Prediction of Distribution of Neutral, Acidic and Basic Structurally Diverse Compounds Between Blood and Brain by the Nonlinear Methodology

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Abstract: The methodology for predicting the distribution of compounds between Blood and Brain, i.e. their brain/blood partition coefficients (logBB values), was studied using a nonlinear regression analysis in this work. The equations were established on the basis of the different states (neutral, cationic and anionic) of the compounds distributing into the three dominating composition (lipid, protein and water) of the brain. The equations bear strong fitting and predictive power for the distribution of compounds (total set: n=160, r=0.906, s=0.326; training set: n=139, r=0.908, s=0.320; testing set: n=21, r=0.903, s=0.297), and can describe the distribution of the different states of the compounds in three compositions of brain. The compounds in the dataset contained many different types, such as drug molecules, small structure-simple molecules, carboxylic acids and also alkaloids. Therefore the equations were very useful and instructional for the prediction of the compound distribution into the brain and blood. Finally, the percentages of the amount of a compound in lipid, protein and water in brain were calculated using the model, such subdivision will be very useful in drug research and discovery. By an analysis of the percentages a conclusion can be obtained that a well distributed drug is mainly affected by distribution of lipid and protein.

Key Words: logBB, nonlinear regression analysis, QSAR model, correlation coefficients, absorption, distribution, blood-brain barrier, pKa, weight fraction.

INTRODUCTION

Brain/blood partition coefficient logBB, the logarithm of the ratio of equilibrium concentrations of the compounds in the brain and blood, log (C_{brain}/C_{blood}), is very significative in drug design. In recent years the combinatorial chemistry and high-throughput screening (HTS) technology have largely enhanced the speed of the development of drug candidates. However, the bottleneck problem in drug distribution into human body turns to be more and more critical. It has been pointed out that more than 40% drug candidates were eliminated owing to their poor properties in absorption, distribution, metabolism, excretion (ADME) [1-5]. In addition, prediction of brain distribution by *in vivo* and *in vitro* methods are experimentally laborious, this is time-consuming, and expensive, since it involves the direct measurement of the drug concentration in the brain and blood of laboratory animals, and requires the synthesis of the pure compounds, often in radioactively-labeled form to obtain reliable experimental data. Obviously to establish convenient and fast computational methodology for brain/blood distribution has been becoming necessary and important.

Plenty of new work has been done during recent years. Young *et al.* [6] made a equation with logBB and ΔlogP for 20 structure-diverse histamine H_2 receptor antagonists.

$$\log BB=-0.485(\pm 0.160)\ \Delta\log P+0.889(\pm 0.500) \quad (1)$$

n=20, r=0.831, s=0.439, F=40.23

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Here ΔlogP is defined as the difference between $\log P_{oct}$ and $\log P_{cyclo}$, which are the 1-octanol/water and cyclohexane/water partition coefficient respectively.

Kansy and van de Waterbeemd [7] cited the same 20 compounds to establish another important regression equation using the polar surface area and also the molecular volume. This was the first purely computational approach to logBB prediction without any experimental parameters .

$$\log BB=-0.021(\pm 0.003)PSA-0.003(\pm 0.001)Mol\_Vol+1.643\ (\pm 0.465) \quad (2)$$

n=20, r=0.835, s=0.448, F=19.5

This model avoided the necessary of any experimentally determined parameters. However, other research proved that this model showed poor predictive power for other compounds that outside the training set [8].

Lombardo *et al.* [9] used conformation analysis and semi-empirical quantum chemical calculation method to establish a simple model for 57 compounds, two of which were deleted as outliers:

$$\log BB=0.054(\pm 0.005)\ \Delta G^{o}_{w}+0.43(\pm 0.07) \quad (3)$$

n=55, r=0.82, s=0.41, F=108.3

Here ΔG^{o}_{w} is the computed free energy of solvation of a compound in water.

Kimberly Rose *et al.* [10] did regression analyses for logBB and hydrogen bond parameters using E-state hydrogen bond descriptors and got good models(n=102, r=0.812, s=0.45, F=62.4). Four molecules were omitted.

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In the series work of M.H. Abraham *et al.* [11], they established a model as follow:

$$SP = c + e.E + s.S + a.A + b.B + v.V \quad (4)$$

Here SP is a set of solute properties such as logBB values**,** E is an excess molar refraction, S is the dipolarity/polarisability, A and B are the hydrogen-bond acidity and basicity respectively, V is the solute McGowan volume in units of ($cm^3mol^{-1}/100$). There were 157 compounds in their dataset, after omitting nine outliers of them, an equation was obtained, whose r value was 0.843, the s value was 0.367 and the F value was 71. In succession they used another indicator variable I_1, which was set to be 1 for a compound containing carboxylic acid fragment and 0 otherwise. Since the intercorrelations of the descriptors E, S, B, and V were large, they re-established the equation with principal component regression. Five principal components were found to be significant and then were transformed back into E, S, A, B, and V. Finally they obtained following equation:

$$\log BB = 0.062 + 0.469E - 0.864S - 0.586A - 0.713B + 0.895V - 0.564I_1 \quad (5)$$

n=148, r=0.863, s=0.342, F=83

Model (4) was also use to calculate the PS value, which was the permeability-surface area product expressing the rate of transfer from saline or blood to brain in units of $cm^3s^{-1}g^{-1}$. The equations were as follows [12]:

$$\log PS = -0.639(\pm 0.408) + 0.312(\pm 0.515)E - 1.009(\pm 0.158)S - 1.895(\pm 0.385)A - 1.636(\pm 0.410)B + 1.709(\pm 0.392)V \quad (6)$$

n = 30, r = 0.933, s = 0.52, F = 32.2

$$\log PS = -0.716(\pm 0.383) - 0.974(\pm 0.146)S - 1.802(\pm 0.349)A - 1.603(\pm 0.401)B + 1.893(\pm 0.245)V \quad (7)$$

n = 30, r = 0.932, s = 0.52, F = 41.2

Abraham also pointed out that the molecular size would benefit the permeation rate, whereas dipolarity/polarizability, hydrogen bond acidity and hydrogen bond basicity decreased the rate. The 30 data were all neutral molecules, for there seemed to be difficulties for acids and bases which would partially ionized at pH 7.4, because it was not possible to assess the rate of permeation of the resulting ionic species with respect to the neutral species [12].

T. J. Hou *et al.* [13] made use of the high-charged polar surface area (*HCPSA*) and established following equation:

$$\log BB = 0.589 - 0.0177HCPSA \quad (8)$$

n=78, r=0.779, s=0.468, F=117.4

After introduced logP values and the molecular weight factors, the equation was further improved:

$$\log BB = 0.00845 + 0.197\log P - 0.0135HCPSA - 0.014 <MW\text{-}360> \quad (9)$$

n=78, r=0.876, s=0.364, F=81.5

For studying the influence of the molecular weight, they first introduced the parameter <*MW-a*>, when the molecular weight was larger than *a*, the <*MW-a*> value was the difference, and when the molecular weight was less than *a*, the <*MW-a*> value was fixed to be zero. And then a systematical search was used to change *a* from 100 to 400 using a step of 10. Finally they determined that the parameter <*MW-360*> was the best one.

Our previous work had also made progress in prediction of logBB [14,15,16]. Different from above studies, our work made use of nonlinear equations, which would be listed in detail as follow, and the most important, the equations not only could give results of logBB prediction, but also could express the distribution of the compounds into the three predominant tissue compositions, lipid, protein and water. Also, the equations took into account of the three states of compounds (neutral, cationic and anionic) owing to the alkalescence of the blood in the particular human body surroundings and its pH value is approximately to 7.4, which offered detailed and useful information for logBB prediction. However, the molecules used for the dataset were a little simple and structural-unitary, and there were only cationic compounds for ionic forms, or the compounds were all big and complex, the dataset indeed needs to be combined and expanded, and our previous studies were about tissue/blood partition coefficients of seven human tissues. So we reinforced to give more reliable prediction models of the individual tissue such as brain/blood.

Same to our previous work, this work referred to all the three states of the compounds that probably existed in human brain: neutral, cationic and anionic. Types of compounds were extended and many diverse molecules of different series were introduced, also the most improvement was the method to search the lowest energy conformation for each compound. We used the systematic search method. The calculated descriptors that relied on the structure were had a little difference compared with our previous work. These descriptors were used to develop a new nonlinear predicting model. The factors that influenced the different states distributing in different composition of the brain were displayed. Compared with earlier computational models of logBB which described above, the correlation coefficients we made were much higher in despite of the similar descriptors we used. We established on the basis of the different states (neutral, cationic and anionic) of the compounds distributing into the three dominating composition (lipid, protein and water) of the brain, this could describe the molecules absorption and distribution more truly or much more approach to the reality. This model would give important and significant theoretical guidance for the new drug design. the percentages of the amount of a compound in lipid,protein and water in brain were calculated in this work. We had a conclusion that a well distributed drug is mainly affected by distribution of lipid and protein.

MATERIALS AND METHODS

Brain/Blood Partition Coefficient

The brain/blood partition coefficients logBB were taken from several references [10, 14-18]. The molecular structures and the pKa values were looked up with the program Scifinder Scholar (Version 2006) offered by American Chemical Society, the values on the program were calculated using

Advanced Chemistry Development (ACD/Labs) Software V8.19 for Solaris (1994-2006 ACD/Labs). Some researches had shown that tissue/blood partition coefficients of human, rat and rabbit were compatible and were often used in regression analysis together since their weight fractions are basically identical in the same tissues [15,17,19,20].

