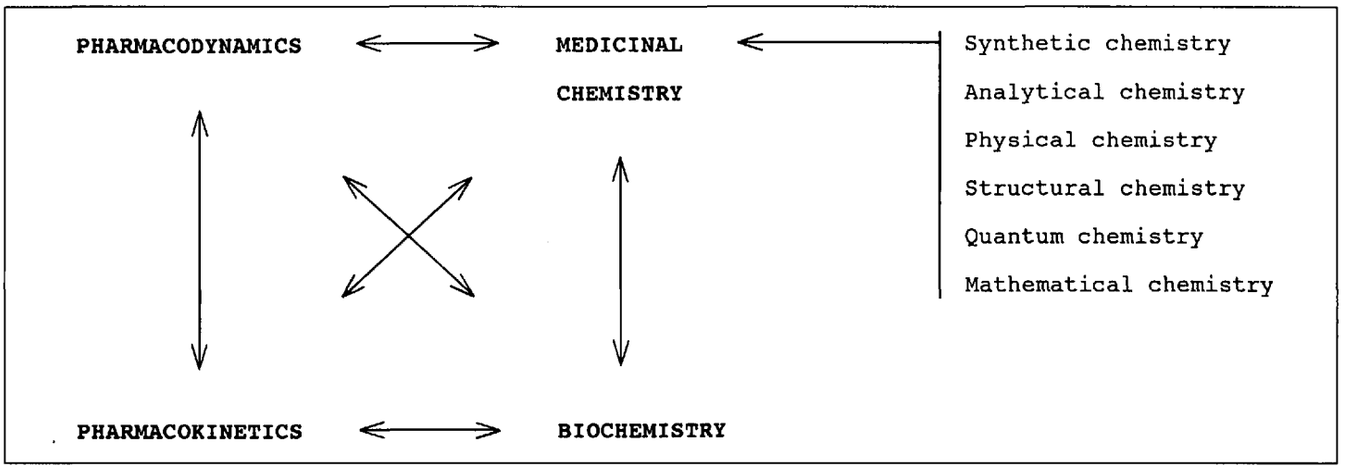


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receptor histamine antagonists [3][4]. From further investigation, a new concept emerged. It was found that a good correlation exists between the logarithm of the equilibrium brain/blood concentration ratios and the differences $\Delta\log P$ ($= \log P_{oct} - \log P_{chex}$) of partition coefficients in two different solvent systems. The *Ganellin-Young* group believed that $\Delta\log P$ accounts for H-bonding ability and reflects two distinct processes [3][4]. The $\log P_{chex}$ parameter could reflect partitioning into nonpolar regions of the brain, while $\log P_{oct}$ might account for protein binding in the peripheral blood. To target compounds into the brain by passive diffusion, therefore, one should minimize polar H-bonding groups and molecular size.

This $\Delta\log P$ concept has also been explored for skin penetration [5]. Skin penetration can be rationalized by considering inter- and intracellular routes. *Testa* and coworkers demonstrated that $\Delta\log P$ contains information on the capacity of a solute to donate H-bonds. In their view, the rate-limiting step in brain penetration is the donation of H-bonds of a solute to the hydrophilic parts of lipids in the blood-brain barrier [5][6].

### 1.2. *H-Bonding*

H-Bonding capacity has been extensively studied in solvatochromic equations for identifying the physicochemical properties governing solubility and partitioning phenomena [6][7]. Compilations of H-bond donor acidity ($\alpha$) and acceptor basicity ($\beta$) can be found in the literature. However, these solvatochromic parameters can only be obtained with great experimental difficulty. Very recently, a new approach has been presented to assess $\alpha$ and $\beta$ from log P data.

By various lines of evidence it can be shown that log P is a composite parameter, consisting of a cavity and a polarity term:

$$\log P = aV + \Lambda \qquad (1)$$

where $V$ is the *van der Waals* volume and $\Lambda$ accounts for polarity of the molecule including H-bonding capacity, and, therefore, $\Lambda = 0$ for alkanes. $\Lambda$ for polar compounds is calculated from the difference in log P between the experimental value and the one calculated from the molar volume using the reference equation for the alkanes (*e.g. Eqns. 2* and *3*).

