Convenient Nonlinear Model for Predicting the Tissue/Blood Partition Coefficients of Seven Human Tissues of Neutral, Acidic, and Basic Structurally Diverse Compounds

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In this work, the tissue/blood partition coefficients of seven human tissues were calculated using a nonlinear regression analysis. The dataset contained 80 structurally diverse compounds distributing into the brain, kidney, muscle, lung, liver, heart, and fat, whose acidic and basic properties were also considered by introducing the three possible forms of the compound in the human body (neutral, cationic, and anionic forms). A total of 248 data points were there in the training set (eq 5: $r = 0.877$, $s = 0.352$; eq 6: $r = 0.869$, $s = 0.362$) and 49 data points in the testing set (eq 5: $r = 0.844$, $s = 0.342$; eq 6: $r = 0.860$, $s = 0.311$). It was also concluded that the same state (neutral, cation, and anion) of a compound has essentially identical partition coefficients between the same tissue composition and the blood in these tissues. Only the different content of the three tissue compositions (lipid, protein, and water) lead to the different partition coefficient in different tissues, which offered a significant conclusion for the drug's distribution research.

Introduction

Combinatorial chemistry and high-throughput screening technology have greatly expedited the synthesis and screening of the drug candidates. However, a large proportion of drugs fail in development because of poor absorption, distribution, metabolism, and elimination (ADME) properties. Modern drug design focuses not only on the pharmacological activity of a compound but also considers a range of other properties including its pharmacokinetic behavior. In recent years, there has been an enormous interest in the prediction of human pharmacokinetic properties using different methods ranging from computational approaches to the use of data in vitro and in vivo. The aim of these studies is to provide screening tools for drugs. At the present time, it has been suggested that computational models should work for reliable prediction of ADME properties and for designing more successful combinatorial libraries. Parameters that define ADME properties of drug candidates are important determinants of therapeutic efficacy and thus should be optimized during early stages of drug discovery.[1] Animal pharmacokinetic studies are a routine tool to predict drug behavior in men. It seems undeniable that predictive ADME models can play an important role in improving and promoting the drug development process. Thus, it demands that the aim of our work be establishing new computational methodology that can give good predictive results without any experimental data with little consumption of time and money.

For physiologically based pharmacokinetic (PBPK) modeling, the tissue/blood partition coefficients of the drug in various tissues need to be known.[2] Although in vitro techniques for the prediction of brain penetration are available, they are experimentally laborious, time consuming, and expensive because it involves the direct measurement of the drug concentration in the brain and blood of laboratory animals and requires the synthesis of pure compounds, often in a radiolabled form to obtain reliable experimental data. Therefore, it is desirable to predict the tissue−blood distribution ratio of complex molecules from physicochemical parameters or from their molecular structures. A reliable and accurate computational model for predicting tissue/blood partition coefficients will, therefore, have a significant impact on drug research and development.

The work of our present article can be considered to be an extension of the Hansch equation,[3] which has become increasingly helpful in understanding many aspects of chemical−biological interactions in drug and pesticide research as well as many areas of toxicology.[4,5] There are generally two aspects that can be studied to obtain better models. One is to develop new descriptors,[6−11] such as hydrogen bond descriptors, solvatochromic descriptors, and polar surface area (PSA),[12−16] and so forth. The other is to set up new equations such as the Balaz's nonlinear model.[17] Poulin et al. have also done a lot of studies in tissue/plasma partition coefficient prediction.[18−20] They developed and validated two mechanistic equations in 1999 for predicting a priori the rabbit, rat, and mouse $P_{t:p}$ of nonadipose and nonexcretory tissues(bone, brain, heart, intestine, lung muscle, skin, and spleen) for 65 structurally unrelated drugs, and they evaluated the adequacy of using the $P_{t:p}$ of muscle as predictors for the $P_{t:p}$ of other tissues.[20] The first equation predicts $P_{t:p}$ at steady state, assuming a homogeneous distribution and passive diffusion of drugs in tissues, from a ratio of solubility and macromolecular binding between tissues and drugs and lipid and water levels in tissues and plasma, whereas the ratio of macromolecular binding for drugs was estimated from tissue interstitial fluid-to-plasma concentration ratios of albumin, globulins, and lipoproteins. The second equation predicts the $P_{t:p}$ of drugs residing predominantly in the interstitial space of tissues. Therefore, the fractional volume content of the interstitial space in each tissue replaced drug solubility in the first equation. Following the development of these equations, regression analyses between the $P_{t:p}$ of muscle and those of the other tissues were examined. The practical aim of this study is a worthwhile goal for pharmacokinetic screening of new drug candidates. However, this method still needs enough experimental data to acquire essential data.

Recently, we already developed several nonlinear model equations based on tissue composition for the tissue/blood partition coefficients. The dataset of one is only composed of neutral compounds. On the basis of this model, the nonlinear

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regression analysis for neutral compounds partitioning into kidney, brain, muscle, lung, liver, heart, and fat resulted in equations with high fitting power (training set: $n = 166$, $r = 0.922$, $s = 0.260$, $Q = 0.912$) and strong predictive power(test set: $n = 49$, $r = 0.922$, $s = 0.246$,$Q = 0.914$).[21] Another work did further research on both the neutral and the cationic forms of the compounds. On the basis of this model, the nonlinear regression analysis for neutral and ionized compounds partitioning into the seven tissues also resulted in excellent achievement (training set: $n = 201$, $r = 0.905$, $s = 0.291$, $Q = 0.890$; test set: $n = 64$, $r = 0.906$, $s = 0.247$).[22] However, in both of these works, the molecules used for the dataset were a little simple and structurally unitary, and there were only cationic compounds for ionic forms. The dataset indeed needs to be expanded and reinforced to give more reliable prediction models.

In present work, all of the three states of the compound that probably exist in human body are referred to as neutral, cationic, and anionic. Also, the most improvement is to extend the types of the compounds, and we introduced many diverse molecules of different series and developed a new nonlinear predicting mode. The special research of the present work on the distribution of clinical drugs will give important and significant theoretical guidance.

Materials and Methods

Tissue/Blood Partition Coefficient. In this research, the following two experimental datasets were used: the tissue/blood partition coefficients PC_t for human fat, liver, brain, kidney, muscle, lung, and heart were taken from ref 2 and 20. Their pK_a values were partly cited from ref 25, and for other compounds that were not referred to in ref 25, the values were looked up with the program Scifinder Scholar (Version 2004.2) offered by the American Chemical Society, which are calculated using Advanced Chemistry Development (ACD/Labs) Software V8.14 for Solaris (1994−2005 ACD/Labs). The Partition coefficients and pKa values are listed in Table 1. Some researchers have shown that tissue/blood partition coefficients of humans, rats, and rabbits are compatible and are often used together in regression analysis.[3,19,20,22]

Nonlinear Model. As referred to in our previous work,[21,22] the model was set up by the following method. The tissue /blood(or plasma) partition coefficient PC_t is defined as the ratio of the equilibrium concentrations C of the compound in the tissue and in blood or plasma.

The partition coefficient for a compounds partitioning between tissue (t) and blood or plasma (b) is

$$PC_t = C_t/C_b = (A_t/V_t)/C_b \quad (1)$$

With amount (A) in tissue $A_t = \Sigma C_{ij} V_i$ ($i = l, p, w$; $j = ui, +,-$).

Here, C_{ij} is the concentration of different ionic forms of the compounds in tissue composition, V_i is the volume of the tissue composition. (Subscripts l, p, and w indicate the lipid, protein, and water in tissue, respectively, and subscripts ui and $+,-$ indicate the neutral form, cationic form, and anionic form of a compound, respectively).

We obtain

$$PC_t = (\Sigma C_{ij} V_i/V_t)/C_b$$

$$= \Sigma (V_i/V_t)(C_{ij}/C_b)\ (i = l, p, w; j = ui, +,-) \quad (2)$$

Since

$$C_b = C_{bj}/f_j\ (j = ui, +,-)$$

Here, f_j is the fraction of the compound in the neutral, cationic, and anionic forms at a given pH of the aqueous phase.