Nonlinear Model

The methodology was deduced in our previous work [14, 15, 16]:

$$\log PC_t=\log(f_{(ui)}(10^{(\log Tl(ui)+\log wl)}+10^{(\log Tp(ui)+\log wp)}+10^{(\log Tw(ui)+\log ww)})+f_{(+)}(10^{(\log Tl(+)+\log wl)}+10^{(\log Tp(+)+\log wp)}+10^{(\log Tw(+)+\log ww)})+f_{(-)}(10^{(\log Tl(-)+\log wl)}+10^{(\log Tp(-)+\log wp)}+10^{(\log Tw(-)+\log ww)})) \quad (10)$$

$$\log T_{l(ui)} = a_{1(ui)}X_{1(ui)} + a_{2(ui)}X_{2(ui)} + ... + a_{0(ui)}$$

$$\log T_{p(ui)} = b_{1(ui)}X_{1(ui)} + b_{2(ui)}X_{2(ui)} + ... + b_{0(ui)}$$

$$\log T_{w(-)} = c_{1(-)}X_{1(-)} + c_{2(-)}X_{2(-)} + ... + c_{0(-)}$$

$$\log T_{l(+)} = a_{1(+)}X_{1(+)} + a_{2(+)}X_{2(+)} + ... + a_{0(+)}$$

$$\log T_{p(+)} = b_{1(+)}X_{1(+)} + b_{2(+)}X_{2(+)} + ... + b_{0(+)}$$

$$\log T_{w(+)} = c_{1(+)}X_{1(+)} + c_{2(+)}X_{2(+)} + ... + c_{0(+)}$$

$$\log T_{l(-)} = a_{1(-)}X_{1(-)} + a_{2(-)}X_{2(-)} + ... + a_{0(-)}$$

$$\log T_{p(-)} = b_{1(-)}X_{1(-)} + b_{2(-)}X_{2(-)} + ... + b_{0(-)}$$

$$\log T_{w(-)} = c_1.C_{1(-)} + c_{2(-)}X_{2(-)} + ... + c_{0(-)}$$

Here subscripts l, p, w indicate lipid, protein and water in tissue respectively; w_l, w_p and w_w are the weight fractions of lipid, protein and water respectively; subscripts ui, +, - indicate neutral form, cationic form and anionic form of a compound respectively. PC_t is the tissue /blood (or plasma) partition coefficient, T is the tissue /blood (or plasma) partition coefficient of the different states of compounds (neutral molecule, cation and anion) in each tissue composition (lipid, protein and water), X are descriptors and a, b, c are regression coefficients. The symbols and their description are listed in Table **1**.

For the prediction of brain/blood coefficient, w_l, w_p and w_w turn to be constant, so $\log w_l$, $\log w_p$, and $\log w_w$ can be combined into $\log T_l$, $\log T_p$, and $\log T_w$, respectively. Meanwhile, since the particular structure of brain tissue, there may not be that many sub-equations, i.e., some of them may disappear because of the much too feeble effect, which will be recounted in detail.

Computational Methodologies

All of the molecules' structures in both the training and testing sets were built on Sybyl 7.0. Minimization was performed using the Tripos force field and the conjugate gradient method. The obtained structure was subjected to a systematic search method. The rotatable bonds in 10^0 increments from $0^0$to 359^0 and rotatable rings in default parameters. Energies of the conformation were computed and the 10 lowest energy structures were obtained. Every conformer was re-optimized with AM1 method, a semi-empirical method. Then the conformer of the lowest energy for every molecule was selected to be the final structure. After all of these, all the physicochemical parameters were computed and collected either from the log documents or fast calculating using the QSAR properties item of the Hyperchem 7.0. The calculation of solvation free energies (ΔGw) for all of the molecules were performed using the AMSOL 6.8 program. The solvation free energies in water were computed with the AM1-SM 5.4A solvation model [16]. Parameters for describing the cationic and anionic forms of the compounds were also obtained by the methods mentioned above. The com-

Table 1. The Symbols and Descriptors in Equations and Their Description

Symbol	Description	Descriptor	Description
$\log T_{l(ui)}$	neutral form partitioning into lipid	$\Delta Gw_{(ui)}$	free energies of salvation of neutral form
$\log T_{p(ui)}$	neutral form partitioning into protein	$<M\text{-}360>_{(ui)}$	The indicator variable of molecular weight of neutral form
$\log T_{w(ui)}$	neutral form partitioning into water	$MR_{(ui)}$	molecular refraction of neutral form
$\log T_{l(+)}$	cationic form partitioning into lipid	$Q^{-max}{}_{(ui)}$	the maximum negative atomic charge of neutral form
$\log T_{p(+)}$	cationic form partitioning into protein	$\log P_{(ui)}$	lipid-water partition coefficient of neutral form
$\log T_{w(+)}$	cationic form partitioning into water	$\mu_{(ui)}$	dipole moment of neutral form
$\log T_{l(-)}$	anionic form partitioning into lipid	$V_{(ui)}$	molecular volume of neutral form
$\log T_{p(-)}$	anionic form partitioning into protein	$\log P_{(+)}$	lipid-water partition coefficient of cationic form
$\log T_{w(-)}$	anionic form partitioning into water	$\Delta Gw_{(+)}$	free energies of salvation of cationic form
		$<M\text{-}360>_{(+)}$	the indicator variable of molecular weight of cationic form
		$\Sigma Q^{-}{}_{(+)}$	the sum of all negative atomic charges of cationic form
		$\mu_{(-)}$	dipole moment of anionic form
		$\log P_{(-)}$	lipid-water partition coefficient of anionic form

puter time of several minutes was usually taken for a typical drug sized molecule to obtain the 3D descriptors

Physicochemical Descriptors and Methods

In the regression analysis, several physicochemical descriptors which could be easily obtained from Hyperchem 7.0 were used. These referred parameters were the maximum negative atomic charge (Q^{-max}), the maximum positive atomic charge (Q^{+max}), the sum of all negative atomic charges (ΣQ^-) , the sum of all positive atomic charges (ΣQ^+), and the dipole moment (μ), the energy of the lowest unoccupied molecular orbital (E_{lumo}), the highest occupied molecular orbit (E_{homo}), which obtained from the log documents of every molecules, in addition, molecular polarization (MP), molecular volume (V), molecular refraction (MR), the lipid-water partition coefficient logP calculating by Hyperchem7.0 and also the solvation free energies (ΔG_w) of the compounds. Also the indicator variable of molecular weight <*MW-360*>which Hou *et al.* established was used in this work [13]. When the molecular weight was larger than 360, the <*MW-360*> value was the difference, and when the molecular weight was less than 360, the <*MW-360*> value was fixed to be zero. The descriptors and their description are listed in Table **1**.

The fractions of neutral and ionized compounds were calculated at pH7.4 using the following formula [15, 21]:

For the basic molecules, $f_{ui}=1/(1+10^{pKa-7.4})$, $f_+=1-f_{ui}$;

and for acidic molecules, $f_{ui}=1/(1+10^{7.4-pKa})$, $f_-= 1-f_{ui}$

Nonlinear regression analyses were performed using a standard regression program (GFA BASIC 4.38). In the regression equations *n* is the number of data points considered, r is the correlation coefficient, *s* is the standard error of the estimate, F is the Fisher value, Q is the cross validated correlation coefficient derived from the predictive residual sum of squares (PRESS, leave-one-out method). Regression coefficients are given with their 95% confidence intervals.

RESULTS AND DISCUSSION

Totally there were 168 compounds in the dataset, unfortunately eight outliers that the residuals between the calculated and exprimental values were bigger than 1 were omitted. They were 2,4-Dichlorophenoxyacetic acid, Bromperidol, Fluphenazine, Haloperidol, Org12962, BBcpd11, BBcpd10 and Trifluoroperazine , of which BBcpd11 were also omitted by Rose *et al.* [10], also Fluphenazine and Org12962 were omitted by Platts, J.A. *et al.* [11]. In addition, there were also several molecules which were omitted by other researchers reversely had excellent results in our work. They suggested that such outliers might be caused by factors such as inaccurate data due to experimental difficulties or metabolic effects not accounted for in log BB measurement [22].

All the physicochemical parameters referred above, such as Q^{-max}, Q^{+max}, ΣQ^-, ΣQ^+, μ, E_{lumo}, E_{homo} , MP, V, MR, logP, ΔG_w and M, were taken into the regression in a stepwise manner until the statistical result can't be further improved.

An initial regression of all 160 log BB values with the following descriptors showed a reasonably accurate fit, The other coefficients had little change when we increased or deleted any of the descriptors. These show the following equations were very robust. The sub-equations for the different components were obtained through comparing with the equations in our previous work [16].

$$\log BB = \log(f_{(ui)}(10^{\log T_{l(ui)}} + 10^{\log T_{p(ui)}} + 10^{\log T_{w(ui)}}) + f_{(+)} (10^{\log T_{l(+)}} + 10^{\log T_{p(+)}}) + f_{(-)}(10^{\log T_{l(-)}} + 10^{\log T_{w(-)}})) \quad (11)$$

$$\log T_{l\ (ui)} = 0.055(\pm 0.016)\ \Delta Gw_{(ui)} - 0.043(\pm 0.028)\langle M\text{-}360\rangle_{(ui)} + 0.018(\pm 0.005)MR_{(ui)} + 1.242(\pm 0.833)\ Q^{-max}{}_{(ui)} \quad (11\text{-}1)$$

$$\log T_{p(ui)} = 0.220(\pm 0.113)\log P_{(ui)} - 0.753(\pm 0.344)\mu_{(ui)} \quad (11\text{-}2)$$

$$\log T_{w(ui)} = -0.0018(\pm 0.0004)V_{(ui)} \quad (11\text{-}3)$$

$$\log T_{l(+)} = 0.360(\pm 0.138)\log P_{(+)} + 0.026(\pm 0.013)\Delta Gw_{(+)} - 0.019(\pm 0.009)\langle M\text{-}360\rangle_{(+)} + 1.261(\pm 0.949) \quad (11\text{-}4)$$

$$\log T_{p(+)} = 0.267(\pm 0.068)\Sigma Q^-{}_{(+)} \quad (11\text{-}5)$$

$$\log T_{l(-)} = -0.069(\pm 0.015)\mu_{(-)} \quad (11\text{-}6)$$

$$\log T_{w(-)} = -0.586(\pm 0.254)\log P_{(-)} \quad (11\text{-}7)$$

n=160, r=0.906, s=0.326, F=47.96, Q=0.885

Then the 160 compounds were randomly divided into two data sets: 139 in the training set and 21 in the testing set. Finally the following equations were obtained, both training set and testing set obtained satisfactory results.

$$\log BB = \log(f_{(ui)}(10^{\log T_{l(ui)}} + 10^{\log T_{p(ui)}} + 10^{\log T_{w(ui)}}) + f_{(+)} (10^{\log T_{l(+)}} + 10^{\log T_{p(+)}}) + f_{(-)}(10^{\log T_{l(-)}} + 10^{\log T_{w(-)}})) \quad (12)$$

$$\log T_{l(ui)} = 0.056(\pm 0.019)\ \Delta Gw_{(ui)} - 0.042(\pm 0.030)\langle M\text{-}360\rangle_{(ui)} + 0.018(\pm 0.006)MR_{(ui)} + 1.248(\pm 0.880)\ Q^{-max}{}_{(ui)} \quad (12\text{-}1)$$

$$\log T_{p(ui)} = 0.223(\pm 0.117)\log P_{(ui)} - 0.760(\pm 0.348)\mu_{(ui)} \quad (12\text{-}2)$$

$$\log T_{w(ui)} = -0.0017(\pm 0.0004)V_{(ui)} \quad (12\text{-}3)$$

$$\log T_{l(+)} = 0.353(\pm 0.142)\log P_{(+)} + 0.029(\pm 0.015)\Delta Gw_{(+)} - 0.018(\pm 0.009)\langle M\text{-}360\rangle_{(+)} + 1.409(\pm 1.022) \quad (12\text{-}4)$$

$$\log T_{p(+)} = 0.262(\pm 0.068)\Sigma Q^-{}_{(+)} \quad (12\text{-}5)$$

$$\log T_{l(-)} = -0.066(\pm 0.014)\mu_{(-)} \quad (12\text{-}6)$$

$$\log T_{w(-)} = -0.653(\pm 0.327)\log P_{(-)} \quad (12\text{-}7)$$

n=139, r=0.908, s=0.320, F=41.82, Q=0.883

Some relevant correlation matrixes with acceptable descriptor inter-correlation coefficient are presented in Table **1**, the calculated and experimental logBB values see Table **2** and the physicochemical parameters see Table **3**.

