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PHYSICOCHEMICAL ANALYSIS OF THE FACTORS GOVERNING DISTRIBUTION OF SOLUTES BETWEEN BLOOD AND BRAIN

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Abstract: An equation is described that relates the equilibrium distribution of compounds between blood and brain to various solute descriptors, for 57 varied compounds. It is shown that the main factors influencing the distribution are solute size that favours brain, and solute dipolarity/ polarisability, hydrogen-bond acidity and hydrogen-bond basicity that favour blood. The descriptors can be obtained from measurements on compound substructures, so that the blood-brain distribution can be predicted for drug molecules without the necessity for synthesis.

It has been estimated that diseases of the brain affect more people than cancer or heart disease[1]. However, the development of therapeutic drugs for the brain has been hindered, due to the so-called blood-brain barrier[2], which prevents free distribution of molecules into the brain. Thus it has become increasingly important in drug design studies to know how compounds will distribute between blood and brain[3]. However, the experimental determination of the blood-brain concentration ratio, BB, defined by eq.(1), is both difficult and time consuming[4], so that there have been several attempts to set up physicochemical correlation equations for the prediction of logBB values.

$$BB = \text{concentration in brain/concentration in blood} \quad (1)$$

Young, Mitchell et al.[5] (Y-M) showed that for 20 drug molecules there was little connection between BB and the water-octanol partition coefficient, P_{oct}, as protagonised by Hansch et al..[6,7] However Y-M demonstrated that there were better correlations with the water- cyclohexane partition coefficient, P_{cyc}, and especially with the ΔlogP parameter of Seiler,[8] defined as $\Delta\log P = \log P_{oct} - \log P_{cyc}$:

$$\log BB = 0.266 \log P_{oct} - 1.22 \quad (2)$$

$n = 20 \quad \rho = 0.436 \quad sd = 0.71 \quad F = 4.2$

$$\log BB = 0.250 \log P_{cyc} - 0.47 \quad (3)$$

n = 20 ρ =0.732 sd = 0.54 F = 20 7

$$\log BB = -0.485 \Delta \log P + 0.89 \quad (4)$$

n = 20 ρ =0.831 sd = 0.44 F = 40.2

Here, n is the number of data points, ρ is the correlation coefficient, sd is the standard deviation, and F is the Fisher F-statistic. More recently, van der Waterbeemd and Kansy[9] re-examined the Y-M data set and obtained:

$$\log BB = - 0.338 \Lambda_{cyc} + 0.007 V_M + 1.730 \quad (5)$$

n = 20 ρ = 0.934 sd = 0.29 F = 58.0

Λ_{cyc} is defined through eq.(6), where V_M is a calculated molar volume.

$$\Lambda = - \log P_{cyc} + 0.039 V_M + 1.098 \quad (6)$$

The problem with the above equations for logBB is that they lead to little understanding of the factors that influence the blood-brain distribution. Furthermore, they all have a large constant term [1.730 in eq.(5)]. This means that for a small, nonpolar solute such as methane, logBB is predicted by eq.(5) to be no less than 1.62, whereas the value given by Abraham and Weathersby[10] (A-W) is only 0.04 log units. Thus all the previously generated equations for logBB must be regarded as specific to the Y-M data set, and not general.

We have analysed the Y-M data set using the solvation equation of Abraham:[11]

$$\log SP = c + rR_2 + s\pi^H_2 + a\Sigma\alpha^H_2 + b\Sigma\beta^H_2 + vVx \quad (7)$$

Here, SP is a chemical or biological property of a series of solutes in a fixed system and can be for example, *P*, the partition coefficient for a series of solutes or LD_{50}. The descriptors are solute properties as follows: R_2 is an excess molar refraction[12]; π^H_2 is the solute dipolarity/polarisability[13-15]; $\Sigma\alpha^H_2$ and $\Sigma\beta^H_2$ are the summation hydrogen-bond acidity and basicity respectively[11]; and Vx is the characteristic volume of McGowan[16]. Descriptors are currently available for over 2000 different compounds [11,17]. However for the large and complex Y-M drug compounds, descriptors had to be obtained, (listed in Table 1). These were determined using the principles of additivity, by the summation of substructure fragments. Descriptors for compounds used as substructures were sometimes available,[11,17] or were obtained exactly as described before.[17] The method uses

known equations that relate logP values for a number of water-solvent partitions to compound descriptors, via eq.(7). Then if logP values for partition between water and various solvents are known for a given compound or substructure, the descriptors π^H_2, $\Sigma\alpha^H_2$, and $\Sigma\beta^H_2$ can be obtained through solution of a set of simultaneous equations. Note that R_2 and Vx can always be obtained by simple addition. The entire list of descriptors for substructures of the Y-M molecules will be available. [18] The advantage of this procedure is that descriptors can be obtained for potential drug molecules without the necessity of synthesising the drug molecules themselves. All that is needed is information on fragments, or substructures, much of which is already available.