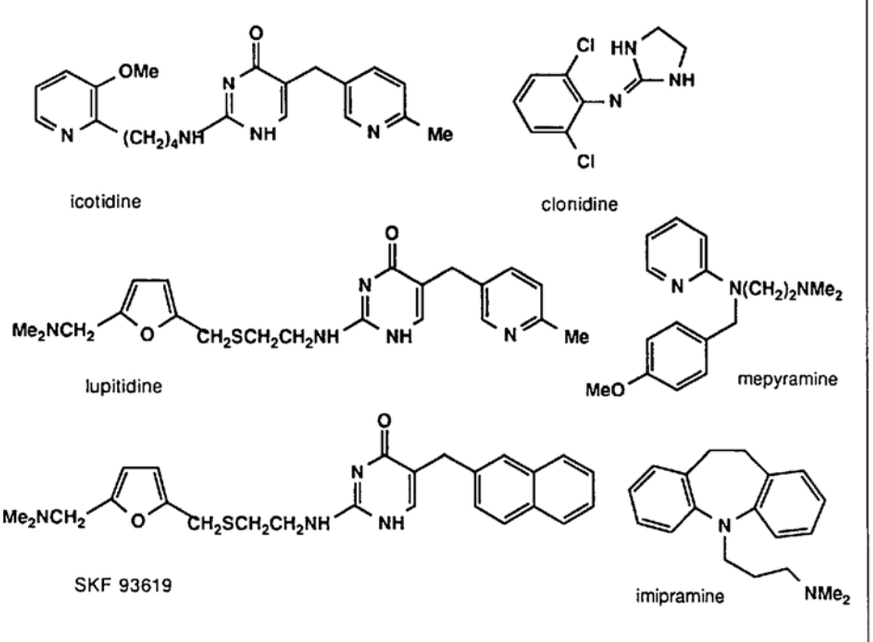
It was observed that $\Lambda$ calculated from $\log P_{oct}$ values ($\Lambda_{oct}$) correlate quite well with H-bond acceptor basicity ($\beta$), while $\Lambda$ calculated from log P values measured in alkane/$H_2O$ systems $\log P_{alk}$ ($\Lambda_{alk}$) correlate with total H-bond capacity ($\alpha$ and $\beta$). Thus, experimental log P values and calculated molar volumes give elegant access to H-bonding capacities [8].

Table 1. *Physicochemical Properties of Alkanes*

| Compound | $V_M$ [a] | $V_W$ [b] | $V^0_{aq}$ [c] |
|---|---|---|---|
| Methane | 30.3 | 17.1 | 37.3 |
| Ethane | 47.5 | 27.3 | 51.2 |
| Propane | 65.0 | 37.6 | 67.0 |
| Butane | 82.6 | 47.8 | |
| Pentane | 99.5 | 56.3 | |
| Hexane | 116.7 | 65.8 | |
| Heptane | 133.8 | 75.5 | |
| Octane | 150.6 | 85.2 | |

[a]) Molar volume calculated with our in-house program MOLOC. [b]) Molar volume taken from [8]. [c]) Experimental partial molar volume [8].

*Test compounds for brain penetration.*




### 1.3. *log P Measurement and Calculation*

The measurement of $\Delta\log P$ values is quite time-consuming, even with modern approaches such as centrifugal partition chromatography [9]. For certain series of compounds, it might even be excluded, since the log P of the compounds lies beyond the limits of reliable log P measurement. In such cases, calculated log P values might be of help, but of course only when such calculations are highly reliable. $\log P_{oct}$ can be calculated using the *Rekker* or *Leo-Hansch* fragmental approach [10]. *Rekker* and *Mannhold* recently have extended this approach and suggest an additive scheme for calculations of log P in alkane/$H_2O$ [11]. A very crude estimate of $\Delta\log P$ values, therefore, can now be made, but great care is warranted.

As we have seen above, H-bonding properties are believed to play an important role in brain penetration processes. Taking advantage of these new $\Lambda$ parameters, we have reinvestigated the brain penetration of $H_2$ antagonists, and consid-