The percentages of the amount of a compound in lipid, protein and water in brain were calculated using the equations above. The different states of the compounds distributed into the same composition of the brain that multiplied with the fractions of neutral and ionized compounds respectively were added and the percentages were calculated. The calculated values also were presented in Table **3**.

Table 2. Some Correlation Matrixes (r-value) between Descriptors in Eqs 12

Neutral

	$logP_{(ui)}$
$\mu_{(ui)}$	-0.295

	$\Delta Gw_{(ui)}$	$<M\text{-}360>_{(ui)}$	$MR_{(ui)}$	$Q^{-max}{}_{(ui)}$
$\Delta Gw_{(ui)}$	1			
$<M\text{-}360>_{(ui)}$	-0.234	1		
$MR_{(ui)}$	-0.391	0.542	1	
$Q^{-max}{}_{(ui)}$	0.298	-0.078	-0.305	1

Cationic

	$logP_{(+)}$	$\Delta Gw_{(+)}$	$<M\text{-}360>_{(+)}$
$logP_{(+)}$	1		
$\Delta Gw_{(+)}$	0.154	1	
$<M\text{-}360>_{(+)}$	0.092	-0.260	1

Table 3. Calculated logBB Values and Experimental logBB Values of the Compounds and Calculated Percentages of the Amount of a Compound in Lipid, Protein and Water in Brain

NO	Name	logBB (calc.)	logBB (exp.)	Lipid %	Protein%	Water%	NO	Name	logBB (calc.)	logBB (exp.)	Lipid %	Protein%	Water %
1	1-Butanol	-0.077	-0.210	59.943	9.828	30.229	85	Lupitidine	-1.072	-1.060	0.464	98.490	1.046
2	5-Butyl barbitones	-0.039	0.176	79.245	13.611	7.144	86	Promazine	0.544	1.230	93.705	6.286	0.009
3	5-Ethyl barbitones	-0.151	-0.137	71.860	12.436	15.704	87	Physostigmine[d]	0.147	0.079	85.024	14.700	0.276
4	5-Heptyl barbitones	0.186	0.000	83.233	14.634	2.133	88	Nevirapine	-0.113	0.000	89.020	4.961	6.019
5	5-Methyl barbitones	-0.199	-0.222	64.674	12.537	22.789	89	Thioperamide	-0.340	-0.160	85.860	9.041	5.098
6	5-Octyl barbitones	0.265	0.230	83.687	14.892	1.421	90	BBcpd13	-0.548	-0.660	83.171	0.092	16.736
7	5-Pentyl barbitones	0.036	0.079	81.199	13.991	4.810	91	BBcpd16	-0.700	-1.570	14.947	83.214	1.839
8	5-Propyl barbitones	-0.098	0.079	76.831	12.539	10.631	92	BBcpd60	-1.111	-0.730	1.953	96.869	1.178
9	9-Hydroxy risperidone	-1.010	-0.670	13.643	83.619	2.738	93	SKF101468	0.086	-0.300	83.955	16.022	0.022
10	Alfentanil[d]	-0.669	-0.886	72.381	26.025	1.594	94	Zidovudine	-1.235	-0.720	0.083	2.939	96.977
11	Biperiden[d]	1.062	0.845	98.772	1.227	0.001	95	Chlorambucil[d]	-1.461	-1.700	95.291	3.605	1.104

(Table 3. Contd….)

NO	Name	logBB (calc.)	logBB (exp.)	Lipid %	Protein%	Water%	NO	Name	logBB (calc.)	logBB (exp.)	Lipid %	Protein%	Water %
12	2-chloro-1,1-difluoroethyl-ene	0.253	0.100	66.109	14.137	19.753	96	BBcpd22	0.253	-0.020	86.581	13.352	0.067
13	Clomipramine	0.978	1.025	97.363	2.635	0.002	97	Carba-mazepine[d]	-0.062	-0.140	91.696	0.914	7.390
14	Clotiazepam	0.455	0.505	98.835	0.027	1.138	98	Cimetidine[d]	-0.752	-1.420	25.548	55.018	19.433
15	Clozapine	0.621	1.301	97.076	2.525	0.399	99	BBcpd57	-0.728	-1.150	49.020	15.911	35.069
16	Cotinine	-0.286	-0.377	69.984	9.969	20.047	100	Pentobarbital[d]	0.033	0.120	84.946	9.919	5.135
17	Cyclohexane	0.769	0.920	38.343	57.842	3.815	101	SB-222200	0.116	0.300	90.816	8.347	0.837
18	Cyclopropane	0.512	0.000	31.634	56.682	11.684	102	BBcpd15	-0.404	-0.180	33.213	62.844	3.943
19	Dichloro-methane	0.204	-0.110	68.686	8.143	23.171	103	Ibuprofen[d]	-1.012	-0.180	99.217	0.334	0.449
20	Divinyl ether	0.078	0.110	71.129	5.503	23.368	104	Clonidine[d]	0.024	0.110	37.745	60.921	1.334
21	Domperidone	-0.943	-0.780	12.181	87.606	0.212	105	Y-G19	-0.371	-0.430	30.637	68.512	0.851
22	Ethoxyben-zamide	-0.295	-0.009	77.159	0.071	22.771	106	Antipyrine[d]	-0.034	-0.097	90.071	0.068	9.860
23	Fentanyl[d]	0.717	0.556	97.413	2.581	0.006	107	Theophylline	0.003	-0.290	12.984	0.136	86.879
24	Glycyrrhetinic acid	-1.562	-1.398	99.933	0.000	0.066	108	Acetylsalicylic acid[d]	-0.484	-0.500	94.389	0.000	5.611
25	Inaperisone	0.835	1.079	96.020	3.977	0.003	109	Y-G20	-0.301	0.250	8.681	90.908	0.411
26	Methoxyflu-rane[d]	0.158	0.250	72.945	12.836	14.219	110	BCNU	-0.102	-0.520	83.596	3.460	12.944
27	Mianserin	0.832	0.990	90.808	9.117	0.075	111	Icotidine	-1.609	-2.000	43.183	10.770	46.046
28	Miloxacin	-0.623	-0.921	39.906	0.003	60.091	112	Y-G15	0.177	-0.060	70.091	29.713	0.196
29	Mirtazapine	0.660	0.530	92.985	6.860	0.155	113	p-acetamidophenol	-0.508	-0.310	54.874	0.171	44.955
30	Nalidixic acid	-0.979	-0.658	66.605	0.000	33.395	114	Enflurane[d]	0.114	0.240	61.777	21.833	16.390
31	Nicotine	0.033	0.322	63.950	34.098	1.952	115	Isoflurane	-0.017	0.420	75.879	1.647	22.474
32	Nitrazepam[d]	0.078	0.322	93.060	2.864	4.076	116	Y-G14	0.050	-0.420	56.629	43.320	0.052
33	Org13011	0.287	0.160	94.724	4.529	0.747	117	Valproic acid	-0.519	-0.220	99.126	0.002	0.872
34	Org32104	0.094	0.520	80.860	19.124	0.016	118	Salicylic acid	-0.655	-1.100	94.035	0.000	5.965
35	Org34167	0.070	0.000	73.062	26.873	0.065	119	Fluroxene	0.042	0.130	78.500	0.391	21.109
36	Org4428	0.467	0.820	92.667	7.297	0.037	120	Y-G16	-0.344	-0.420	12.147	85.153	2.700
37	Org5222	0.506	1.030	89.557	10.434	0.009	121	Bishydroxy L-663,581	-1.739	-1.820	5.131	0.477	94.392
38	Pentazocine[d]	1.091	0.637	98.292	1.701	0.007	122	Heptane	0.920	0.810	33.966	64.266	1.767
39	Phenytoin[d]	0.096	-0.040	94.943	0.828	4.229	123	3-Methylhexane	0.910	0.900	35.243	62.836	1.921
40	Pipemidic acid	-0.904	-1.000	28.583	0.000	71.417	124	Teflurane	0.282	0.270	79.376	5.879	14.746
41	p-phenylbenzoic acid	-1.173	-1.260	98.865	0.039	1.095	125	Toluene	0.628	0.370	40.946	53.856	5.198

(Table 3. Contd….)