Therefore

$$PC_t = \Sigma f_j (V_i/V_t)(C_{ij}/C_{bj})\ (i = l, p, w; j = ui, +,-) \quad (3)$$

With

$$\text{Volume fraction } \upsilon_i = V_i/V_t\ (i = l, p, w)$$

$$\text{Partition coefficient } P_{ij} = C_{ij}/C_{bj}\ (i = l, p, w; j = ui, +,-)$$

eq 3 is transformed to eq 4

$$\log PC_t = \log(\Sigma f_j\ 10^{\log Pij + \log \upsilon_i})\ (i = l, p, w; j = ui, +,-) \quad (4)$$

by assuming that $\log P_{ij}$ can be linearly described by corresponding physicochemical descriptors X_{ij}, such as the partition coefficients of neutral and cationic and anionic forms of a compound between octanol and water, respectively

$$\log P_{lui} = a_{1ui}X_{1ui} + a_{2ui}X_{2ui} + ... + a_{0ui}$$

$$\log P_{pui} = b_{1ui}X_{1ui} + b_{2ui}X_{2ui} + ... + b_{0ui}$$

$$\log P_{wui} = c_{1ui}X_{1ui} + c_{2ui}X_{2ui} + ... + c_{0ui}$$

$$\log P_{l+} = a_{1+}X_{1+} + a_{2+}X_{2+} + ... + a_{0+}$$

$$\log P_{p+} = b_{1+}X_{1+} + b_{2+}X_{2+} + ... + b_{0+}$$

$$\log P_{w+} = c_{1+}X_{1+} + c_{2+}X_{2+} + ... + c_{0+}$$

$$\log P_{l-} = a_{1-}X_{1-} + a_{2-}X_{2-} + ... + a_{0-}$$

$$\log P_{p-} = b_{1-}X_{1-} + b_{2-}X_{2-} + ... + b_{0-}$$

$$\log P_{w-} = c_{1-}X_{1-} + c_{2-}X_{2-} + ... + c_{0-}$$

Computational Methodologies. The structures of all of the molecules were built on Hyperchem7.0. Because many of the molecules used in this study were quite flexible, the initial conformations of the solutes were generated by carrying out the conformational search program in Hyperchem7.0. In each Monte Carlo search, 2000 possible conformers were generated. For each molecule, 25 conformations with the lowest energies were obtained. Because the computation was very slow and time consuming, the MM+ force field was applied to complete the conformation search,[11] and then, every conformer was reoptimized with AM1 method, the semiempirical method. Then, the conformer of the lowest energy for every molecule was selected to be the final structure. After all of these, all of the physicochemical parameters were computed and collected either from the log documents or fast calculating using the QSAR properties item of the Hyperchem7.0. The calculation of solvation free energies (ΔG_w) for all of the molecules was also performed using the AMSOL 6.8 program. The solvation free energies in water were computed with the AM1-SM 5.4A solvation model.

The parameters for describing the cationic and anionic forms of the compounds were also obtained by the methods mentioned above.

Physicochemical Descriptors and Methods. In the regression analysis, several physicochemical descriptors, which can be easily obtained from Hyperchem, were used. These reference parameters are the energies of the lowest unoccupied molecular

orbital (E_{lumo}), the highest occupied molecular orbit (E_{homo}), the maximum positive atomic charge (Q^{+max}), the maximum negative atomic charge (Q^{-max}), the sum of all positive atomic charges (ΣQ^+), the sum of all negative atomic charges (ΣQ^-), and the dipole moment (μ), which were obtained from the log documents of every molecule, in addition to molecular polarization (*MP*), molecular volume (*V*), molecular refraction (*MR*), the lipid-water partition coefficient log*P* calculated by Hyperchem and also the solvation free energies (ΔG_w) of the compounds.

The fractions of neutral and ionized compounds were calculated at pH 7.4 using the following formula:[23]

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

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

All descriptor values are listed in Table 2.

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, *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

First of all, 80 compounds were randomly divided into two data sets: 67 compounds in Table 1.1 as a training set and 13 compounds in Table 1.2 as a testing set.

For the analysis of the data in the training set in Table 1.1, we used eq 4 to describe the distribution of a compound between seven tissues and blood. We tested the property descriptors (Table 2), and the weight fractions were taken from ref 18 and listed in Table 3. The volume fractions (v_l,v_p, and v_w) in eq 4 can be replaced by approximately corresponding weight fractions (w_l,w_p, and w_w).[17,21,22] Some researchers have shown that the values of weight fractions are very similar among rats, rabbits, and humans.[24] Therefore, we used the weight fractions of humans instead of those of rats and rabbits in the equation.

We introduced the descriptors referred to above (E_{lumo}, E_{homo}, Q^{+max}, Q^{-max}, ΣQ^+, ΣQ^-, μ, *MP*, *V*, *MR*, log*P*, ΔG_w) into eq 4 in a stepwise manner until the statistical result cannot be further improved, and the following eqs 5 and 6 were obtained

$$\log PC_t = \log(f_{(ui)}(10^{(\log P_{l(ui)}+\log w_l)} + 10^{(\log P_{p(ui)}+\log w_p)} + 10^{(\log P_{w(ui)}+\log w_w)}) + f_{(+)}(10^{(\log P_{l(+)}+\log w_l)} + 10^{(\log P_{p(+)}+\log w_p)} + 10^{(\log P_{w(+)}+\log w_w)}) + f_{(-)}(10^{(\log P_{l(-)}+\log w_l)} + 10^{(\log P_{p(-)}+\log w_p)} + 10^{(\log P_{w(-)}+\log w_w)})) \quad (5)$$

$$\log PC_{l(ui)} = 0.286(\pm 0.084)\log P_{(ui)} \quad (5.1)$$

$$\log PC_{p(ui)} = 0.158(\pm 0.125)\log P_{(ui)} - 0.0442(\pm 0.030)E\mathrm{homo}_{(ui)} \quad (5.2)$$

$$\log PC_{w(ui)} = 0 \quad (5.3)$$

$$\log PC_{l(+)} = 0.00164(\pm 0.00023)V_{(+)} \quad (5.4)$$

$$\log PC_{p(+)} = 0.061(\pm 0.033)\mu_{(+)} + 0.398(\pm 0.126)\log P_{(+)} \quad (5.5)$$

$$\log PC_{w(+)} = 0 \quad (5.6)$$

$$\log PC_{l(-)} = -1.384(\pm 1.001) \quad (5.7)$$

$$\log PC_{p(-)} = -0.069(\pm 0.040)\,E\mathrm{homo}_{(-)} - 0.094(\pm 0.057)\log P_{(-)} \quad (5.8)$$

$$\log PC_{w(-)} = -0.019(\pm 0.009)MR_{(-)} \quad (5.9)$$

$$n = 248\ r = 0.877\ s = 0.352\ Q = 0.863$$

$$\log PC_t = \log(f_{(ui)}(10^{(\log P_{l(ui)}+\log w_l)} + 10^{(\log P_{p(ui)}+\log w_p)} + 10^{(\log P_{w(ui)}+\log w_w)}) + f_{(+)}(10^{(\log P_{l(+)}+\log w_l)} + 10^{(\log P_{p(+)}+\log w_p)} + 10^{(\log P_{w(+)}+\log w_w)}) + f_{(-)}(10^{(\log P_{l(-)}+\log w_l)} + 10^{(\log P_{p(-)}+\log w_p)} + 10^{(\log P_{w(-)}+\log w_w)})) \quad (6)$$

$$\log PC_{l(ui)} = 0.289(\pm 0.087)\log P_{(ui)} \quad (6.1)$$

$$\log PC_{p(ui)} = 0.241(\pm 0.092)\log P_{(ui)} - 0.021(\pm 0.020)\,\Delta G_{w(ui)} \quad (6.2)$$

$$\log PC_{w(ui)} = 0 \quad (6.3)$$

$$\log PC_{l(+)} = -0.021(\pm 0.004)\,\Delta G_{w(+)} \quad (6.4)$$

$$\log PC_{p(+)} = 0.063(\pm 0.030)\mu_{(+)} + 0.414(\pm 0.118)\log P_{(+)} \quad (6.5)$$

$$\log PC_{w(+)} = 0 \quad (6.6)$$

$$\log PC_{l(-)} = -1.344(\pm 0.927) \quad (6.7)$$

$$\log PC_{p(-)} = -0.003(\pm 0.002)\,\Delta G_{w(-)} - 0.106(\pm 0.066)\log P_{(-)} \quad (6.8)$$

$$\log PC_{w(-)} = -0.015(\pm 0.006)\mathrm{MR}_{(-)} \quad (6.9)$$

$$n = 248\ r = 0.869\ s = 0.363\ Q = 0.852$$

Here, the regression coefficients in parentheses are the regression coefficients of 95% confidence intervals.

Other descriptors were also used in regression analysis; however, they hardly improved these results. Furthermore, some relevant correlation matrixes with acceptable descriptor intercorrelation coefficients are presented in Table 4.