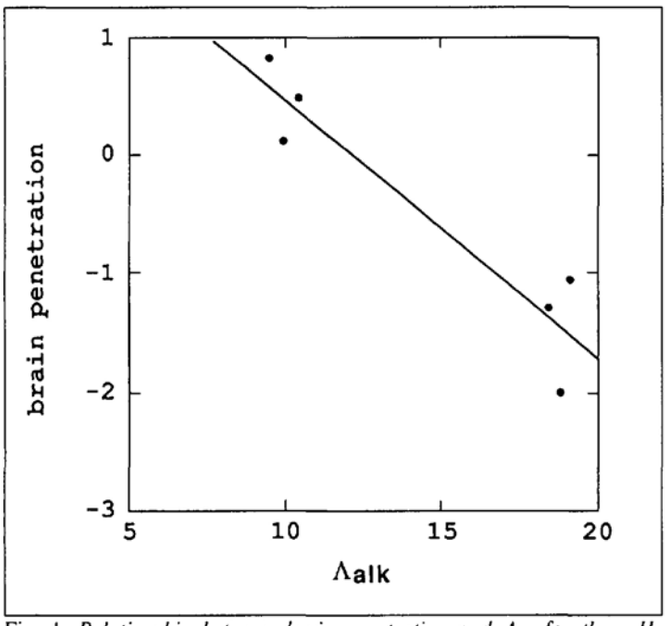



Fig. 1. *Relationship between brain penetration and $\Lambda_{alk}$ for three $H_2$ receptor antagonists and clonidine, imipramine, and mepyramine.* Brain penetration is defined as log ($C_{brain}/C_{blood}$).

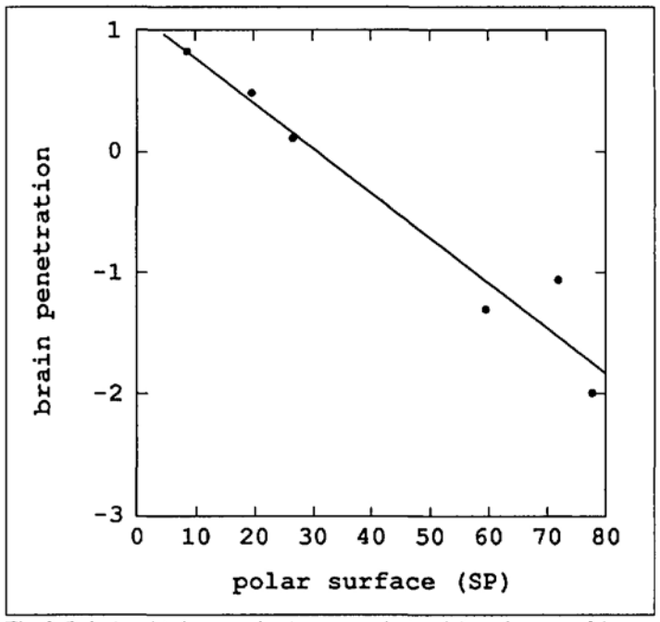



Fig. 2. *Relationship between brain penetration and the polar part of the* van der Waals *surface for three $H_2$ receptor antagonists and clonidine, imipramine, and mepyramine*

Table 2. *Physicochemical Properties of $H_2$-Antagonists and other CNS Penetrating Compounds*

| Compound | log BB[a]) | log $P_{oct}$[b]) | log $P_{alk}$[c]) | Δlog P[d]) | $V_M$[e]) | $\Lambda_{oct}$[f]) | $\Lambda_{alk}$[g]) |
|---|---|---|---|---|---|---|---|
| Icotidine | –2.00 | 2.58 | –2.60 | 5.18 | 387.0 | 10.34 | 18.79 |
| Lupitidine | –1 .06 | 2.33 | –1.48 | 3.81 | 424.9 | 11.84 | 19.1 |
| SKF 93619 | –1.30 | 4.57 | 0.47 | 4.10 | 456.7 | 10.65 | 18.44 |
| Clonidine | 0.11 | 1.59 | –0.85 | 2.44 | 205.9 | 5.35 | 9.98 |
| Mepyramine | 0.49 | 3.30 | 2.59 | 0.71 | 306.6 | 6.97 | 10.47 |
| Imipramine | 0.83 | 4.42 | 3.57 | 0.85 | 308.3 | 5.90 | 9.55 |
| **2**[h]) | –0.04 | 1.24 | –2.79 | 4.03 | 151.3 | 3.90 | 9.79 |
| **12** | –1.17 | 1.19 | –2.05 | 3.24 | 204.0 | 5.69 | 11.10 |
| 15 | –0.67 | 1.75 | –1.34 | 3.09 | 281.9 | 7.70 | 13.43 |
| **19** | –0.18 | 2.64 | –1.28 | 3.92 | 210.7 | 4.46 | 10.60 |
| **20** | –1.15 | 1.41 | –3.19 | 4.60 | 220.4 | 6.01 | 12.88 |
| **23** | –1.54 | 1.60 | –2.66 | 4.26 | 300.7 | 8.47 | 15.49 |
| **24** | –1.12 | 1.64 | –1.48 | 3.12 | 311.7 | 8.79 | 14.73 |
| **25** | –0.73 | 3.65 | 1.11 | 2.54 | 405.1 | 9.87 | 15.79 |
| **26** | –0.27 | 3.10 | 0.22 | 2.88 | 316.9 | 7.51 | 13.24 |
| **30** | –0.46 | 2.15 | 0.22 | 1.93 | 304.5 | 8.05 | 12.75 |
| **31** | –0.24 | 3.97 | 2.18 | 1.79 | 360.3 | 8.07 | 12.97 |
| **34** | –0.02 | 2.78 | 1.31 | 1.47 | 256.1 | 5.82 | 9.78 |
| **36** | 0.69 | 4.29 | 3.23 | 1.06 | 333.6 | 6.87 | 10.88 |
| **41** | 0.14 | 5.41 | 3.72 | 1.69 | 390.9 | 7.64 | 12.62 |