NO	Name	logBB (calc.)	logBB (exp.)	Lipid %	Protein%	Water%	NO	Name	logBB (calc.)	logBB (exp.)	Lipid %	Protein%	Water %
42	Prednisolone[d]	0.249	-0.319	97.992	0.654	1.354	126	Halothane	0.266	0.350	79.209	7.210	13.581
43	Propofol	0.587	0.914	76.160	21.744	2.095	127	Sulphur hex-afluoride	0.573	0.360	12.789	76.981	10.230
44	Risperidone	-0.573	-0.020	63.810	35.218	0.972	128	Benzene	0.677	0.370	34.023	60.280	5.697
45	S-Etodolac	-1.112	-1.337	87.235	0.095	12.670	129	2,2-Dimethylbutane	0.833	1.040	34.051	62.985	2.964
46	Sevoflurane	0.097	0.340	82.797	1.317	15.886	130	Methylcyclo-pentane	0.723	0.930	37.581	58.286	4.133
47	Tibolone	0.799	0.400	99.512	0.070	0.418	131	2-Methylpentane	0.824	0.970	34.736	62.427	2.837
48	Tolbutamide[d]	-0.404	-1.013	92.228	0.001	7.772	132	3-Methylpentane	0.822	1.010	34.792	62.244	2.964
49	Trichloromethane	0.362	0.290	73.260	13.179	13.561	133	1,1,1-Trifluoro-2-chloroethane	0.143	0.080	73.062	4.049	22.890
50	Trihexyphenidyl	1.255	1.326	99.165	0.835	0.000	134	Butanone	-0.122	-0.080	62.106	1.633	36.261
51	Indinavir	-0.729	-0.745	0.000	99.403	0.597	135	Diethylether	0.115	0.000	68.925	12.427	18.649
52	Temelastine	-1.876	-1.880	6.029	20.363	73.609	136	Pentane	0.751	0.760	32.859	63.138	4.003
53	2-Propanol	-0.079	-0.150	54.046	7.998	37.956	137	1,1,1-Trichloroethane	0.206	0.400	75.626	8.374	16.000
54	2-Propanone	-0.160	-0.150	50.067	1.062	48.872	138	Trichloroethene	0.404	0.340	65.388	23.866	10.746
55	Nitrous oxide	-0.034	0.030	0.012	42.957	57.031	139	1-Propanol	-0.100	-0.160	49.348	11.345	39.307
56	Carbon disul-phide	0.307	0.600	10.906	69.224	19.870	140	5-Hexyl barbi-tones[t]	0.113	0.362	82.209	14.581	3.210
57	Nitrogen	0.489	0.030	43.595	37.638	18.767	141	2-Methylpropanol[t]	-0.031	-0.170	58.844	13.378	27.778
58	Methane	0.487	0.040	25.421	57.088	17.491	142	Hexane[t]	0.836	0.800	33.331	64.035	2.634
59	Zolantidine	0.522	0.140	95.712	4.278	0.010	143	ICI 17148[t]	-0.373	-0.040	11.155	87.418	1.427
60	BBcpd26	0.426	0.220	93.955	6.032	0.014	144	Caffeine[t]	-0.332	-0.055	77.030	0.209	22.761
61	BBcpd14	-0.385	-0.120	96.147	0.042	3.811	145	Didanosine[t]	-0.990	-1.300	13.403	0.000	86.597
62	BBcpd21	0.525	-0.240	96.320	3.668	0.011	146	carbamazepine-10,11-epoxide[t,d]	-0.451	-0.350	82.168	0.512	17.320
63	Hydroxyzine	0.480	0.390	98.410	1.210	0.380	147	Oxazepam[t,d]	-0.074	0.610	94.024	0.200	5.776
64	L-663,581	-1.035	-0.300	73.799	1.407	24.794	148	Desipramine[t]	0.437	1.200	90.409	9.589	0.001
65	Indomethacin	-0.963	-1.260	96.650	0.007	3.342	149	Ranitidine[t]	-0.810	-1.230	29.271	69.310	1.419
66	Verapamil[d]	-0.636	-0.700	60.397	39.541	0.062	150	Tertbutylchlo-rambucil[t]	0.989	1.000	92.034	7.826	0.140
67	Phenserine	0.787	1.000	96.811	3.158	0.031	151	Thioridazine[t,d]	0.563	0.240	96.472	3.526	0.002
68	BBcpd18	-0.565	-0.270	51.443	47.749	0.808	152	BBcpd19[t]	-0.197	-0.280	85.434	13.342	1.224
69	BBcpd23	0.686	0.690	96.818	3.171	0.012	153	Monohydroxy L-663,581[t]	-1.450	-1.340	31.110	8.241	60.649
70	BBcpd24	0.277	0.440	92.590	7.377	0.033	154	Ethanol[t]	-0.115	-0.160	42.268	7.137	50.595
71	Midazolam	0.433	0.360	98.187	0.632	1.181	155	R-Etodolac[t]	-0.738	-1.509	94.637	0.001	5.362

(Table 3. Contd….)

NO	Name	logBB (calc.)	logBB (exp.)	Lipid %	Protein%	Water%	NO	Name	logBB (calc.)	logBB (exp.)	Lipid %	Protein%	Water %
72	BBcpd17	-0.714	-1.120	38.830	59.821	1.349	156	Promethazine[t,d]	0.806	1.301	96.684	3.301	0.014
73	BBcpd58	-1.013	-1.540	32.173	46.679	21.148	157	Pefloxacin[t]	-1.290	-0.854	47.069	0.000	52.931
74	Codeine	-0.014	0.550	76.403	23.090	0.507	158	Org30526[t]	0.150	0.390	73.896	26.099	0.005
75	SK&F93619	-1.127	-1.300	0.283	98.863	0.854	159	Methanol[t]	-0.110	-0.170	31.149	6.576	62.276
76	Alprazolam	0.178	0.044	97.605	0.036	2.359	160	Diazepam[t,d]	0.346	0.520	97.356	0.681	1.963
77	Mepyramine	0.594	0.490	94.137	5.847	0.016	161	2,4-Dichloro-phenoxyacetic acid[u]	-0.907	0.152	97.283	0.000	2.717
78	Imipramine[d]	0.808	1.060	96.253	3.743	0.004	162	Trifluoroperazine[u]	-0.060	1.440	87.250	12.528	0.222
79	BBcpd20	-0.118	-0.460	78.605	21.299	0.096	163	Haloperidol[u]	0.043	1.340	80.435	19.380	0.185
80	Amitriptyline[d]	1.065	0.886	97.818	2.177	0.004	164	Bromperidol[u]	-0.439	1.380	42.231	57.246	0.523
81	Chlorpromazi-ne[d]	0.760	1.060	95.865	4.130	0.005	165	Org12962[u]	0.193	1.640	83.628	14.790	1.583
82	Tiotidine	-0.965	-0.820	5.251	87.806	6.943	166	BBcpd11[u]	-0.272	-2.150	93.130	0.254	6.616
83	BBcpd12	-0.414	-0.670	90.089	0.008	9.903	167	BBcpd10[u]	-0.239	-1.170	37.940	61.983	0.077
84	SKF89124	-0.195	-0.060	71.503	28.466	0.031	168	Fluphenazine[u]	-1.144	1.510	50.190	37.904	11.906

[t] testing set [u] omitted during the regression [d] clinical drugs.

Table 4. Physicochemical Property Data of the Compounds

NO	Name	$Q^{-max}_{(ui)}$	$\mu_{(ui)}$	$V_{(ui)}$	$MR_{(ui)}$	$logP_{(ui)}$	$\Delta Gw_{(ui)}$	$<M\text{-}360>_{(ui)}$	$\Sigma Q^{-}_{(+)}$
1	1-Butanol	-0.326	1.703	348.720	22.130	0.940	-5.054	0.000	/
2	5-Butyl barbitones	-0.374	1.408	655.280	50.710	1.220	-9.074	0.000	/
3	5-Ethyl barbitones	-0.373	1.375	546.650	41.510	0.430	-9.557	0.000	/
4	5-Heptyl barbitones	-0.374	1.423	814.870	64.510	2.410	-8.519	0.000	/
5	5-Methyl barbitones	-0.373	1.315	503.430	36.910	0.030	-10.197	0.000	/
6	5-Octyl barbitones	-0.374	1.417	866.690	69.110	2.800	-8.353	0.000	/
7	5-Pentyl barbitones	-0.374	1.421	708.140	55.310	1.610	-8.868	0.000	/
8	5-Propyl barbitones	-0.374	1.415	599.750	46.110	0.820	-9.162	0.000	/
9	9-Hydroxy risperidone	-0.372	3.540	1159.860	116.100	1.360	-22.229	66.490	-3.677
10	Alfentanil	-0.375	3.282	1204.440	118.590	2.470	-8.923	56.520	-4.093
11	Biperiden	-0.322	2.256	965.360	97.010	3.470	0.369	0.000	-3.237
12	2-chloro-1,1-difluoroethylene	-0.245	1.114	263.880	16.020	1.120	1.694	0.000	/
13	Clomipramine	-0.268	1.985	946.420	95.410	4.520	-4.775	0.000	-2.296
14	Clotiazepam	-0.369	4.749	870.620	89.630	2.210	-12.064	0.000	/
15	Clozapine	-0.258	3.111	928.410	94.840	3.450	-12.547	0.000	-2.289
16	Cotinine	-0.349	2.011	574.820	48.350	1.050	-15.310	0.000	-1.373
17	Cyclohexane	-0.155	0.000	379.860	27.610	2.380	0.993	0.000	/

(Table 4. Contd….)

NO	Name	$Q^{-max}_{(ui)}$	$\mu_{(ui)}$	$V_{(ui)}$	$MR_{(ui)}$	$logP_{(ui)}$	$\Delta Gw_{(ui)}$	$<M\text{-}360>_{(ui)}$	$\Sigma Q^{-}_{(+)}$
18	Cyclopropane	-0.215	0.000	245.760	13.800	1.190	0.641	0.000	/
19	Dichloromethane	-0.103	1.503	252.180	16.440	1.150	-2.161	0.000	/
20	Divinyl ether	-0.268	1.663	323.410	20.190	0.370	-1.657	0.000	/
21	Domperidone	-0.350	2.138	1167.410	115.810	1.870	-19.225	65.920	-3.800
22	Ethoxybenzamide	-0.410	4.814	548.080	44.980	0.950	-12.315	0.000	/
23	Fentanyl	-0.364	3.389	1068.520	103.480	3.770	-7.800	0.000	-3.290
24	Glycyrrhetinic acid	-0.324	7.651	1240.180	134.270	7.040	-19.720	110.690	/
25	Inaperisone	-0.289	3.440	837.870	76.350	3.150	-4.495	0.000	-2.148
26	Methoxyflurane	-0.308	1.527	403.260	27.970	1.910	-1.624	0.000	/
27	Mianserin	-0.257	0.555	809.190	84.500	3.990	-5.906	0.000	-2.042
28	Miloxacin	-0.393	5.565	684.280	61.630	-0.180	-19.136	0.000	/
29	Mirtazapine	-0.259	1.642	801.900	82.620	3.850	-10.963	0.000	-2.023
30	Nalidixic acid	-0.356	7.942	677.260	62.340	0.810	-15.749	0.000	/
31	Nicotine	-0.255	2.447	572.770	49.590	1.950	-9.894	0.000	-1.320
32	Nitrazepam	-0.359	1.438	767.390	76.430	-1.670	-15.298	0.000	/
33	Org13011	-0.353	2.245	1039.400	94.460	2.750	-10.935	10.420	-3.361
34	Org32104	-0.332	2.381	806.530	82.650	2.430	-11.029	0.000	-2.375
35	Org34167	-0.347	3.050	824.480	80.720	3.770	-13.234	0.000	-1.881
36	Org4428	-0.332	2.080	855.910	87.950	2.790	-9.144	0.000	-2.529
37	Org5222	-0.247	2.595	804.220	81.650	3.620	-7.982	0.000	-1.805
38	Pentazocine	-0.257	1.639	903.450	89.510	4.280	-7.448	0.000	-2.667
39	Phenytoin	-0.389	3.129	723.750	68.110	1.970	-10.800	0.000	/
40	Pipemidic acid	-0.360	7.988	842.900	81.360	0.190	-20.814	0.000	/
41	p-phenylbenzoic acid	-0.365	2.793	619.910	57.950	3.430	-9.109	0.000	/
42	Prednisolone	-0.340	3.267	947.050	98.490	2.450	-18.893	0.450	/
43	Propofol	-0.260	1.318	638.220	56.130	4.150	-3.584	0.000	/
44	Risperidone	-0.360	2.778	1154.120	114.610	1.940	-21.011	50.490	-3.542
45	S-Etodolac	-0.363	1.853	856.800	82.090	1.660	-10.498	0.000	/
46	Sevoflurane	-0.264	3.040	410.400	23.300	2.360	-1.223	0.000	/
47	Tibolone	-0.308	4.045	923.930	91.730	3.230	-7.898	0.000	/
48	Tolbutamide	-0.947	5.022	816.990	69.270	1.940	-15.884	0.000	/
49	Trichloromethane	-0.041	1.155	295.830	21.360	1.610	-1.801	0.000	/
50	Trihexyphenidyl	-0.330	2.188	965.640	93.200	3.970	0.528	0.000	-3.141
51	Indinavir	-0.374	2.099	1725.380	174.080	3.880	-24.458	253.800	-6.193
52	Temelastine	-0.328	6.241	1170.200	113.840	5.100	-49.500	82.360	-3.393
53	2-Propanol	-0.326	1.691	291.980	17.430	0.490	-4.412	0.000	/
54	2-Propanone	-0.292	2.920	275.400	16.190	0.380	-6.793	0.000	/