Eq 5 was used to calculate logPC_t values of the training set and the test set. The results are presented in Table 1.1 and 1.2. During model building, eight data points in the dataset were deleted as outliers, which are Alfentanil and Thioridazine in brain, trans-Retinoic acid in heart, Promethazine in lung, Ceftazidime and Penicillin in kidney, Alfentanil in muscle and Procainamide in fat. The possible reason may be that the measured results were influenced by metabolic factors and other experimental difficulties.[11] However, although the experimental data came from many different laboratories, the final models

Table 1. Logarithm of Experimental and Calculated Tissue/Blood Partition Coefficients (logPC_t) and pK_a Values of the Training Set and the Testing Set

1. Training Set

		brain			muscle		
no.	compound	exp.	eq 5	eq 6	exp.	eq 5	eq 6
1	Biperiden	0.845	1.023	0.930	0.491	1.129	1.173
2	Chlorpromazine	1.061	1.425	1.488	0.716	1.696	1.780
3	Clomipramine	1.025	1.259	1.288	0.792	1.498	1.576
4	Clotiazepam	0.505	0.226	0.240	0.204	0.259	0.282
5	Diazepam	0.505	0.336	0.368	0.152	0.349	0.407
6	Haloperidol	1.338	0.853	0.739	0.857	0.743	0.762
7	Inaperisone	1.079	0.828	0.783	0.613	0.952	0.995
8	Lidocaine		0.694	0.671		0.732	0.764
9	Midazolam	0.519	0.390	0.480	0.114	0.385	0.555
10	Nitrazepam	0.322	−0.025	−0.050	0.230	0.021	−0.028
11	Pentazocin	0.637	0.971	0.958	0.770	1.123	1.181
12	Trihexyphenidyl	1.326	0.991	0.889	1.121	1.098	1.142
13	R−Carvedilol		0.755	0.843	−0.102	0.358	0.411
14	S−Carvedilol		0.781	0.534	0.204	0.334	0.227
15	5-Methyl barbitones	−0.222	0.006	−0.043	−0.222	0.088	−0.004
16	5-Ethyl barbitones	−0.137	0.030	−0.020	−0.086	0.111	0.018
17	5-Propyl barbitones	0.079	0.059	0.010	0.146	0.138	0.046
18	5-Butyl barbitones	0.176	0.091	0.046	0.114	0.168	0.081
19	5-Pentyl barbitones	0.079	0.131	0.090	0.301	0.202	0.122
20	5-Hexyl barbitones	0.362	0.174	0.140	0.301	0.237	0.168
21	5-Heptyl barbitones	0.000	0.223	0.197	0.176	0.276	0.221
22	5-Octyl barbitones	0.230	0.278	0.262	−0.086	0.318	0.280
23	5-Nonyl barbitones		0.337	0.331	0.362	0.362	0.342
24	Nalidixic acid	−0.658	−0.696	−0.706	−0.444	−0.495	−0.508
25	Phenobarbitone		−0.027	−0.050	0.124	0.048	0.004
26	Phenytoin	−0.269	0.164	0.156	−0.357	0.213	0.194
27	Tolbutamide	−1.013	−0.767	−0.857	−0.886	−0.512	−0.623
28	Valproic acid	−1.155	−0.664	−0.677	−0.796	−0.542	−0.563
29	Dicloxacillin		−0.945	−1.030	−1.292	−0.643	−0.736
30	S-Etodolac	−1.337	−0.922	−1.010		−0.658	−0.763
31	P−Phenylbenzoic acid	−1.260	−0.874	−0.910	−1.097	−0.702	−0.755
32	Salicylic acid	−1.222	−0.561	−0.568	−0.783	−0.430	−0.441
33	N−Acetylprocainamide		0.641	0.444		0.351	0.298
34	Bromperidol	1.380	1.118	1.023		1.213	1.261
35	Cefazolin		−0.994	−1.019	−0.770	−0.693	−0.720
36	Ceftazidime		−0.842	−0.676	−0.921	−0.525	−0.354
37	Clobazam		0.351	0.354	0.415	0.367	0.401
38	Cotinine	−0.377	0.011	−0.010	−0.053	0.065	0.024
39	2,4-Dichlorophenoxyacetic acid	0.152	−0.744	−0.781		−0.582	−0.638
40	2,3-Dideoxyinosine	−0.337	−0.592	−0.552	−0.161	−0.344	−0.295
41	Digoxin		0.302	0.248	0.146	0.339	0.219
42	Fleroxacin		−0.331	−0.326	0.301	−0.224	−0.217
43	Fluphenazine	1.489	1.341	1.384		1.585	1.675
44	Flurazepam		1.252	1.181	0.690	1.403	1.462
45	Glycyrrhetinic acid	−1.398	−1.208	−1.156	−1.000	−1.115	−1.038
46	Glycyrrhizin		−1.299	−1.283	−1.260	−1.004	−0.986
47	Medazepam		0.583	0.624	0.342	0.575	0.649
48	Methotrexate		−0.878	−0.832	−0.824	−0.579	−0.530
49	*N*-Methylpentobarbital		0.485	0.456	0.114	0.417	0.423
50	Miloxacin	−0.921	−0.711	−0.747		−0.463	−0.508
51	Neostigmine		1.272	1.145		1.368	1.421
52	Nicotine	0.322	0.236	0.493	0.021	0.103	0.176
53	Norfloxacin		0.130	0.184	−0.036	0.174	0.272
54	Penicillin		−0.891	−0.945	−1.222	−0.614	−0.677
55	Pentobarbital	0.188	0.108	0.065	−0.097	0.180	0.096
56	Prazepam		0.448	0.495	0.255	0.431	0.522
57	Prednisolone	−0.319	0.269	0.335	−0.456	0.309	0.427
58	Propofol	0.914	0.520	0.522		0.477	0.468
59	Propranolol		0.913	0.961		1.063	1.122
60	Pyridostigmine		0.295	0.323	−0.284	0.094	0.103
61	trans-Retinoic acid		−1.157	−1.205	−0.155	−0.935	−1.000
62	Tetrachlorodibenzo-p-dioxin		0.674	0.709	0.643	0.587	0.658
63	Tetracycline		0.872	0.981	0.293	0.321	0.396
64	Theophyllin	−0.444	−0.464	−0.462	−0.222	−0.239	−0.237
65	Thiobarbital		0.039	0.025	−0.222	0.099	0.072
66	Thiopental		0.126	0.131	−0.301	0.165	0.169
67	Thioridazine	0.146	1.433	1.443		1.657	1.736
	R values of each tissue		0.919	0.912		0.880	0.874
	S values of each tissue		0.280	0.295		0.283	0.300

Table 1 (Continued)

		lung			kidney		
no.	compound	exp.	eq 5	eq 6	exp.	eq 5	eq 6
1	Biperiden	1.785	1.131	1.186	1.041	1.165	1.183
2	Chlorpromazine	1.806	1.710	1.796		1.704	1.785
3	Clomipramine	2.159	1.511	1.592		1.511	1.581
4	Clotiazepam	1.041	0.255	0.279		0.284	0.306
5	Diazepam	0.529	0.344	0.404		0.386	0.440
6	Haloperidol	1.728	0.721	0.757		0.831	0.812
7	Inaperisone	1.519	0.956	1.006	1.763	0.982	1.008
8	Lidocaine		0.729	0.765		0.778	0.797
9	Midazolam	0.653	0.377	0.555	0.663	0.429	0.586
10	Nitrazepam	0.255	0.020	−0.031		0.017	−0.032
11	Pentazocin	1.431	1.130	1.193	1.301	1.150	1.194
12	Trihexyphenidyl	1.869	1.101	1.155		1.133	1.149
13	R−Carvedilol		0.271	0.312	0.431	0.551	0.623
14	S−Carvedilol		0.229	0.167	0.845	0.551	0.370
15	5-Methyl barbitones	−0.215	0.090	−0.006	0.114	0.093	0.002
16	5-Ethyl barbitones	0.000	0.113	0.015	0.255	0.119	0.027
17	5-Propyl barbitones	0.176	0.140	0.043	0.591	0.149	0.059
18	5-Butyl barbitones	0.176	0.169	0.078	0.643	0.182	0.098
19	5-Pentyl barbitones	0.230	0.202	0.119	0.462	0.220	0.144
20	5-Hexyl barbitones	0.079	0.237	0.165	0.322	0.260	0.195
21	5-Heptyl barbitones	0.114	0.275	0.217	0.322	0.304	0.253
22	5-Octyl barbitones	0.491	0.315	0.275	0.398	0.352	0.317
23	5-Nonyl barbitones	0.342	0.358	0.336	0.929	0.402	0.385
24	Nalidixic acid	−0.481	−0.484	−0.498	−0.268	−0.494	−0.507
25	Phenobarbitone	−0.114	0.049	0.003	−0.137	0.059	0.017
26	Phenytoin	−0.022	0.211	0.192	0.204	0.234	0.216
27	Tolbutamide	−0.602	−0.498	−0.610	−0.658	−0.512	−0.623
28	Valproic acid	−0.377	−0.537	−0.559	0.176	−0.545	−0.566
29	Dicloxacillin	−0.921	−0.627	−0.720	0.114	−0.641	−0.734
30	S-Etodolac		−0.644	−0.750	−0.409	−0.656	−0.761
31	P−Phenylbenzoic acid	−0.553	−0.693	−0.748	−0.523	−0.702	−0.756
32	Salicylic acid	−0.721	−0.424	−0.435	−0.357	−0.434	−0.445
33	N−Acetylprocainamide		0.295	0.271		0.494	0.381
34	Bromperidol		1.215	1.273		1.252	1.272
35	Cefazolin	−0.602	−0.677	−0.704	0.447	−0.690	−0.718
36	Ceftazidime	−0.357	−0.508	−0.337	0.681	−0.523	−0.353
37	Clobazam		0.362	0.399		0.404	0.432
38	Cotinine	−0.180	0.064	0.022		0.065	0.024
39	2,4-Dichlorophenoxyacetic acid		−0.574	−0.631		−0.584	−0.640
40	2,3-Dideoxyinosine		−0.330	−0.281		−0.344	−0.295
41	Digoxin		0.336	0.209		0.368	0.259
42	Fleroxacin	0.332	−0.221	−0.213		−0.216	−0.209
43	Fluphenazine		1.597	1.691		1.597	1.680
44	Flurazepam		1.409	1.477		1.431	1.467
45	Glycyrrhetinic acid	−0.658	−1.113	−1.034		−1.076	−1.003
46	Glycyrrhizin	−1.260	−0.988	−0.970		−0.999	−0.981
47	Medazepam		0.567	0.644		0.628	0.696
48	Methotrexate		−0.563	−0.514		−0.577	−0.528
49	*N*-Methylpentobarbital		0.402	0.412		0.481	0.477
50	Miloxacin	−0.292	−0.450	−0.495		−0.463	−0.508
51	Neostigmine		1.370	1.435		1.408	1.427
52	Nicotine	0.176	0.079	0.113		0.166	0.320
53	Norfloxacin		0.171	0.274		0.190	0.285
54	Penicillin		−0.599	−0.662	0.568	−0.613	−0.675
55	Pentobarbital		0.180	0.093		0.197	0.117
56	Prazepam		0.422	0.518		0.481	0.564
57	Prednisolone		0.306	0.429		0.336	0.448
58	Propofol		0.464	0.454		0.536	0.530
59	Propranolol		1.070	1.129		1.089	1.146
60	Pyridostigmine		0.058	0.063		0.182	0.200
61	trans-Retinoic acid		−0.924	−0.989		−0.927	−0.990
62	Tetrachlorodibenzo-p-dioxin		0.568	0.644		0.664	0.726
63	Tetracycline		0.167	0.221		0.595	0.692
64	Theophyllin		−0.227	−0.225		−0.241	−0.238
65	Thiobarbital		0.099	0.071		0.113	0.087
66	Thiopental	0.041	0.162	0.167	0.491	0.192	0.197
67	Thioridazine		1.669	1.751		1.673	1.741
	R values of each tissue		0.936	0.950		0.842	0.841
	S values of each tissue		0.220	0.203		0.299	0.316