[a]) log $C_{brain}/C_{blood}$. [b]) Partition coefficient of the neutral form in octan-1-ol/$H_2O$. [c]) Partition coefficient of the neutral form in cyclohexane/$H_2O$. [d]) log $P_{oct}$ – log $P_{alk}$. [e]) Molar volume calculated with our in-house modeling program MOLOC. [f]) H-bond parameter calculated using *Eqn. 2*. [g]) H-bond parameter calculated using *Eqn. 3*. [h]) Same compound numbering as in [3].

ered alternative theoretical approaches, which might replace or complement experimental log P measurements.

## 2. Results and Discussion

Since calculated molar volumes depend on the algorithm and parametrization of the program, we also have recalculated the molar volumes of alkanes. As seen in *Table 1* our calculated molar volumes are close to the experimental ones.

The present reference lines for the alkanes are given by:

$$\log P_{oct} = 0.033(\pm 0.001)\, V_M + 0.147(\pm 0.071)$$
$$n = 8,\ r = 0.999,\ s = 0.081,\ F = 2115 \quad (2)$$

$$\log P_{alk} = 0.039(\pm 0.001)\, V_M + 1.098(\pm 0.035)$$
$$n = 8,\ r = 1.000,\ s = 0.040,\ F = 11830 \quad (3)$$

where $n$ is the number of compounds, $r$ the correlation coefficient, $s$ the standard error of the regression, and F the *Fisher* test for significance of the equation. In brackets the standard error of the regression coefficients are given.

$\Lambda$ parameters are calculated from experimental log P values [3][4] and calcu-

Table 3. *H-Bonding Capacity*

| Compound | HD[a]) | HA[b]) | HB[c]) | HT[d]) |
|---|---|---|---|---|
| Icotidine | 2 | 5 | 7 | 7 |
| Lupitidine | 2 | 6 | 7 | 8 |
| SKF 93619 | 2 | 5 | 6 | 7 |
| Clonidine | 2 | 3 | 4 | 5 |
| Mepyramine | 0 | 4 | 4 | 4 |
| Imipramine | 0 | 2 | 2 | 2 |

[a]) Number of donor H-bonds. [b]) Number of acceptor H-bonds. [c]) Total number of atoms capable of H-bonding. [d]) Total of potential acceptor and donor H-bonds.

Table 4. *Molecular Surface and Solvent Accessible Surface*

| Compound | Hydrophilic *van der Waals* surface SP | Hydrophobic *van der Waals* surface SNP | Hydrophilic water accessible surface SPW[a]) | Hydrophobic water accessible surface SNPW[a]) |
|---|---|---|---|---|
| Icotidine | 77.7 | 355.5 | 102.3 | 610.0 |
| Lupitidine | 71.9 | 401.9 | 100.3 | 674.8 |
| SKF 93619 | 59.6 | 445.1 | 77.0 | 746.1 |
| Clonidine | 26.7 | 204.5 | 24.2 | 395.8 |
| Mepyramine | 19.7 | 325.6 | 26.4 | 530.9 |
| Imipramine | 8.7 | 327.9 | 7.2 | 537.9 |
| 2[b]) | 72.7 | 98.6 | 146.4 | 197.6 |
| **12** | 83.3 | 137.3 | 170.3 | 247.5 |
| **15** | 81.2 | 226.9 | 149.0 | 398.2 |
| **19** | 73.1 | 155.2 | 144.5 | 281.4 |
| **20** | 98.6 | 142.5 | 209.5 | 238.4 |
| **23** | 131.2 | 194.0 | 253.5 | 323.2 |
| **24** | 82.5 | 260.9 | 139.2 | 473.9 |
| **25** | 80.3 | 352.0 | 116.9 | 612.9 |
| **26** | 82.7 | 253.4 | 133.6 | 434.9 |
| **30** | 45.8 | 278.8 | 90.7 | 490.5 |
| **31** | 45.8 | 335.1 | 88.8 | 565.8 |
| **34** | 34.0 | 242.5 | 71.8 | 435.7 |
| **36** | 36.4 | 318.4 | 47.5 | 581.0 |
| **41** | 37.3 | 357.0 | 44.8 | 631.3 |