(Table 4. Contd….)

NO	Name	$Q^{-max}_{(ui)}$	$\mu_{(ui)}$	$V_{(ui)}$	$MR_{(ui)}$	$logP_{(ui)}$	$\Delta Gw_{(ui)}$	$<M\text{-}360>_{(ui)}$	$\Sigma Q^{-}_{(+)}$
55	Nitrous oxide	-0.280	0.637	162.790	8.860	0.370	-66.759	0.000	/
56	Carbon disulphide	-0.543	0.000	230.840	22.370	0.660	-6.637	0.000	/
57	Nitrogen	0.000	0.000	138.890	5.400	0.290	0.581	0.000	/
58	Methane	-0.266	0.000	158.150	6.350	1.090	1.974	0.000	/
59	Zolantidine	-0.320	1.816	1157.400	113.980	4.530	-18.287	21.540	-3.343
60	BBcpd26	-0.254	1.671	1133.990	107.540	4.180	-22.271	5.480	-3.132
61	BBcpd14	-0.423	6.321	1054.590	104.010	-1.330	-24.251	8.450	-3.544
62	BBcpd21	-0.364	2.675	1123.850	104.760	3.380	-13.407	0.000	-3.440
63	Hydroxyzine	-0.330	3.034	1122.070	107.070	3.490	-7.094	14.910	-2.983
64	L-663,581	-0.325	4.440	959.670	95.310	2.180	-43.531	0.000	/
65	Indomethacin	-0.366	2.906	956.640	95.250	2.310	-17.353	0.000	/
66	Verapamil	-0.264	5.120	1323.360	132.650	5.050	-9.678	94.610	-3.919
67	Phenserine	-0.368	1.623	1006.370	98.170	4.190	-11.348	0.000	-3.041
68	BBcpd18	-0.420	7.247	945.380	95.020	-4.030	-17.409	0.000	-3.222
69	BBcpd23	-0.261	2.344	1022.720	100.480	3.750	-13.939	0.000	-3.087
70	BBcpd24	-0.474	1.992	1000.480	97.960	2.340	-15.948	0.000	-3.246
71	Midazolam	-0.171	3.476	870.410	91.200	3.410	-17.532	0.000	-2.035
72	BBcpd17	-0.382	7.251	901.850	91.640	-5.480	-22.074	0.000	-3.415
73	BBcpd58	-0.479	6.810	905.400	87.560	1.530	-42.262	0.000	-2.992
74	Codeine	-0.315	2.491	819.520	84.600	1.570	-10.844	0.000	-2.288
75	SK&F93619	-0.336	5.538	1259.600	134.630	2.030	-48.422	88.580	-4.160
76	Alprazolam	-0.158	5.673	847.430	88.110	4.680	-21.274	0.000	/
77	Mepyramine	-0.274	1.323	922.400	87.710	3.670	-7.169	0.000	-2.512
78	Imipramine	-0.267	1.417	901.990	90.610	4.010	-4.700	0.000	-2.383
79	BBcpd20	-0.379	5.300	961.180	84.590	1.470	-10.523	0.000	-2.956
80	Amitriptyline	-0.263	1.253	900.610	92.330	4.520	-5.793	0.000	-2.376
81	Chlorpromazine	-0.293	1.101	893.740	93.760	3.820	-9.452	0.000	-2.437
82	Tiotidine	-0.488	5.488	866.450	84.180	0.080	-46.110	0.000	-3.469
83	BBcpd12	-0.435	5.289	829.560	82.650	-2.300	-24.532	0.000	/
84	SKF89124	-0.329	3.422	891.830	81.340	2.170	-14.639	0.000	-2.816
85	Lupitidine	-0.331	6.970	1176.150	120.890	0.830	-64.299	53.540	-3.956
86	Promazine	-0.290	1.624	851.820	88.950	3.300	-10.882	0.000	-2.515
87	Physostigmine	-0.378	1.949	844.180	77.400	2.230	-12.563	0.000	-2.521
88	Nevirapine	-0.360	2.698	779.370	75.140	2.830	-18.591	0.000	-2.246
89	Thioperamide	-0.358	7.379	904.590	90.070	1.750	-28.259	0.000	-2.434
90	BBcpd13	-0.432	5.650	774.030	75.030	-3.100	-25.186	0.000	-2.844
91	BBcpd16	-0.483	3.537	793.780	76.240	0.030	-36.422	0.000	-2.830

(Table 4. Contd….)

NO	Name	$Q^{-max}_{(ui)}$	$\mu_{(ui)}$	$V_{(ui)}$	$MR_{(ui)}$	$logP_{(ui)}$	$\Delta Gw_{(ui)}$	$<M\text{-}360>_{(ui)}$	$\Sigma Q^{-}_{(+)}$
92	BBcpd60	-0.418	7.845	1168.520	120.620	-3.710	-25.540	54.520	-4.131
93	SKF101468	-0.337	2.221	870.220	79.650	2.460	-7.136	0.000	-2.695
94	Zidovudine	-0.363	3.609	730.130	63.140	-0.110	-88.377	0.000	/
95	Chlorambucil	-0.365	1.987	884.720	79.680	4.140	-9.714	0.000	/
96	BBcpd22	-0.331	1.781	833.080	74.360	2.010	-6.876	0.000	-2.342
97	carbamazepine	-0.406	3.485	697.910	70.890	2.450	-15.091	0.000	/
98	Cimetidine	-0.314	2.391	748.600	72.480	-0.590	-53.318	0.000	-2.221
99	BBcpd57	-0.487	2.239	686.240	67.850	0.400	-28.921	0.000	-2.257
100	Pentobarbital	-0.374	1.569	682.340	55.260	1.550	-8.154	0.000	/
101	SB-222200	-0.372	3.147	1147.060	115.950	6.400	-11.814	20.490	/
102	BBcpd15	-0.492	2.482	649.530	63.150	1.190	-24.982	0.000	-1.970
103	Ibuprofen	-0.363	1.768	706.240	60.730	3.830	-6.634	0.000	/
104	Clonidine	-0.277	0.741	626.620	57.600	2.950	-18.075	0.000	-1.070
105	Y-G19	-0.457	2.535	643.930	61.990	0.490	-10.420	0.000	-1.968
106	Antipyrine	-0.306	4.441	608.000	56.420	0.790	-12.384	0.000	/
107	Theophylline	-0.360	3.262	520.110	43.240	-1.600	-22.801	0.000	/
108	Acetylsalicylic acid	-0.314	4.492	536.460	43.950	1.240	-18.305	0.000	/
109	Y-G20	-0.336	4.239	549.830	51.650	-1.310	-24.222	0.000	-1.277
110	BCNU	-0.381	2.312	578.720	45.980	0.870	-9.223	0.000	/
111	Icotidine	-0.331	5.618	1132.780	107.640	3.590	-49.020	19.460	-3.493
112	Y-G15	-0.272	1.376	561.260	46.910	1.540	-10.328	0.000	-1.311
113	p-acetamidophenol	-0.353	4.487	499.550	40.830	0.610	-18.692	0.000	/
114	Enflurane	-0.356	1.431	392.850	23.060	2.420	-1.064	0.000	/
115	Isoflurane	-0.291	3.098	389.150	23.040	2.480	-3.243	0.000	/
116	Y-G14	-0.311	1.250	515.310	41.610	1.180	-11.114	0.000	-1.191
117	Valproic acid	-0.304	4.388	547.670	40.250	2.610	-12.533	0.000	/
118	Salicylic acid	-0.312	6.127	423.540	34.510	1.460	-21.198	0.000	/
119	Fluroxene	-0.251	3.468	370.320	21.920	1.210	-2.465	0.000	/
120	Y-G16	-0.457	2.728	428.320	36.340	-0.970	-10.322	0.000	-1.465
121	Bishydroxy L-663,581	-0.333	5.590	1031.370	103.360	0.840	-46.511	43.820	/
122	Heptane	-0.210	0.006	487.190	34.010	3.280	1.951	0.000	/
123	3-Methylhexane	-0.211	0.011	471.720	33.960	3.210	2.083	0.000	/
124	Teflurane	-0.150	1.727	321.100	19.710	1.630	0.357	0.000	/
125	Toluene	-0.179	0.265	383.940	31.100	2.510	-1.567	0.000	/
126	Halothane	-0.218	1.731	351.250	24.630	1.970	-0.002	0.000	/
127	Sulphur hexafluoride	-0.523	0.000	243.700	9.010	2.060	3.065	0.000	/
128	Benzene	-0.130	0.000	331.570	26.060	2.050	-1.610	0.000	/

(Table 4. Contd….)