Table 1 (Continued)

		liver			heart		
no.	compound	exp.	eq 5	eq 6	exp.	eq 5	eq 6
1	Biperiden		1.216	1.210	0.845	1.222	1.191
2	Chlorpromazine		1.762	1.812	1.146	1.739	1.786
3	Clomipramine		1.549	1.608	1.611	1.531	1.582
4	Clotiazepam		0.306	0.327	0.415	0.321	0.338
5	Diazepam		0.421	0.470	0.356	0.443	0.485
6	Haloperidol		0.889	0.857	1.155	0.940	0.880
7	Inaperisone	1.531	1.030	1.036	0.869	1.032	1.022
8	Lidocaine		0.833	0.833		0.850	0.841
9	Midazolam	0.944	0.471	0.618	0.623	0.498	0.627
10	Nitrazepam		0.000	−0.049	0.146	0.000	−0.046
11	Pentazocin	0.362	1.182	1.224	0.735	1.180	1.209
12	Trihexyphenidyl		1.174	1.176	1.358	1.181	1.155
13	R−Carvedilol	0.643	0.638	0.723	0.544	0.746	0.838
14	S−Carvedilol	1.079	0.643	0.443	0.869	0.760	0.535
15	5-Methyl barbitones	0.447	0.094	0.001	−0.260	0.091	0.005
16	5-Ethyl barbitones	0.568	0.123	0.029	−0.161	0.122	0.036
17	5-Propyl barbitones	0.462	0.157	0.066	0.041	0.158	0.074
18	5-Butyl barbitones	0.477	0.195	0.110	0.279	0.198	0.120
19	5-Pentyl barbitones	0.505	0.238	0.161	0.380	0.244	0.173
20	5-Hexyl barbitones	0.447	0.283	0.216	0.362	0.292	0.231
21	5-Heptyl barbitones	0.146	0.332	0.279	0.204	0.345	0.297
22	5-Octyl barbitones	0.204	0.386	0.348	0.204	0.403	0.368
23	5-Nonyl barbitones	0.322	0.443	0.420	0.591	0.464	0.442
24	Nalidixic acid	−0.237	−0.473	−0.493	−0.310	−0.493	−0.512
25	Phenobarbitone	0.255	0.070	0.027	0.161	0.072	0.032
26	Phenytoin	0.362	0.253	0.234	−0.377	0.263	0.245
27	Tolbutamide	−0.523	−0.479	−0.606	−0.569	−0.506	−0.629
28	Valproic acid	0.255	−0.548	−0.567	−0.367	−0.561	−0.578
29	Dicloxacillin	−0.367	−0.600	−0.709	−1.131	−0.630	−0.737
30	S-Etodolac	−0.886	−0.625	−0.741	−0.347	−0.651	−0.765
31	P−Phenylbenzoic acid	−0.456	−0.692	−0.748	−0.638	−0.710	−0.763
32	Salicylic acid	−0.638	−0.434	−0.445	−0.721	−0.449	−0.459
33	N−Acetylprocainamide		0.573	0.432	0.335	0.659	0.489
34	Bromperidol		1.306	1.301		1.314	1.284
35	Cefazolin		−0.650	−0.693	−0.921	−0.679	−0.721
36	Ceftazidime		−0.479	−0.328	−0.658	−0.509	−0.359
37	Clobazam		0.437	0.460		0.457	0.473
38	Cotinine		0.055	0.015	−0.319	0.055	0.018
39	2,4-Dichlorophenoxyacetic acid		−0.578	−0.637		−0.595	−0.651
40	2,3-Dideoxyinosine		−0.319	−0.277		−0.345	−0.304
41	Digoxin		0.397	0.285	0.130	0.413	0.312
42	Fleroxacin		−0.202	−0.197	0.407	−0.207	−0.202
43	Fluphenazine		1.673	1.707		1.654	1.680
44	Flurazepam		1.484	1.494		1.482	1.469
45	Glycyrrhetinic acid		−1.015	−0.963	−0.921	−1.003	−0.957
46	Glycyrrhizin		−0.957	−0.953	−1.602	−0.984	−0.979
47	Medazepam		0.683	0.737		0.713	0.759
48	Methotrexate		−0.535	−0.504		−0.563	−0.533
49	*N*-Methylpentobarbital		0.524	0.517		0.563	0.549
50	Miloxacin		−0.436	−0.491		−0.462	−0.516
51	Neostigmine		1.449	1.454		1.458	1.430
52	Nicotine		0.200	0.392	−0.009	0.251	0.486
53	Norfloxacin		0.202	0.300		0.211	0.300
54	Penicillin		−0.580	−0.654	−1.000	−0.607	−0.680
55	Pentobarbital		0.214	0.133	0.241	0.219	0.145
56	Prazepam		0.529	0.600	−0.174	0.559	0.620
57	Prednisolone		0.361	0.472	0.393	0.376	0.475
58	Propofol		0.593	0.575		0.630	0.613
59	Propranolol		1.144	1.181		1.141	1.178
60	Pyridostigmine		0.228	0.248	0.041	0.294	0.321
61	trans-Retinoic acid		−0.893	−0.966	0.301	−0.912	−0.981
62	Tetrachlorodibenzo-p-dioxin		0.735	0.778		0.784	0.816
63	Tetracycline		0.701	0.814		0.835	0.953
64	Theophyllin		−0.220	−0.225		−0.244	−0.248
65	Thiobarbital		0.124	0.098		0.129	0.105
66	Thiopental	0.362	0.219	0.220	0.093	0.233	0.234
67	Thioridazine		1.725	1.767		1.709	1.741
	R values of each tissue		0.834	0.814		0.899	0.885
	S values of each tissue		0.298	0.324		0.263	0.283