[a]) SPW and SNPW are calculated for an $H_2O$ molecule with radius of 1.45 Å. [b]) Compound numbers are those of *Young et al.* [3].

lated molar volumes (*Table 2*). Taking first the initial set of *Ganellin et al.* [3][4], *i.e.* the first six compounds of *Table 2*, an apparently good correlation is obtained between brain uptake and $\Lambda_{alk}$:

$$\log (C_{brain}/C_{blood}) = -0.22(\pm 0.04)\ \Lambda_{alk} + 2.66(\pm 0.60)$$

$$n = 6,\ r = 0.939,\ s = 0.431,\ F = 30 \qquad (4)$$

However, as shown in *Fig. 1*, this straight line is formed by two small clusters, therefore, the correlation coefficient is misleading and more data are required (see below). Using $\Delta$log P in the correlation, only a slightly better correlation was found ($r = 0.980$) [3][4]. The correlation with $\Lambda_{oct}$ is of lesser quality ($r = 0.852$, $n = 6$). This result suggests that brain penetration correlates with total H-bonding capacity. It further implies that it is sufficient to measure log P values in an alkane/$H_2O$ system (hexane, cyclohexane, heptane) and to calculate the molar volumes of the compounds. Remember that the $\Delta$log P approach requires the measurement of log P values in two solvent systems.

In the following part, we will explore if H-bonding capacity can be directly derived from the molecular structure or can be easily calculated. From an inspection of the molecular structures an estimate can be made on the number of H-bond accepting and donating groups (*Table 3*). Furthermore the, *van der Waals* molecular surface and volume, as well as the solvent accessible surface and volume [12] have been calculated and explored (*Table 4*). Defining oxygen and nitrogen as hydrophilic and all other atom types as hydrophobic, we have separately considered hydrophobic and hydrophilic contributions to volume and surface, as well as their ratio, and the fraction of polar surface.

Using the data in *Table 3*, no significant correlations could be found. However, it appears that brain penetration correlates quite well with the hydrophilic part of the *van der Waals* surface (SP) (*Fig. 2*) or the $H_2O$ accessible hydrophilic surface (SPW).

$$\log C_{brain}/C_{blood} = -0.037(\pm 0.004)\ SP + 1.156(\pm 0.231)$$

$$n = 6;\ r = 0.972;\ s = 0.294;\ F = 69.3 \qquad (5)$$

$$\log C_{brain}/C_{blood} = -0.025(\pm 0.004)\ SPW + 0.945(\pm 0.28)$$

$$n = 6;\ r = 0.952;\ s = 0.387;\ F = 38.3 \qquad (6)$$

From *Eqns. 4–6* follows that $\Lambda_{alk}$, the total H-bonding capacity, is strongly correlated with SP ($r = 0.970$) and SPW ($r = 0.978$). SP correlates also very well with the total H-bonding capacity (see *Table 3*) HT ($r = 0.944$), which, therefore, in turn is correlated to log $C_{brain}/C_{blood}$ ($r = 0.889$). Based on this small set of six compounds, it is concluded that brain penetration can be predicted by calculated descriptors, without using experimental log P and $\Delta$log P values.

This first set of compounds has then been extended to the same 20 compounds discussed by the *Young-Ganellin* group [3]. Compared to the promising correlations obtained with the first six compounds (*Eqns. 4–6*), this is no longer the case for the larger data set including all 20 compounds (*Fig. 3*). Both using $\Lambda_{alk}$ ($r = 0.778$) or SP ($r = 0.781$) poorer results are obtained. However, when the most deviant outlier (compound **20**) is removed, the correlations improve for $\Lambda_{alk}$ ($r = 0.839$, $n = 19$) to the same level as was found with $\Delta$log P ($r = 0.831$, $n = 20$). Removal of compound **20** can be justified by the fact that its log P values, used to calculate $\Lambda_{alk}$ and $\Lambda_{oct}$, are uncertain [3].