NO	Name	$Q^{-max}_{(ui)}$	$\mu_{(ui)}$	$V_{(ui)}$	$MR_{(ui)}$	$logP_{(ui)}$	$\Delta Gw_{(ui)}$	$<M\text{-}360>_{(ui)}$	$\Sigma Q^{-}_{(+)}$
129	2,2-Dimethylbutane	-0.210	0.005	406.490	29.230	2.850	1.933	0.000	/
130	Methylcyclopentane	-0.204	0.035	386.140	27.550	2.310	1.146	0.000	/
131	2-Methylpentane	-0.211	0.013	422.830	29.360	2.820	1.898	0.000	/
132	3-Methylpentane	-0.210	0.017	412.720	29.360	2.820	1.877	0.000	/
133	1,1,1-Trifluoro-2-chloroethane	-0.182	2.191	290.870	16.760	1.860	-1.133	0.000	/
134	Butanone	-0.290	2.809	328.940	20.820	1.010	-5.972	0.000	/
135	Diethylether	-0.283	1.246	359.220	22.510	0.700	-1.649	0.000	/
136	Pentane	-0.210	0.006	378.190	24.810	2.490	1.598	0.000	/
137	1,1,1-Trichloroethane	-0.230	1.746	345.150	26.220	2.040	-1.667	0.000	/
138	Trichloroethene	-0.153	0.789	330.050	25.290	1.710	-0.672	0.000	/
139	1-Propanol	-0.330	1.537	295.600	17.530	0.550	-5.435	0.000	/
140	5-Hexyl barbitones	-0.374	1.414	761.040	59.910	2.010	-8.703	0.000	/
141	2-Methylpropanol	-0.329	1.469	343.210	22.010	0.950	-4.265	0.000	/
142	Hexane	-0.210	0.000	434.450	29.410	2.880	1.778	0.000	/
143	ICI 17148	-0.499	2.234	490.970	43.290	-0.250	-25.091	0.000	-1.577
144	Caffeine	-0.362	3.567	570.230	48.140	-1.350	-15.053	0.000	/
145	Didanosine	-0.328	12.647	646.800	59.210	-0.920	-70.407	0.000	/
146	carbamazepine-10,11-epoxide	-0.396	4.113	709.100	68.980	1.720	-22.462	0.000	/
147	Oxazepam	-0.330	4.505	767.320	76.100	2.910	-18.430	0.000	/
148	Desipramine	-0.298	0.924	861.180	85.310	3.640	-7.651	0.000	-2.223
149	Ranitidine	-0.461	9.427	945.470	87.390	-5.050	-22.798	0.000	-3.539
150	Tertbutylchlorambucil	-0.360	1.626	1090.620	98.260	5.010	-5.823	0.320	-3.021
151	Thioridazine	-0.372	3.324	1049.650	113.670	4.180	-11.778	10.570	-3.385
152	BBcpd19	-0.420	7.547	981.240	96.950	-1.760	-18.302	0.000	-3.320
153	Monohydroxy L-663,581	-0.324	3.679	975.180	97.020	1.170	-47.908	13.800	/
154	Ethanol	-0.327	1.684	240.440	13.010	0.080	-5.533	0.000	/
155	R-Etodolac	-0.327	3.955	840.650	82.090	1.660	-15.840	0.000	/
156	Promethazine	-0.285	2.424	843.160	88.500	3.660	-8.605	0.000	-2.551
157	Pefloxacin	-0.411	7.857	917.770	89.980	0.980	-21.914	0.000	/
158	Org30526	-0.273	2.693	752.340	76.350	3.260	-10.350	0.000	-1.650
159	Methanol	-0.326	1.621	184.580	8.260	-0.270	-6.319	0.000	/
160	Diazepam	-0.331	3.281	796.180	79.810	3.010	-11.878	0.000	/
161	2,4-Dichlorophenoxy-acetic acid	-0.296	2.823	567.060	48.220	2.370	-12.030	0.000	/
162	Trifluoroperazine	-0.306	3.501	1076.890	110.970	3.990	-8.236	47.500	-3.465

(Table 4. Contd….)

NO	Name	$Q^{-max}_{(ui)}$	$\mu_{(ui)}$	$V_{(ui)}$	$MR_{(ui)}$	$logP_{(ui)}$	$\Delta Gw_{(ui)}$	$<M\text{-}360>_{(ui)}$	$\Sigma Q^{-}_{(+)}$
163	Haloperidol	-0.319	1.226	1042.150	102.590	3.380	-10.352	15.870	-3.141
164	Bromperidol	-0.318	1.301	1060.450	105.410	3.650	-10.873	60.320	-3.222
165	Org12962	-0.274	4.666	669.410	61.240	2.910	-11.348	0.000	-1.735
166	BBcpd11	-0.313	4.745	848.600	82.030	3.310	-24.251	0.000	/
167	BBcpd10	-0.279	3.657	644.710	58.070	2.220	-32.952	0.000	-1.693
168	Fluphenazine	-0.330	3.972	1146.330	117.270	3.540	-8.172	77.520	-3.768

NO	Name	$logP_{(+)}$	$\Delta Gw_{(+)}$	$<M\text{-}360>_{(+)}$	$\mu_{(-)}$	$logP_{(-)}$	fui[a]	f(+)[a]	f(-)[a]
1	1-Butanol	/	/	/	/	/	1.000	0.000	0.000
2	5-Butyl barbitones	/	/	/	7.356	2.380	0.780	0.000	0.220
3	5-Ethyl barbitones	/	/	/	6.154	1.590	0.780	0.000	0.220
4	5-Heptyl barbitones	/	/	/	11.252	3.570	0.784	0.000	0.216
5	5-Methyl barbitones	/	/	/	6.019	1.190	0.780	0.000	0.220
6	5-Octyl barbitones	/	/	/	12.934	3.960	0.776	0.000	0.224
7	5-Pentyl barbitones	/	/	/	8.482	2.770	0.799	0.000	0.201
8	5-Propyl barbitones	/	/	/	6.766	1.980	0.780	0.000	0.220
9	9-Hydroxy risperidone	0.640	-75.449	67.490	/	/	0.258	0.743	0.000
10	Alfentanil	1.750	-56.800	57.520	/	/	0.392	0.608	0.000
11	Biperiden	2.750	-45.618	/	/	/	0.004	0.996	0.000
12	2-chloro-1,1-difluoroethylene	/	/	/	/	/	1.000	0.000	0.000
13	Clomipramine	3.800	-61.466	/	/	/	0.009	0.991	0.000
14	Clotiazepam	/	/	/	/	/	1.000	0.000	0.000
15	Clozapine	2.720	-64.019	/	/	/	0.645	0.355	0.000
16	Cotinine	0.780	-71.075	/	/	/	0.998	0.002	0.000
17	Cyclohexane	/	/	/	/	/	1.000	0.000	0.000
18	Cyclopropane	/	/	/	/	/	1.000	0.000	0.000
19	Dichloromethane	/	/	/	/	/	1.000	0.000	0.000
20	Divinyl ether	/	/	/	/	/	1.000	0.000	0.000
21	Domperidone	1.150	-84.515	66.920	/	/	0.024	0.976	0.000
22	Ethoxybenzamide	/	/	/	/	/	1.000	0.000	0.000
23	Fentanyl	3.050	-61.512	/	/	/	0.021	0.979	0.000
24	Glycyrrhetinic acid	/	/	/	23.722	8.460	0.002	0.000	0.998
25	Inaperisone	2.430	-49.892	/	/	/	0.005	0.995	0.000
26	Methoxyflurane	/	/	/	/	/	1.000	0.000	0.000
27	Mianserin	3.270	-61.331	/	/	/	0.124	0.876	0.000
28	Miloxacin	/	/	/	18.885	1.240	0.137	0.000	0.863

(Table 4. Contd….)

NO	Name	$logP_{(+)}$	$\Delta Gw_{(+)}$	$<M\text{-}360>_{(+)}$	$\mu_{(-)}$	$logP_{(-)}$	fui[a]	f(+)[a]	f(-)[a]
29	Mirtazapine	3.120	-64.163	/	/	/	0.166	0.834	0.000
30	Nalidixic acid	/	/	/	17.550	2.230	0.000	0.000	1.000
31	Nicotine	1.230	-70.850	/	/	/	0.201	0.799	0.000
32	Nitrazepam	/	/	/	/	/	1.000	0.000	0.000
33	Org13011	2.030	-46.167	11.420	/	/	0.866	0.134	0.000
34	Org32104	1.820	-70.683	/	/	/	0.005	0.995	0.000
35	Org34167	3.330	-91.607	/	/	/	0.020	0.980	0.000
36	Org4428	2.070	-59.005	/	/	/	0.031	0.969	0.000
37	Org5222	2.900	-68.068	/	/	/	0.007	0.993	0.000
38	Pentazocine	3.550	-54.146	/	/	/	0.032	0.968	0.000
39	Phenytoin	/	/	/	11.386	3.130	0.895	0.000	0.105
40	Pipemidic acid	/	/	/	22.000	1.610	0.000	0.000	1.000
41	p-phenylbenzoic acid	/	/	/	17.952	4.850	0.001	0.000	0.999
42	Prednisolone	/	/	/	/	/	1.000	0.000	0.000
43	Propofol	/	/	/	/	/	1.000	0.000	0.000
44	Risperidone	1.220	-53.925	51.490	/	/	0.245	0.755	0.000
45	S-Etodolac	/	/	/	17.988	3.080	0.001	0.000	0.999
46	Sevoflurane	/	/	/	/	/	1.000	0.000	0.000
47	Tibolone	/	/	/	/	/	1.000	0.000	0.000
48	Tolbutamide	/	/	/	6.645	2.320	0.005	0.000	0.995
49	Trichloromethane	/	/	/	/	/	1.000	0.000	0.000
50	Trihexyphenidyl	3.250	-44.932	/	/	/	0.004	0.996	0.000
51	Indinavir	3.160	-87.012	254.800	/	/	0.994	0.006	0.000
52	Temelastine	4.660	-101.081	83.360	/	/	0.981	0.019	0.000
53	2-Propanol	/	/	/	/	/	1.000	0.000	0.000
54	2-Propanone	/	/	/	/	/	1.000	0.000	0.000
55	Nitrous oxide	/	/	/	/	/	1.000	0.000	0.000
56	Carbon disulphide	/	/	/	/	/	1.000	0.000	0.000
57	Nitrogen	/	/	/	/	/	1.000	0.000	0.000
58	Methane	/	/	/	/	/	1.000	0.000	0.000
59	Zolantidine	3.810	-63.045	22.540	/	/	0.032	0.968	0.000
60	BBcpd26	3.460	-72.560	6.480	/	/	0.032	0.968	0.000
61	BBcpd14	-1.770	-61.081	9.450	/	/	0.999	0.001	0.000
62	BBcpd21	2.660	-63.500	/	/	/	0.032	0.968	0.000
63	Hydroxyzine	2.770	-52.708	15.910	/	/	0.950	0.050	0.000
64	L-663,581	/	/	/	/	/	1.000	0.000	0.000
65	Indomethacin	/	/	/	14.905	3.740	0.000	0.000	1.000

(Table 4. Contd….)