Table 1 (Continued)

no.	compound	fat exp.	fat eq 5	fat eq 6	pka[c]	no.	compound	fat exp.	fat eq 5	fat eq 6	pka[c]
1	Biperiden	1.763	1.541	1.138	8.800 [a]	37	Clobazam		0.827	0.785	/
2	Chlorpromazine	1.613	1.605	1.567	9.300 [a]	38	Cotinine		−0.116	−0.130	6.330
3	Clomipramine	1.934	1.531	1.357	8.500 [a]	39	2,4-Dichlorophenoxyacetic acid		−1.012	−1.046	4.720
4	Clotiazepam	0.771	0.600	0.594	3.600 [a]	40	2,3-Dideoxyinosine		−0.800	−0.759	9.000[a]
5	Diazepam		0.822	0.815	3.500 [a]	41	Digoxin		0.731	0.706	13.500
6	Haloperidol	1.447	1.538	1.321	7.800 [a]	42	Fleroxacin		−0.208	−0.208	/
7	Inaperisone	1.204	1.298	1.056	9.700	43	Fluphenazine		1.624	1.451	7.030
8	Lidocaine		1.245	1.157	8.530	44	Flurazepam		1.722	1.279	7.210
9	Midazolam	0.954	0.927	0.930	5.650	45	Glycyrrhetinic acid		−0.625	−0.638	9.760
10	Nitrazepam	0.362	−0.318	−0.342	3.190	46	Glycyrrhizin		−1.218	−1.199	4.710
11	Pentazocin	0.398	1.412	1.239	8.900	47	Medazepam		1.190	1.181	2.750
12	Trihexyphenidyl	1.881	1.504	1.047	8.700 [a]	48	Methotrexate		−0.927	−0.898	2.610
13	R−Carvedilol		1.531	1.645	8.030	49	*N*-Methylpentobarbital		1.080	1.020	5.090
14	S−Carvedilol		1.570	1.264	8.030	50	Miloxacin		−0.892	−0.927	8.220
15	5-Methyl barbitones	−0.456	0.032	0.003	7.950[b]	51	Neostigmine		1.818	1.261	2.740
16	5-Ethyl barbitones	−0.143	0.126	0.100	7.950[b]	52	Nicotine		0.777	1.219	8.000
17	5-Propyl barbitones	0.114	0.225	0.201	7.950[b]	53	Norfloxacin		0.387	0.401	8.000
18	5-Butyl barbitones	0.255	0.325	0.303	7.950[b]	54	Penicillin		−0.993	−1.034	7.030
19	5-Pentyl barbitones	0.544	0.429	0.409	7.950[b]	55	Pentobarbital		0.395	0.374	7.880
20	5-Hexyl barbitones	1.079	0.533	0.514	7.950[b]	56	Prazepam		1.021	1.013	8.050
21	5-Heptyl barbitones	0.940	0.642	0.624	7.950[b]	57	Prednisolone		0.669	0.676	3.440
22	5-Octyl barbitones	0.663	0.752	0.734	7.950[b]	58	Propofol		1.143	1.124	9.430
23	5-Nonyl barbitones	0.699	0.860	0.843	7.950[b]	59	Propranolol		1.352	1.392	11.000
24	Nalidixic acid	−1.000	−0.787	−0.794	5.950	60	Pyridostigmine		0.907	0.962	9.140
25	Phenobarbitone	−0.523	0.160	0.146	7.630	61	trans-Retinoic acid		−0.989	−1.011	/
26	Phenytoin	0.255	0.491	0.480	8.330	62	Tetrachlorodibenzo-p-dioxin		1.366	1.348	4.790
27	Tolbutamide	−0.886	−0.923	−1.008	/	63	Tetracycline		1.685	1.817	/
28	Valproic acid	−0.824	−0.940	−0.947	4.820	64	Theophyllin		−0.723	−0.723	9.690
29	Dicloxacillin		−1.004	−1.065	2.600	65	Thiobarbital		0.260	0.250	1.050
30	S-Etodolac	−0.770	−1.015	−1.079	4.310	66	Thiopental	0.892	0.530	0.520	7.860
31	P−Phenylbenzoic acid	−1.229	−1.045	−1.070	4.190	67	Thioridazine		1.763	1.510	7.760
32	Salicylic acid		−0.917	−0.920	3.010		R values of each tissue		0.917	0.903	
33	N−Acetylprocainamide		1.376	1.085			S values of each tissue		0.350	0.344	
34	Bromperidol		1.658	1.271	9.750						
35	Cefazolin		−1.038	−1.055	/						
36	Ceftazidime		−0.914	−0.789	8.250						
					2.600						

2. Testing Set

no.	compound	brain exp.	brain eq 5	brain eq 6	muscle exp.	muscle eq 5	muscle eq 6
test-1	Alfentanil	−0.886	0.501	0.323	−0.509	0.403	0.364
test-2	Fentanyl	0.556	0.981	0.767	0.494	0.897	0.903
test-3	Promethazine	1.301	0.863	0.811	1.188	0.996	1.042
test-4	Hexobarbitone		0.068	0.028	−0.201	0.130	0.053
test-5	R-Etodolac	−1.509	−0.922	−1.008		−0.658	−0.760
test-6	Ethoxybenzamide	−0.009	0.219	0.188	−0.094	0.254	0.187
test-7	Methicillin		−0.921	−0.919	−0.721	−0.639	−0.636
test-8	Pefloxacin	−0.854	−0.332	−0.294	0.354	−0.229	−0.167
test-9	Pipemidic acid	−1.000	−0.016	0.004	−0.284	0.047	0.083
test-10	Procainamide		0.574	0.469	0.490	0.402	0.390
test-11	Morphine		0.546	0.670	0.398	0.488	0.538
test-12	Clozapine	1.301	0.555	0.605		0.632	0.743
test-13	Promazine	1.796	1.207	1.256		1.447	1.520
	R values of each tissue		0.920	0.937		0.822	0.852
	S values of each tissue		0.305	0.273		0.314	0.293

no.	compound	lung exp.	lung eq 5	lung eq 6	kidney exp.	kidney eq 5	kidney eq 6
test-1	Alfentanil	−0.108	0.384	0.361	−0.086	0.476	0.394
test-2	Fentanyl	1.139	0.879	0.909	1.079	0.980	0.930
test-3	Promethazine	2.179	1.001	1.054		1.024	1.053
test-4	Hexobarbitone	0.519	0.130	0.049	0.176	0.140	0.064
test-5	R-Etodolac		−0.644	−0.747	−0.921	−0.656	−0.758
test-6	Ethoxybenzamide	−0.009	0.251	0.180		0.278	0.215
test-7	Methicillin	−0.553	−0.624	−0.621		−0.638	−0.635
test-8	Pefloxacin		−0.225	−0.162		−0.220	−0.160
test-9	Pipemidic acid		0.047	0.084		0.052	0.088
test-10	Procainamide		0.370	0.373		0.501	0.456
test-11	Morphine		0.473	0.513	0.978	0.552	0.628

Table 1 (Continued)

		2. Testing Set				
test-13	Promazine	1.459	1.534		1.459	1.528
	R values of each tissue	0.827	0.828		0.898	0.923
	S values of each tissue	0.352	0.358		0.273	0.252

		liver			heart		
no.	compound	exp.	eq 5	eq 6	exp.	eq 5	eq 6
test-1	Alfentanil	0.000	0.525	0.421	−0.260	0.571	0.435
test-2	Fentanyl	0.580	1.041	0.964	0.658	1.087	0.965
test-3	Promethazine		1.061	1.080	1.544	1.062	1.062
test-4	Hexobarbitone	0.778	0.146	0.067	0.041	0.149	0.077
test-5	R-Etodolac	−0.921	−0.636	−0.739	−0.745	−0.662	−0.762
test-6	Ethoxybenzamide		0.297	0.234	0.009	0.310	0.254
test-7	Methicillin		−0.615	−0.613	−0.602	−0.643	−0.640
test-8	Pefloxacin		−0.209	−0.147	0.348	−0.213	−0.154
test-9	Pipemidic acid		0.054	0.091	−0.201	0.055	0.090
test-10	Procainamide		0.560	0.501		0.624	0.544
test-11	Morphine	0.079	0.599	0.687		0.637	0.742
test-12	Clozapine		0.700	0.796		0.710	0.795
test-13	Promazine		1.489	1.557		1.472	1.535
	R values of each tissue		0.718	0.698		0.800	0.841
	S values of each tissue		0.444	0.477		0.398	0.347

		fat			pK_a[c]
no.	compound	exp.	eq 5	eq 6	
test-1	Alfentanil	0.230	1.127	0.743	6.500 [b]
test-2	Fentanyl	1.431	1.671	1.207	8.990 [b]
test-3	Promethazine	2.124	1.329	1.029	8.980
test-4	Hexobarbitone	0.204	0.199	0.183	8.380
test-5	R-Etodolac	−1.167	−1.012	−1.077	4.310
test-6	Ethoxybenzamide		0.567	0.564	13.500
test-7	Methicillin		−1.007	−1.005	6.180
test-8	Pefloxacin		−0.205	−0.185	8.760
test-9	Pipemidic acid		0.024	0.036	7.880
test-10	Procainamide	−0.886	1.260	1.074	12.470
test-11	Morphine		1.157	1.352	8.140
test-12	Clozapine		1.030	0.996	6.650
test-13	Promazine		1.477	1.443	9.860
	R values of each tissue		0.879	0.900	
	S values of each tissue		0.598	0.463	

[a] Cited from ref 25. [b] The same value as that of barbitone, for it could not be obtained using the methods described below for other molecules. But their structure properties were similar to those of barbitone. [c] Looked up with the program Scifinder Scholar (Version 2004.2) offered by the American Chemical Society, calculated using Advanced Chemistry Development (ACD/Labs) Software V8.14 for Solaris (1994−2005 ACD/Labs).

still offerred quite satisfactory results for the distribution prediction, suggesting that the models have very strong predictive power.