So far only simple linear regression have been considered. Since it seems unlikely that brain penetration depends on one single factor [3], multiple linear relationships have been evaluated. Including molecular size, often mentioned as an important factor for brain uptake, we could improve our equations using the molar volume ($V_M$):

$$\log (C_{brain}/C_{blood}) = -0.338(\pm 0.032)\,\Lambda_{alk} + 0.007(\pm 0.001)\,V_M + 1.730(\pm 0.297)$$

$$n = 20;\ r = 0.934;\ s = 0.290;\ F = 58 \qquad (7)$$

$$\log (C_{brain}/C_{blood}) = -0.021(\pm 0.003)\,SP - 0.003(\pm 0.001)\,V_M + 1.643(\pm 0.465)$$

$$n = 20;\ r = 0.835;\ s = 0.448;\ F = 19.5 \qquad (8)$$

*Eqn. 7* indicates that a highly significant estimate of brain uptake can be made using the calculated molar volume of the molecule and a descriptor derived from experimental log P measurements in an alkane/$H_2O$ system. A more crude, but still acceptable estimate of brain uptake can be made using calculable surface and volume descriptors. *Eqn. 8* has the same statistical quality as the relationship previously presented by *Ganellin-Young* [3][4] using experimental $\Delta$log P values.

In *Eqns. 7* and *8*, $V_M$ can also be replaced by the hydrophobic part of the molecular surface (SNP), giving equations of similar statistical quality, *i.e.* $r = 0.941$ ($\Lambda_{alk}$ and SNP) and $r = 0.845$ (SP and SNP), respectively.

Our present findings will be tested by the evaluation of brain uptake data of various other classes of compounds.

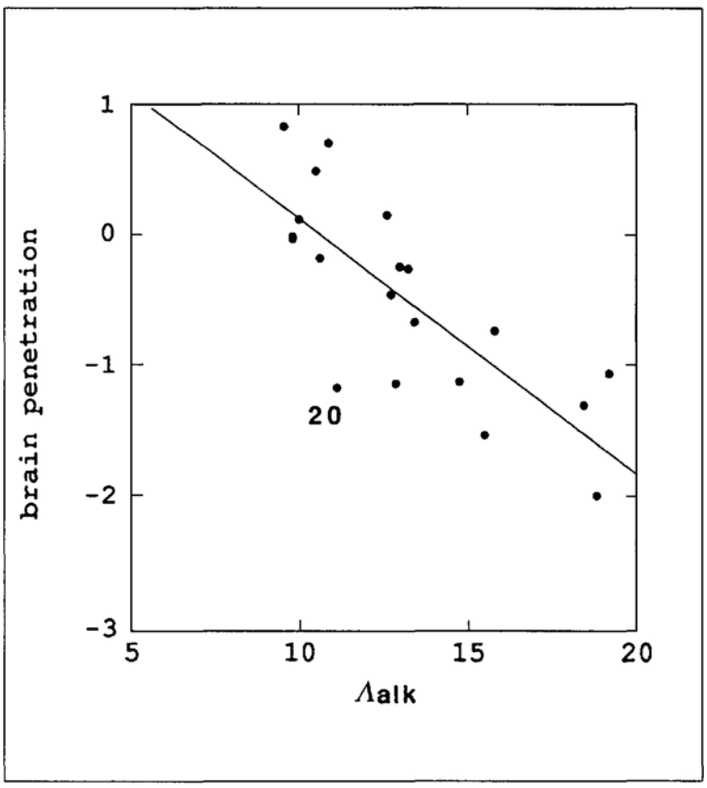



Fig. 3. *Relationship between brain penetration and $\Lambda_{alk}$ for 20 different compounds*

## 3. Concluding Remarks

The present study shows that it does not seem necessary to measure log P values in two solvent systems, *i.e.* octan-1-ol/$H_2O$ and alkane/$H_2O$, in order to derive $\Lambda$log P values for correlation with brain uptake data. log $P_{alk}$ values from which $\Delta_{alk}$ can be derived using the calculated molar volumes are sufficient. A first estimate of brain penetration can even be obtained from calculated hydrophilic and hydrophobic surface contributions of the molecules.

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