NO	Name	$logP_{(+)}$	$\Delta Gw_{(+)}$	$<M\text{-}360>_{(+)}$	$\mu_{(-)}$	$logP_{(-)}$	fui[a]	f(+)[a]	f(-)[a]
66	Verapamil	4.330	-70.617	95.610	/	/	0.026	0.974	0.000
67	Phenserine	3.470	-63.656	/	/	/	0.099	0.901	0.000
68	BBcpd18	-4.750	-80.709	/	/	/	0.091	0.909	0.000
69	BBcpd23	3.030	-62.217	/	/	/	0.032	0.968	0.000
70	BBcpd24	1.620	-59.810	/	/	/	0.032	0.968	0.000
71	Midazolam	3.220	-60.149	/	/	/	0.986	0.014	0.000
72	BBcpd17	-6.200	-64.150	/	/	/	0.091	0.909	0.000
73	BBcpd58	0.920	-122.808	/	/	/	0.725	0.276	0.000
74	Codeine	0.840	-72.345	/	/	/	0.124	0.876	0.000
75	SK&F93619	1.310	-133.958	89.580	/	/	0.091	0.909	0.000
76	Alprazolam	/	/	/	/	/	1.000	0.000	0.000
77	Mepyramine	2.940	-64.968	/	/	/	0.023	0.977	0.000
78	Imipramine	3.280	-61.213	/	/	/	0.008	0.992	0.000
79	BBcpd20	0.750	-67.127	/	/	/	0.032	0.968	0.000
80	Amitriptyline	3.800	-58.332	/	/	/	0.016	0.984	0.000
81	Chlorpromazine	3.100	-60.678	/	/	/	0.010	0.990	0.000
82	Tiotidine	-0.530	-137.756	/	/	/	0.228	0.772	0.000
83	BBcpd12	/	/	/	/	/	1.000	0.000	0.000
84	SKF89124	1.450	-78.126	/	/	/	0.007	0.993	0.000
85	Lupitidine	0.110	-131.905	54.540	/	/	0.091	0.909	0.000
86	Promazine	2.580	-62.143	/	/	/	0.009	0.991	0.000
87	Physostigmine	1.510	-64.804	/	/	/	0.107	0.893	0.000
88	Nevirapine	2.270	-57.093	/	/	/	0.999	0.001	0.000
89	Thioperamide	1.000	-70.130	/	/	/	0.821	0.180	0.000
90	BBcpd13	-3.540	-53.723	/	/	/	0.999	0.001	0.000
91	BBcpd16	-0.410	-96.957	/	/	/	0.084	0.916	0.000
92	BBcpd60	-4.430	-65.631	55.520	/	/	0.091	0.909	0.000
93	SKF101468	1.730	-69.534	/	/	/	0.008	0.992	0.000
94	Zidovudine	/	/	/	15.100	1.080	1.000	0.000	0.000
95	Chlorambucil	/	/	/	25.593	5.560	0.005	0.000	0.995
96	BBcpd22	1.290	-58.182	/	/	/	0.032	0.968	0.000
97	carbamazepine	/	/	/	/	/	1.000	0.000	0.000
98	Cimetidine	-1.190	-66.149	/	/	/	0.656	0.344	0.000
99	BBcpd57	-0.040	-91.204	/	/	/	0.977	0.023	0.000
100	Pentobarbital	/	/	/	8.673	2.710	0.751	0.000	0.249
101	SB-222200	/	/	/	/	/	1.000	0.000	0.000
102	BBcpd15	0.740	-87.706	/	/	/	0.201	0.799	0.000

(Table 4. Contd….)

NO	Name	$logP_{(+)}$	$\Delta Gw_{(+)}$	$<M\text{-}360>_{(+)}$	$\mu_{(-)}$	$logP_{(-)}$	fui[a]	f(+)[a]	f(-)[a]
103	Ibuprofen	/	/	/	15.543	5.250	0.001	0.000	0.999
104	Clonidine	2.350	-91.223	/	/	/	0.166	0.834	0.000
105	Y-G19	0.050	-84.349	/	/	/	0.046	0.954	0.000
106	Antipyrine	/	/	/	/	/	1.000	0.000	0.000
107	Theophylline	/	/	/	4.706	-1.690	0.941	0.000	0.059
108	Acetylsalicylic acid	/	/	/	7.741	2.660	0.000	0.000	1.000
109	Y-G20	-1.760	-74.599	/	/	/	0.018	0.982	0.000
110	BCNU	/	/	/	/	/	1.000	0.000	0.000
111	Icotidine	3.150	-104.964	20.460	/	/	0.981	0.019	0.000
112	Y-G15	0.820	-57.603	/	/	/	0.027	0.973	0.000
113	p-acetamidophenol	/	/	/	10.411	2.030	0.997	0.000	0.004
114	Enflurane	/	/	/	/	/	1.000	0.000	0.000
115	Isoflurane	/	/	/	/	/	1.000	0.000	0.000
116	Y-G14	0.570	-62.199	/	/	/	0.004	0.996	0.000
117	Valproic acid	/	/	/	7.947	4.030	0.003	0.000	0.997
118	Salicylic acid	/	/	/	10.354	2.880	0.000	0.000	1.000
119	Fluroxene	/	/	/	/	/	1.000	0.000	0.000
120	Y-G16	-1.410	-80.651	/	/	/	0.066	0.934	0.000
121	Bishydroxy L-663,581	/	/	/	/	/	1.000	0.000	0.000
122	Heptane	/	/	/	/	/	1.000	0.000	0.000
123	3-Methylhexane	/	/	/	/	/	1.000	0.000	0.000
124	Teflurane	/	/	/	/	/	1.000	0.000	0.000
125	Toluene	/	/	/	/	/	1.000	0.000	0.000
126	Halothane	/	/	/	/	/	1.000	0.000	0.000
127	Sulphur hexafluoride	/	/	/	/	/	1.000	0.000	0.000
128	Benzene	/	/	/	/	/	1.000	0.000	0.000
129	2,2-Dimethylbutane	/	/	/	/	/	1.000	0.000	0.000
130	Methylcyclopentane	/	/	/	/	/	1.000	0.000	0.000
131	2-Methylpentane	/	/	/	/	/	1.000	0.000	0.000
132	3-Methylpentane	/	/	/	/	/	1.000	0.000	0.000
133	1,1,1-Trifluoro-2-chloroethane	/	/	/	/	/	1.000	0.000	0.000
134	Butanone	/	/	/	/	/	1.000	0.000	0.000
135	Diethylether	/	/	/	/	/	1.000	0.000	0.000
136	Pentane	/	/	/	/	/	1.000	0.000	0.000
137	1,1,1-Trichloroethane	/	/	/	/	/	1.000	0.000	0.000
138	Trichloroethene	/	/	/	/	/	1.000	0.000	0.000

(Table 4. Contd….)

NO	Name	$logP_{(+)}$	$\Delta Gw_{(+)}$	$<M\text{-}360>_{(+)}$	$\mu_{(-)}$	$logP_{(-)}$	fui[a]	f(+)[a]	f(-)[a]
139	1-Propanol	/	/	/	/	/	1.000	0.000	0.000
140	5-Hexyl barbitones	/	/	/	9.668	3.170	0.799	0.000	0.201
141	2-Methylpropanol	/	/	/	/	/	1.000	0.000	0.000
142	Hexane	/	/	/	/	/	1.000	0.000	0.000
143	ICI 17148	-0.690	-85.821	/	/	/	0.042	0.958	0.000
144	Caffeine	/	/	/	/	/	1.000	0.000	0.000
145	Didanosine	/	/	/	8.887	0.850	0.949	0.000	0.051
146	carbamazepine-10,11-epoxide	/	/	/	/	/	1.000	0.000	0.000
147	Oxazepam	/	/	/	/	/	1.000	0.000	0.000
148	Desipramine	3.040	-71.939	/	/	/	0.001	0.999	0.000
149	Ranitidine	-5.770	-84.100	/	/	/	0.091	0.909	0.000
150	Tertbutylchlorambucil	3.810	-63.597	1.320	/	/	0.998	0.002	0.000
151	Thioridazine	3.460	-64.491	11.570	/	/	0.006	0.994	0.000
152	BBcpd19	-2.480	-105.949	/	/	/	0.371	0.629	0.000
153	Monohydroxy L-663,581	/	/	/	/	/	1.000	0.000	0.000
154	Ethanol	/	/	/	/	/	1.000	0.000	0.000
155	R-Etodolac	/	/	/	11.615	3.080	0.001	0.000	0.999
156	Promethazine	2.940	-56.947	/	/	/	0.026	0.974	0.000
157	Pefloxacin	/	/	/	24.564	2.400	0.000	0.000	1.000
158	Org30526	2.660	-80.225	/	/	/	0.001	0.999	0.000
159	Methanol	/	/	/	/	/	1.000	0.000	0.000
160	Diazepam	/	/	/	/	/	1.000	0.000	0.000
161	2,4-Dichlorophenoxyace-tic acid	/	/	/	13.962	3.790	0.000	0.000	1.000
162	Trifluoroperazine	3.260	-60.235	48.500	/	/	0.134	0.866	0.000
163	Haloperidol	2.660	-73.658	16.870	/	/	0.124	0.876	0.000
164	Bromperidol	2.930	-72.218	61.320	/	/	0.124	0.876	0.000
165	Org12962	2.300	-72.335	/	/	/	0.344	0.656	0.000
166	BBcpd11	/	/	/	/	/	1.000	0.000	0.000
167	BBcpd10	1.030	-83.663	/	/	/	0.006	0.994	0.000
168	Fluphenazine	2.820	-64.360	78.520	/	/	0.780	0.220	0.000

[a] For the basic molecules, $f_{ui}=1/(1+10^{pKa-7.4})$, $f_{+}=1-f_{ui}$;

and for acidic molecules, $f_{ui}=1/(1+10^{7.4-pKa})$, $f_{-}= 1-f_{ui}$

The pKa values were looked up with the program Scifinder Scholar (Version 2006) offered by American Chemical Society, which were calculated using Advanced Chemistry Development (ACD/Labs) Software V8.19 for Solaris (1994-2006 ACD/Labs).