The plots of calculated versus experimental logPC_t values of seven tissues for the training set (248 data points) and the test set (49 data points) are shown in Figures 1−4.From Table 1.1 and 1.2 and Figures 1−4, we can see that both eqs 5 and 6 offerred excellent results for predicting the distribution into the seven tissues. The underling equations of eq 5 and 6 respectively express the distribution equilibrium of every composition (lipid, protein, and water). Also, by modulating the volume fractions or weight fractions of the three tissue compositions in different tissues, we can conveniently obtain the tissue/blood partition coefficients. For the prediction of the training set, generally eq 5 gave better results than eq 6, except for the prediction of the lung, whereas for the compounds in the testing set, the results offerred by eq 6 were better than those by eq 5. That may be caused by the randomness of data selection between the training set and the testing set. In the testing set, the prediction of the distribution in liver is a little poorer than that in others. The reason may probably be that the data of liver used here may not be that reasonable, either caused by errors in measuring methods or the randomness of data selection. Some different training sets and testing sets including different compounds in Table 1.1 and 1.2 were also used to reproduce eqs 5 and 6, and all of the results fluctuated in a tiny scale, and all of them showed high accordance with present results, which shows that eqs 5 and 6 are robust enough.

From eq 5.1, it can be seen that for neutral compounds, log$P$, the *n*-octanol/water partition coefficient, is an important and significant parameter for predicting the absorption mechanism of the drugs that distribute into the lipid in tissues. This equation suggests that log$P$ shows a positive relationship with lipid absorption of drugs. High positive log$P$ values means that the structures of the compunds show more lipophilic properties, which play an essential part in the interaction with the lipid molecules and benefit by the entering into the lipid composition of the tissues.

Eq 5.2 shows that for the protein-binding prediction of the neutral molecules, both log$P$ and E_{homo} are effective and significant descriptors. log$P$ has positive relativity with the protein distribution of the neutral molecules. That means molecules that show more lipophlic properties tend to enter into the protein easily. E_{homo} is the energy of the highest occupied molecular orbit, an electronic parameter. This work shows that the value of E_{homo} has a negative relationship with protein absorption, that is, the lower the energy of the highest occupied molecular orbit, the easier the drug molecule can enter into the protein of the tissues. Traditionally, it is thought that because the highest occupied molecular orbit bears the highest orbital energy of all of the orbits, the electrons on it may have the most active properties in the molecule. However, in our work,

Table 2. Physicochemical Property Data of Compounds (Training Set and Testing Set)

no.	compound	log$P_{(ui)}$	Ehomo$_{(ui)}$	$\Delta G_{w(ui)}$	Volume$_{(+)}$	$\mu_{(+)}$	log$P_{(+)}$
1	Biperiden	3.470	−8.832	−3.911	982.240	12.517	2.750
2	Chlorpromazine	3.820	−7.718	−7.364	917.660	20.048	3.100
3	Clomipramine	4.520	−8.400	−4.614	921.960	12.562	3.800
4	Clotiazepam	2.210	−8.875	−11.900	/	/	/
5	Diazepam	3.010	−9.220	−11.890	/	/	/
6	Haloperidol	3.380	−9.313	−11.874	1063.700	6.495	2.660
7	Inaperisone	3.150	−9.166	−6.886	843.020	12.119	2.430
8	Lidocaine	2.380	−8.903	−5.867	814.940	12.380	1.660
9	Midazolam	3.410	−9.015	−17.493	/	/	/
10	Nitrazepam	−1.670	−9.852	−15.262	770.770	7.413	−1.860
11	Pentazocin	3.330	−8.885	−7.700	890.790	7.302	3.550
12	Trihexyphenidyl	3.970	−9.163	0.546	959.790	8.781	3.250
13	R-Carvedilol	1.050	−8.445	−19.559	1049.860	6.572	0.440
14	S-Carvedilol	1.050	−8.313	−15.551	1074.490	2.969	0.440
15	5-Methyl barbitones	0.340	−11.407	−10.203	/	/	/
16	5-Ethyl barbitones	0.740	−11.372	−9.562	/	/	/
17	5-Propyl barbitones	1.140	−11.366	−9.157	/	/	/
18	5-Butyl barbitones	1.530	−11.363	−9.068	/	/	/
19	5-Pentyl barbitones	1.930	−11.363	−8.860	/	/	/
20	5-Hexyl barbitones	2.320	−11.322	−8.696	/	/	/
21	5-Heptyl barbitones	2.720	−11.254	−8.510	/	/	/
22	5-Octyl barbitones	3.120	−11.206	−8.348	/	/	/
23	5-Nonyl barbitones	3.510	−11.172	−8.172	/	/	/
24	Nalidixic acid	0.810	−9.396	−15.758	/	/	/
25	Phenobarbitone	1.250	−10.004	−11.986	/	/	/
26	Phenytoin	1.970	−9.677	−10.795	/	/	/
27	Tolbutamide	1.940	−10.317	−14.343	/	/	/
28	Valproic acid	2.770	−11.195	−5.665	/	/	/
29	Dicloxacillin	1.300	−9.105	−22.793	/	/	/
30	S-Etodolac	1.660	−8.329	−12.210	/	/	/
31	P-Phenylbenzoic acid	3.430	−9.156	−9.645	/	/	/
32	Salicylic acid	1.460	−9.462	−10.693	/	/	/
33	N-Acetylprocainamide	0.640	−8.960	−14.671	900.040	12.047	−0.080
34	Bromperidol	3.650	−9.307	−7.021	1076.070	13.366	2.930
35	Cefazolin	1.750	−8.920	−55.252	/	/	/
36	Ceftazidime	0.130	−8.551	−111.830	/	/	/
37	Clobazam	2.460	−8.962	−12.085	816.040	6.969	2.190
38	Cotinine	−0.660	−9.689	−15.803	/	/	/
39	2,4-Dichlorophenoxyacetic acid	2.370	−9.383	−8.599	/	/	/
40	2,3-Dideoxyinosine	−0.550	−9.649	−68.716	/	/	/
41	Digoxin	2.670	−10.243	0.000	/	/	/
42	Fleroxacin	0.940	−8.865	−18.214	/	/	/
43	Fluphenazine	3.540	−7.849	−11.791	1160.510	26.384	2.820
44	Flurazepam	3.810	−9.108	−12.028	1077.000	14.892	3.090
45	Glycyrrhetinic acid	7.040	−9.741	−13.236	/	/	/
46	Glycyrrhizin	4.390	−9.941	−34.142	/	/	/
47	Medazepam	4.290	−9.241	−7.691	790.590	9.945	3.100
48	Methotrexate	1.060	−9.103	−82.013	/	/	/
49	*N*-Methylpentobarbital	2.110	−10.778	−6.370	735.570	3.948	1.840
50	Miloxacin	−0.180	−9.094	−20.019	/	/	/
51	Neostigmine	/	/	/	1147.660	8.856	3.900
52	Nicotine	0.220	−9.395	−9.368	575.750	7.216	−0.500
53	Norfloxacin	1.490	−8.619	−21.282	/	/	/
54	Penicillin	0.910	−9.067	−18.260	/	/	/
55	Pentobarbital	1.860	−11.247	−8.364	/	/	/
56	Prazepam	3.720	−9.186	−11.054	914.960	5.007	3.720
57	Prednisolone	2.450	−9.980	−20.245	/	/	/
58	Propofol	4.150	−8.871	−1.475	/	/	/
59	Propranolol	2.800	−8.519	−8.635	849.070	15.033	2.190
60	Pyridostigmine	/	/	/	608.560	6.617	−0.580
61	trans-Retinoic acid	4.730	−8.508	−5.646	/	/	/
62	Tetrachlorodibenzo-p-dioxin	4.930	−8.998	−4.229	/	/	/
63	Tetracycline	−2.210	−9.279	−28.246	1093.670	12.596	−2.930
64	Theophyllin	−1.310	−9.066	−22.723	/	/	/
65	Thiobarbital	1.390	−9.377	−11.589	/	/	/
66	Thiopental	2.510	−9.354	−10.357	/	/	/
67	Thioridazine	4.180	−7.444	−8.464	1071.060	16.924	3.460