For 22 of the Y-M compounds, we obtained the equation:

$$\log BB = 0.09 + 0.26\, R_2 - 0.97\, \pi^H_2 - 0.71\, \Sigma\alpha^H_2 - 0.76\, \Sigma\beta^H_2 + 1.19\, Vx \qquad (8)$$

$$n = 22 \quad \rho = 0.942 \quad sd = 0.27 \quad F = 25.0$$

The set of Y-M compounds covers a wide range of groups and substructures, as can be seen by the five examples given in the Scheme, so that the range in the descriptors is quite large. Thus R_2 varies by 1.66, π^H_2 by 2.39, $\Sigma\alpha^H_2$ by 1.46, $\Sigma\beta^H_2$ by 1.98 and V_x by 1.86 units.

However, we can greatly increase the range of most of the descriptors, and construct a very general equation indeed, by the incorporation of 35 smaller compounds listed by Abraham and Weathersby.[10] These include, rare gases, aliphatic hydrocarbons, ethers, ketones and alcohols, halogenated anesthetics, and aromatic hydrocarbons. The effect of this is that now R_2 varies by 2.69, π^H_2 by 3.39, $\Sigma\alpha^H_2$ still by 1.46, $\Sigma\beta^H_2$ by 2.78, and V_x by no less than 3.18 units in $(cm^3\ mol^{-1})/100$. The latter is rather important because the combined set of 57 compounds extends from helium, of molecular weight 4, to Y-M compound 5 of molecular weight 414, and is thus extraordinarily varied in terms of functional group, size, and molecular weight.

The final equation for the total data set is,

$$\log BB = 0.04 + 0.20\, R_2 - 0.69\, \pi^H_2 - 0.72\, \Sigma\alpha^H_2 - 0.70\, \Sigma\beta^H_2 + 1.00\, Vx \qquad (9)$$

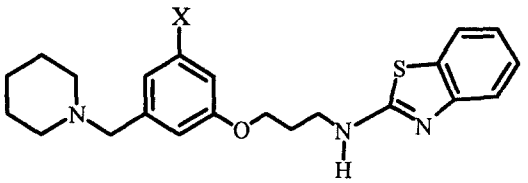
$$n = 57 \quad \rho = 0.952 \quad sd = 0.20 \quad F = 99.2$$

Not only does eq.(9) reproduce logBB values to within 0.20 log units, probably close to the experimental error, and has a near-zero intercept, but it shows exactly the factors that influence blood-brain distribution. Solute excess molar refraction (weakly) and solute size (strongly) increase logBB, whereas solute dipolarity/polarisability, hydrogen-bond acidity, and hydrogen-bond basicity all reduce values of logBB. Brain is therefore more lipophilic than blood, but the latter is more dipolar, more basic and more acidic than is brain; this is as suggested by Abraham and Weathersby, [10] on other grounds. Through eq.(9) it is possible to design drugs with a particular required logBB value, by the summation of substructure fragments as shown above.

Table 1. Solute Descriptors for Y-M [5] molecules.

Compound Description	R_2	π^H_2	$\Sigma\alpha^H_2$	$\Sigma\beta^H_2$	Vx
Y-M Compound 1	1.700	1.730	0.670	2.210	1.956
Y-M Compound 2	1.305	1.000	0.750	0.800	1.138
Y-M Compound 5	2.960	3.390	0.600	2.780	3.178
Y-M Compound 7	1.819	1.920	0.000	1.590	2.387
Y-M Compound 8	1.480	1.750	0.000	1.190	2.402
Y-M Compound 10	2.305	1.980	1.180	2.230	2.276
Y-M Compound 15	2.360	2.360	0.400	1.490	2.179
Y-M Compound 16	2.070	2.160	0.400	1.690	2.004
Y-M Compound 17	2.671	2.680	0.400	1.830	2.753
Y-M Compound 19	1.906	1.520	0.750	0.940	1.605
Y-M Compound 20	2.245	1.950	0.987	1.250	1.705
Y-M Compound 22	2.776	2.920	1.250	1.610	2.002
Y-M Compound 23	2.845	2.550	1.460	2.150	2.298
Y-M Compound 26	2.321	2.250	0.460	1.670	2.409
Y-M Compound 29	2.591	2.510	0.460	2.140	2.548
Y-M Compound 30	1.409	2.400	0.400	1.650	2.432
Y-M Compound 31	2.009	2.540	0.358	1.660	2.899
Y-M Compound 34	1.255	1.520	0.373	1.410	2.093
Y-M Compound 36	1.989	2.300	0.260	1.380	2.701
Y-M Compound 37	2.159	2.340	0.400	1.530	2.626
Y-M Compound 41	2.689	2.640	0.400	1.380	2.995
Y-M Compound 42	2.694	2.690	0.400	1.400	2.890