Fig. (**1**) and Fig. (**2**) showed the calculated logBB values versus experimental logBB values in the training set and testing set respectively. Results showed a good correlation between experimental and calculated values. The training set and testing set also divided several times randomly and the results were similar above. So the model was validated.

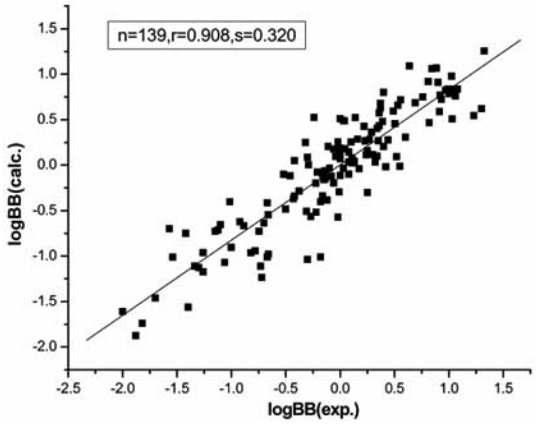

Fig. (1). Calculated logBB values versus experimental logBB values in the training set.

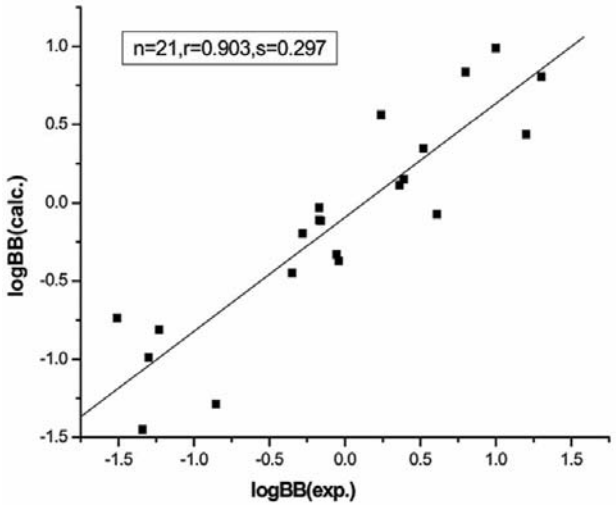

Fig. (2). Calculated logBB values versus experimental logBB values in the testing set.

Only seven sub-equations were obtained. The water term of cationic forms disappeared, and also the protein terms of the anionic forms. For the cationic forms, the error caused by measurement or calculation may be much larger than the water term itself and made the water term disappeared or the result was similar to the result of the constant (logww) and counteracted each other. The anionic forms reversely had the water and lipid terms. This might be because of the anionic forms which usually had $–COO^-$ terminals. Some researches had suggested that acidic drugs tend to bind to albumin present in plasma and blood, and the –COOH group might be removed from the brain by some efflux mechanism [11]. Thus the water term might become more important for the anion forms, it also can ionize the –COOH group, so the compounds might exist in the water most probably. Protein usually interacts with amido terminal, but the contribution of the protein term turned to be so feeble that the protein term of anion forms disappeared.

Equations 11-1 and 12-1 expressed the distribution into the lipid composition of brain of neutral molecules. Here the free energies of solvation in water (ΔG_w), the indicator variable of molecular weight <M-*360*>, the molecular refractivity and also the lowest negative charge Q^{-max} were all significant. The coefficient of the ΔG_w was positive and that result was similar to other studies on the relationship between the ΔG_w and the logBB values [9]. A polar compound well solvated in water would have a relatively large negative value for ΔG_w, the positive coefficient shows that the compound will be difficult to partition into the lipid. Similar to Hou's work [13]. The indicator variable of molecular weight <M-*360* > showed negative correlation with the distribution into lipid of the brain, which suggested that when the molecular weight of the molecule was larger than 360, its molecular size might not fit to penetrate through the tight junction between the brain and blood. We had also tried other *a* values for <M- *a* >, finally when it was 360, this indicator variable was the best, which also supported the conclusion of Hou *et al.* There also showed that if the neutral compounds had higher refractivity, they might easily enter into the lipid of the brain. In several work of Abraham *et al.* they used to introduce the excess molar refraction of molecules into the logBB prediction models [11,22, 23], the coefficients were positive, too. Since the Q^{-max} values were negative, the positive coefficient meant that more negative value of the Q^{-max} would be difficult to partition into lipid of the brain.

There were two significant parameters, logP and dipole moment μ of neutral forms in equations 11-2 and 12-2, which probably expressed the distribution into the protein composition of brain tissue of the neutral molecules. The positive coefficient suggested that logP had positive correlation with the distribution into the protein of neutral forms. It is known larger logP value means that the fragment has better lipophilicity, which would be in favor of the interaction between the compounds and protein of the brain, therefore benefit the distribution into the protein composition of brain. Dipole moment μ had a negative relationship with the distribution into the protein of neutral forms. Iyer M *et al.* [24] suggested that less dipolar and more lipophilic compounds partition more readily into the brain. The coefficient of the dipolar/polarizable was negative indicating that polarity act to keep compounds in blood and out of the brain [11]. So the molecules with less dipole moment value would have better lipophilic properties, therefore benefited its distribution into the protein composition of brain.

Equations 11-3 and 12-3, which expressed the distribution into water of the neutral forms, the negative coefficient suggested that if the neutral compounds had less volume, they might easily enter into the water of the brain. The negative coefficient was same to other studies [7].

Equations 11-4 and 12-4, which expressed the distribution into lipid of the cationic forms, contained logP, ΔG_w, molecular weight <M-360> and also a constant term. The larger the logP values, the better the lipophilicity, so the molecular cationic logP had a positive coefficient with the lipid of the brain. Because the polar had a negative coefficient with the lipid of the brain, a relatively nonpolar compound would yield a more positive value for ΔG_w, which was also consistent with high brain partitioning. This was in agreement with the positive sign for the coefficient of logP. So the nonpolar molecules that bear higher ΔG_w value would have better lipophilic properties, therefore benefited its distribution into the lipid composition of brain. Which was similar to that of the neutral compounds, the descriptor <M-360> showed significance of the cationic molecules. The negative coefficient showed that the larger about the value M-360, the harder was the molecules to penetrate through blood-brain barrier.

For expressing the distribution into protein of the cationic forms, equations 11-5 and 12-5 contained only one parameter, the sum of the negative charges ΣQ^-. So the positive coefficient showed that the molecule with more negative charges would be difficult to partition into protein. It was remarkable that the maximum positive atomic charge Q^{+max}, or the sum of the positive charges ΣQ^+ of the cationic form didn't show significance in the equation, which was out of our expectation.

For prediction of the distribution into brain of the anionic forms, there were two equations available that expressed the distribution into the lipid and water term of anionic fragments. Equation 11-6 and 12-6 contained one descriptor, dipole moment. The same to the equation 11-2 and 12-2, the molecules had less dipole moment were benefited its distribution into the lipid composition of brain.

The equations 11-7 and 12-7 showed the relationship between the logP and water composition. We knew that the large logP value has better lipophilicity and the water interacts with hydrophilic molecules, so the coefficient was negative.

The calculated percentages of amount of a compound in three compositions of the brain could not be validated because there was a lack of experimental values in the public domain. A familiar molecule was selected, such as ethanol, we knew that it can dissolve in water in any proportion and it was a hydrophilic molecule, so a majority of ethanol would distribution into the water. The deduction was accord with our calculated results, the percentage of ethanol that distributed into lipid was 42.3%, into water was 50.6%. Most of ethanol was distributed into the water. Molecules had little solubility in water were used to deduce that they would distributed little in water composition of the brain. For example, benzene distributed into the water was 5.7%, the lipid was 34%, and the protein was 60.3%, the distribution into lipid and protein was dominating.

Some clinical drugs were selected such as Alfentanil, a common anodyne, part of them were ticked in Table **3**. The percentages of the composition of these drugs were analyzed. These drugs distributed into the water was much less than into lipid and protein and generally did not more than 20%.Water and lipid have a large difference, and a well distributed drug is mainly affected by distribution of lipid and protein,some coupling interaction between them may be ignored.

In our work, the molecular dataset contained more series of compounds of all kinds of types and had many clinical drugs, so the model for predicting the absorption and distribution of compounds was more convincible. The physical signification and descriptors such as logP, ΔGw, dipole moment, molecular weight, volume and the charges were also homologous with other studies. But the correlation coefficients we made were much higher. Unfortunately, when we computed molecular weight, there was only one compound which molecular weight was larger than 360 in the dataset of the anionic form. Due to avoiding the results by accident, we did not use that descriptor in the anionic form calculation.

CONCLUSIONS

This work established a new equation for predicting blood/brain partition coefficient. This work took use of nonlinear regression method to predict the distribution into three main composition of brain, such as lipid, protein and water and also the different existing states of the compounds in the particular human body surroundings. Since the blood in human body is a little basic and its pH value is approximately to 7.4, the compounds in it may also ionized into different forms according to the structure properties of themselves. Therefore there would be three probable states of a given compound when it distribute into brain, which are neutral molecules, cations and anions. It was proved that to describe the three forms separately and to divide a tissue based on their composition would be more reasonable because different states usually has different partition coefficient in different chemical compositions. In this work, the equation which can describe the distribution of each state of compounds into each composition of brain, showed strong fitting and predictive power (total set: n=160, r=0.906, s=0.326, training set: n=139, r=0.908, s=0.320; testing set: n=21, r=0.903, s= 0.297). The dataset cited here contained many different molecule types, such as drug molecules, simple small molecules, carboxylic acids and also alkaloids. The versatile dataset made the methodology more credible and also could be applied more widely. It could make use of designing new drug candidates. The percentages of amount of a compound in lipid,protein and water in brain were calculated using the model, furthermore a conclusion can be obtained that a well distributed drug is mainly affected by distribution of lipid and protein..

ACKNOWLEDGEMENTS

This research was financially supported by the Research Fund of the Ministry of Education of China for Homecoming Scholars and National Natural Science Foundation of China (no. 20671013) and the Opening Fund of the Key Laboratory of radiopharmaceuticals of Ministry of Education.

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Received: 29 March, 2007 **Revised: 23 July, 2007** **Accepted: 23 July, 2007**