Table 2 (Continued)

no.	compound	log$P_{(ui)}$	Ehomo$_{(ui)}$	$\Delta G_{w(ui)}$	Volume$_{(+)}$	$\mu_{(+)}$	log$P_{(+)}$
test-1	Alfentanil	2.370	−9.422	−8.507	1233.640	12.307	1.650
test-2	Fentanyl	3.770	−9.004	−8.420	1072.280	5.577	3.050
test-3	Promethazine	3.660	−7.397	−8.599	837.070	8.947	2.940
test-4	Hexobarbitone	0.850	−9.872	−7.638	/	/	/
test-5	R-Etodolac	1.660	−8.173	−9.068	/	/	/
test-6	Ethoxybenzamide	2.140	−8.960	−3.564	/	/	/
test-7	Methicillin	0.850	−9.344	−26.110	/	/	/
test-8	Pefloxacin	0.980	−8.761	−23.080	/	/	/
test-9	Pipemidic acid	0.300	−9.238	−22.691	/	/	/
test-10	Procainamide	1.270	−8.105	−6.036	820.310	10.916	0.540
test-11	Morphine	1.650	−8.692	−13.951	787.720	12.016	0.930
test-12	Clozapine	3.450	−8.434	−14.770	974.930	17.806	2.720
test-13	Promazine	3.300	−7.655	−11.261	879.040	19.196	2.580

no.	compound	ΔG_{w+}	Ehomo$_{(-)}$	log$P_{(-)}$	$MR_{(-)}$	$\Delta G_{w(-)}$
1	Biperiden	−51.341	/	/	/	/
2	Chlorpromazine	−66.048	/	/	/	/
3	Clomipramine	−55.171	/	/	/	/
4	Clotiazepam	/	/	/	/	/
5	Diazepam	/	/	/	/	/
6	Haloperidol	−70.542	/	/	/	/
7	Inaperisone	−49.941	/	/	/	/
8	Lidocaine	−58.431	/	/	/	/
9	Midazolam	/	/	/	/	/
10	Nitrazepam	−65.307	/	/	/	/
11	Pentazocin	−58.067	/	/	/	/
12	Trihexyphenidyl	−44.920	/	/	/	/
13	R-Carvedilol	−87.037	/	/	/	/
14	S-Carvedilol	−68.539	/	/	/	/
15	5-Methyl barbitones	/	−5.222	0.720	36.350	−81.029
16	5-Ethyl barbitones	/	−5.224	1.120	40.950	−79.630
17	5-Propyl barbitones	/	−5.239	1.510	45.550	−79.524
18	5-Butyl barbitones	/	−5.246	1.910	50.150	−79.450
19	5-Pentyl barbitones	/	−5.253	2.310	54.760	−79.063
20	5-Hexyl barbitones	/	−5.257	2.700	59.360	−78.967
21	5-Heptyl barbitones	/	−5.260	3.100	63.960	−78.740
22	5-Octyl barbitones	/	−5.261	3.500	68.560	−78.556
23	5-Nonyl barbitones	/	−5.263	3.890	73.160	−78.418
24	Nalidixic acid	/	−4.823	2.230	62.010	−106.514
25	Phenobarbitone	/	−5.390	1.940	56.450	−83.817
26	Phenytoin	/	−4.582	2.640	66.680	−76.981
27	Tolbutamide	/	−6.278	2.590	66.970	−101.509
28	Valproic acid	/	−4.141	4.030	39.920	−82.853
29	Dicloxacillin	/	−5.337	2.720	109.620	−91.928
30	S-Etodolac	/	−5.044	3.080	81.760	−76.684
31	P-Phenylbenzoic acid	/	−4.864	4.850	57.620	−84.313
32	Salicylic acid	/	−4.577	2.880	34.180	−99.588
33	N-Acetylprocainamide	−55.648	/	/	/	/
34	Bromperidol	−59.407	/	/	/	/
35	Cefazolin	/	−5.246	3.170	114.710	−113.160
36	Ceftazidime	/	−5.621	1.550	137.940	−190.440
37	Clobazam	−58.043	/	/	/	/
38	Cotinine	/	/	/	/	/
39	2,4-Dichlorophenoxyacetic acid	/	−4.772	3.790	47.880	−78.985
40	2,3-Dideoxyinosine	/	−4.326	−0.510	54.530	−121.261
41	Digoxin	/	/	/	/	/
42	Fleroxacin	/	−5.097	2.360	89.710	−98.082
43	Fluphenazine	−70.369	/	/	/	/
44	Flurazepam	−53.612	/	/	/	/
45	Glycyrrhetinic acid	/	−4.535	8.460	133.940	−90.103
46	Glycyrrhizin	/	−4.468	5.810	194.020	−110.928
47	Medazepam	−63.974	/	/	/	/
48	Methotrexate	/	−5.859	2.480	115.360	−104.592
49	*N*-Methylpentobarbital	−53.899	/	/	/	/
50	Miloxacin	/	−4.994	1.240	61.290	−98.444
51	Neostigmine	−53.550	/	/	/	/
52	Nicotine	−66.786	/	/	/	/
53	Norfloxacin	/	−4.941	2.910	85.140	−94.338
54	Penicillin	/	−4.840	2.330	84.100	−89.699
55	Pentobarbital	/	−5.259	2.240	54.700	−78.701
56	Prazepam	−49.800	/	/	/	/

Table 2 (Continued)

no.	compound	ΔG_{w+}	$E\text{homo}_{(-)}$	$\log P_{(-)}$	$MR_{(-)}$	$\Delta G_{w(-)}$
57	Prednisolone	/	/	/	/	/
58	Propofol	/	/	/	/	/
59	Propranolol	−67.899	/	/	/	/
60	Pyridostigmine	−49.921	/	/	/	/
61	trans-Retinoic acid	/	−4.818	6.150	97.460	−82.628
62	Tetrachlorodibenzo-p-dioxin	/	/	/	/	/
63	Tetracycline	−91.216	/	/	/	/
64	Theophyllin	/	−4.138	−1.400	41.520	−97.830
65	Thiobarbital	/	−4.621	1.770	48.940	−77.426
66	Thiopental	/	−4.643	2.890	62.690	−76.579
67	Thioridazine	−62.679	/	/	/	/
test-1	Alfentanil	−58.799	/	/	/	/
test-2	Fentanyl	−59.281	/	/	/	/
test-3	Promethazine	−46.458	/	/	/	/
test-4	Hexobarbitone	/	−5.268	2.010	57.480	−82.523
test-5	R-Etodolac	/	−5.045	3.080	81.760	−77.941
test-6	Ethoxybenzamide	/	/	/	/	/
test-7	Methicillin	/	−4.490	2.270	89.520	−106.161
test-8	Pefloxacin	/	−4.876	2.400	89.650	−111.123
test-9	Pipemidic acid	/	−4.953	1.720	79.780	−103.362
test-10	Procainamide	−54.862	/	/	/	/
test-11	Morphine	−71.420	/	/	/	/
test-12	Clozapine	−59.882	/	/	/	/
test-13	Promazine	−64.760	/	/	/	/

no.	compound	$f_{(ui)}$	$f_{(+)}$	$f_{(-)}$
1	Biperiden	0.038	0.962	0.000
2	Chlorpromazine	0.012	0.988	0.000
3	Clomipramine	0.074	0.926	0.000
4	Clotiazepam	1.000	0.000	0.000
5	Diazepam	1.000	0.000	0.000
6	Haloperidol	0.285	0.715	0.000
7	Inaperisone	0.129	0.871	0.000
8	Lidocaine	0.069	0.931	0.000
9	Midazolam	0.983	0.017	0.000
10	Nitrazepam	1.000	0.000	0.000
11	Pentazocin	0.031	0.969	0.000
12	Trihexyphenidyl	0.048	0.952	0.000
13	R-Carvedilol	0.190	0.810	0.000
14	S-Carvedilol	0.190	0.810	0.000
15	5-Methyl barbitones	0.780	0.000	0.220
16	5-Ethyl barbitones	0.780	0.000	0.220
17	5-Propyl barbitones	0.780	0.000	0.220
18	5-Butyl barbitones	0.780	0.000	0.220
19	5-Pentyl barbitones	0.780	0.000	0.220
20	5-Hexyl barbitones	0.780	0.000	0.220
21	5-Heptyl barbitones	0.780	0.000	0.220
22	5-Octyl barbitones	0.780	0.000	0.220
23	5-Nonyl barbitones	0.780	0.000	0.220
24	Nalidixic acid	0.034	0.000	0.966
25	Phenobarbitone	0.629	0.000	0.371
26	Phenytoin	0.895	0.000	0.105
27	Tolbutamide	0.000	0.000	1.000
28	Valproic acid	0.003	0.000	0.997
29	Dicloxacillin	0.000	0.000	1.000
30	S-Etodolac	0.001	0.000	0.999
31	P-Phenylbenzoic acid	0.001	0.000	0.999
32	Salicylic acid	0.000	0.000	1.000
33	N-Acetylprocainamide	0.005	0.996	0.000
34	Bromperidol	0.124	0.876	0.000
35	Cefazolin	0.000	0.000	1.000
36	Ceftazidime	0.000	0.000	1.000
37	Clobazam	0.849	0.151	0.000
38	Cotinine	0.998	0.002	0.000
39	2,4-Dichlorophenoxyacetic acid	0.000	0.000	1.000
40	2,3-Dideoxyinosine	0.000	0.000	1.000
41	Digoxin	1.000	0.000	0.000
42	Fleroxacin	0.299	0.000	0.701
43	Fluphenazine	0.608	0.392	0.000
44	Flurazepam	0.004	0.996	0.000
45	Glycyrrhetinic acid	0.002	0.000	0.998