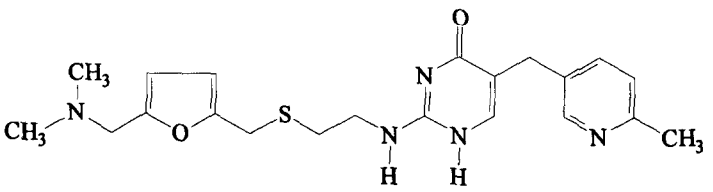
A number of derivatives of the brain penetrating H_2-receptor antagonist *zolantidine* (I) are given in Table 2, as examples of the prediction of logBB values. An alkyl group will lead to a small increase in logBB, a methoxy group will give rise to a small decrease because the increased dipolarity and basicity only just offset the effect of increased volume, and strongly hydrogen-bonding substituents such as OH and NH_2 considerably decrease the value of logBB. In some cases, it is not necessary to sum substructure descriptor values for the entire compound. Thus the effect of the shown *zolantidine* substituents on logBB values can be obtained simply from the effect of aromatic substituents on the descriptors for the 3-substituted anisole substructure. A knowledge of descriptors for 3-substituted anisoles is all that is needed to predict the effect of the substituents on logBB values, as compared to that for *zolantidine* itself.



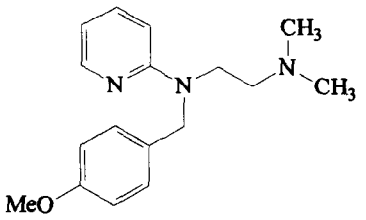
I (X=H, *zolantidine*)

Scheme. Examples of the Young-Mitchell (Y-M) Set of Compounds.

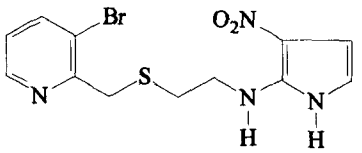
Compound 5



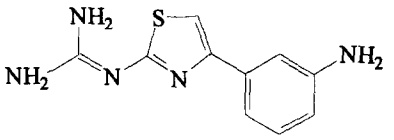
Compound 7



Compound 15



Compound 20



Compound 42

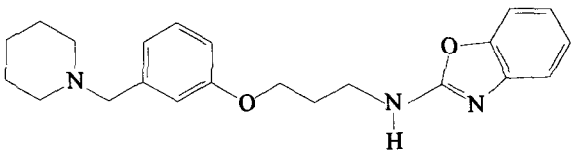


Table 2. The predicted effect on logBB of a substituent in the phenoxy group of *zolantidine* (I).

X	R_2	π^H_2	$\Sigma\alpha^H_2$	$\Sigma\beta^H_2$	Vx	$logBB_{(calc)}$
H	2.69	2.64	0.40	1.38	2.9946	0.42
Me	2.69	2.67	0.40	1.39	3.1355	0.53
Et	2.69	2.67	0.40	1.39	3.2764	0.67
Cl	2.81	2.75	0.40	1.31	3.1170	0.54
OMe	2.80	2.90	0.40	1.54	3.1942	0.35
OH	2.82	3.06	0.99	1.48	3.0533	-0.28
NH_2	3.01	3.11	0.65	1.64	3.0944	-0.11

Of course we recognise that the 57 compounds used to construct eq.(9) constitutes a training set, and that examination of test compounds is necessary to validate the equation. This we have done. For example, Young, Ganellin et al.[19] have determined a value of -0.06 for logBB for 2(β-dimethylaminoethyl)pyridine. This compares with the calculated value of -0.01 through eq.(9).

Thus for the first time an equation has been derived that shows exactly the factors influencing blood-brain distribution, and which can be used to predict logBB values for potential drug molecules without the necessity of synthesis.

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