Table 2 (Continued)

no.	compound	$f_{(ui)}$	$f_{(+)}$	$f_{(-)}$	no.	compound	$f_{(ui)}$	$f_{(+)}$	$f_{(-)}$
46	Glycyrrhizin	0.000	0.000	1.000	64	Theophyllin	0.000	0.000	1.000
47	Medazepam	0.943	0.057	0.000	65	Thiobarbital	0.743	0.000	0.258
48	Methotrexate	0.005	0.000	0.995	66	Thiopental	0.696	0.000	0.304
49	*N*-Methylpentobarbital	0.132	0.869	0.000	67	Thioridazine	0.005	0.995	0.000
50	Miloxacin	0.000	0.000	1.000	test-1	Alfentanil	0.888	0.112	0.000
51	Neostigmine	0.000	1.000	0.000	test-2	Fentanyl	0.025	0.975	0.000
52	Nicotine	0.201	0.799	0.000	test-3	Promethazine	0.026	0.974	0.000
53	Norfloxacin	0.958	0.000	0.042	test-4	Hexobarbitone	0.905	0.000	0.095
54	Penicillin	0.000	0.000	1.000	test-5	R-Etodolac	0.001	0.000	0.999
55	Pentobarbital	0.751	0.000	0.249	test-6	Ethoxybenzamide	1.000	0.000	0.000
56	Prazepam	1.000	0.000	0.000	test-7	Methicillin	0.000	0.000	1.000
57	Prednisolone	1.000	0.000	0.000	test-8	Pefloxacin	0.299	0.000	0.701
58	Propofol	1.000	0.000	0.000	test-9	Pipemidic acid	0.817	0.000	0.183
59	Propranolol	0.018	0.982	0.000	test-10	Procainamide	0.003	0.997	0.000
60	Pyridostigmine	0.000	1.000	0.000	test-11	Morphine	0.154	0.846	0.000
61	trans-Retinoic acid	0.002	0.000	0.998	test-12	Clozapine	0.922	0.078	0.000
62	Tetrachlorodibenzo-p-dioxin	1.000	0.000	0.000	test-13	Promazine	0.009	0.991	0.000
63	Tetracycline	0.005	0.995	0.000					

Table 3. Tissue Composition (Weight Fraction)[a]

tissue	w_l[b]	w_p[b]	w_w[b]
kidney	0.050	0.170	0.770
brain	0.107	0.079	0.790
muscle	0.020	0.170	0.790
lung	0.010	0.177	0.780
liver	0.070	0.180	0.720
fat	0.800	0.050	0.150
heart	0.100	0.167	0.727

[a] Taken from ref 17. [b] w_l, w_p, and w_w are weight fractions of lipid, protein, and water, respectively.

Table 4. Some Correlation Matrixes (*r*-Values) between Descriptors in Eqs 5 and 6

	Neutral		
	$E\text{homo}_{(ui)}$	$\log P_{(ui)}$	$\Delta Gw_{(ui)}$
$E\text{homo}_{(ui)}$	1		
$\log P_{(ui)}$	0.038	1	
$\Delta Gw_{(ui)}$	−0.188	0.324	1
	Cationic		
	$\log P_{(+)}$	$\mu_{(+)}$	
$\log P_{(+)}$	1		
$\mu_{(+)}$	0.146	1	
	Anionic		
	$E\text{homo}_{(-)}$	$\log P_{(-)}$	$\Delta Gw_{(-)}$
$E\text{homo}_{(-)}$	1		
$\log P_{(-)}$	0.361	1	
$\Delta Gw_{(-)}$	0.208	0.143	1

it suggests that to enter into the protein easily, the neutral molecules had better bear a lower energy of the highest occupied orbit. It may be hypothesized that the lower energy of the highest occupied orbit may be more adjacent to that of one certain orbit in the protein, which has certain similarities in the structure or shape of the orbits compared with those of the candidate molecular orbit. Consequently, according to the energy-adjacent principle, there may be some nonbond interaction and even probably bond interaction, thus making the entering of the candidate drug molecules into the protein in tissues easier.

Eq 5.3 suggests that for neutral molecules, the distribution either in the water of the tissues or the blood seems to be generally the same, and the logarithm of their ratio turns out to be zero.

Eqs 5.4 to 5.9 respectively describe the relationship between the absorption situation of the tissues and the present physico-

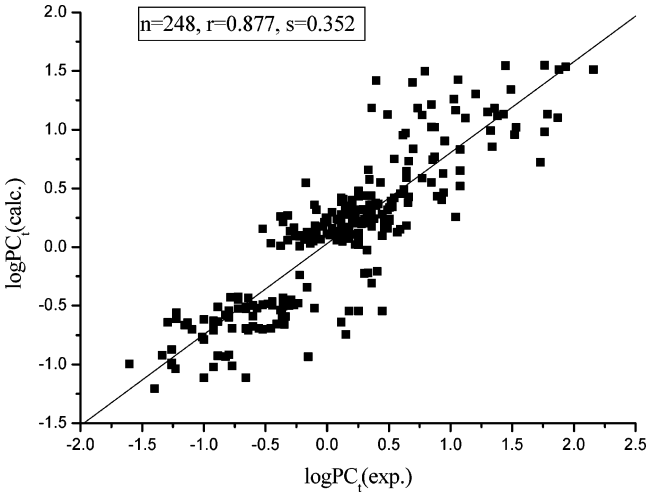

Figure 1. Calculated logPC_t values using eq 5 vs experimental logPC_t values for 248 data points in the training set.

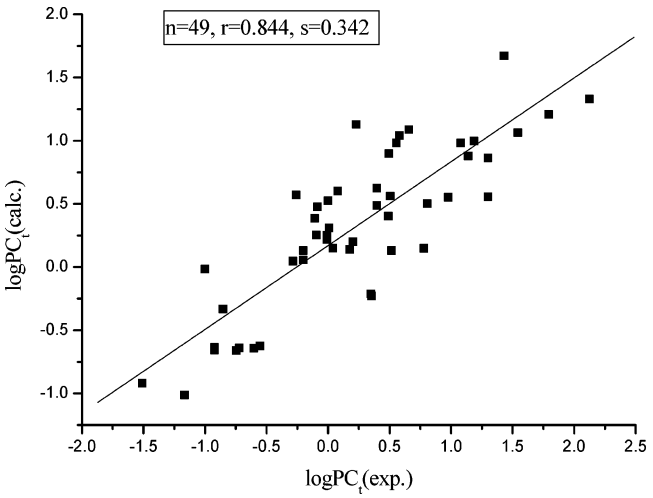

Figure 2. Calculated logPC_t values using eq 5 vs experimental logPC_t values for 49 data points in the testing set.

chemical parameters of the ionic (cationic or anionic) forms of the candidate molecules. Because the body fluid of humans such as blood appears a little basic, the drug molecules in the human body may similarly show their acidity or basicity, and thus, they would exist in the human body in an ionic form. In addition, the neutral and ionized forms of a compound usually have

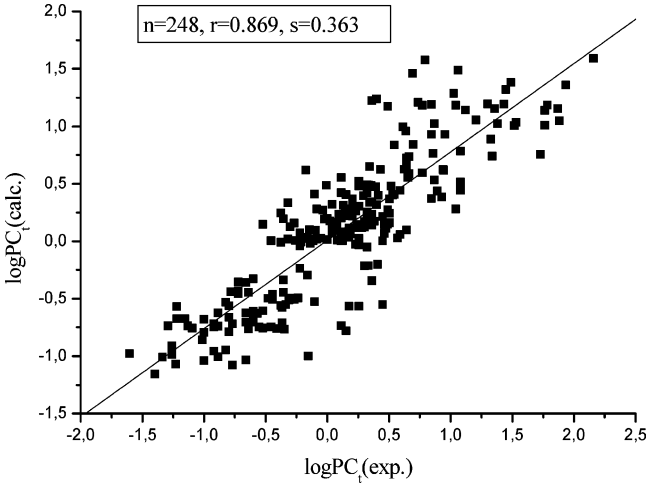

Figure 3. Calculated logPC_t values using eq 6 vs experimental logPC_t values for 248 data points in the training set.

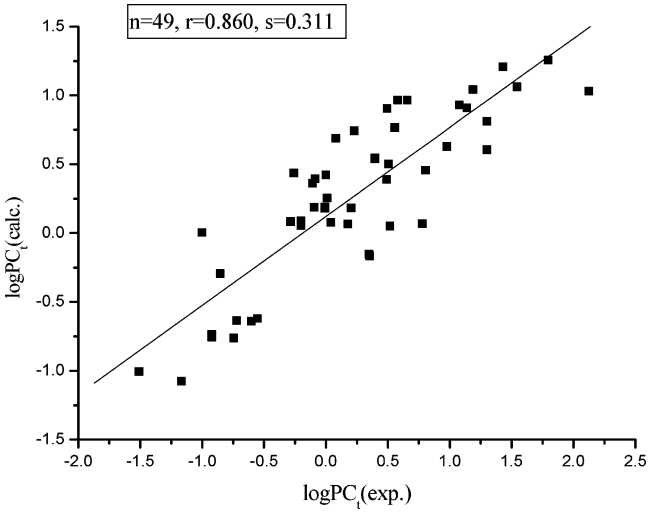

Figure 4. Calculated logPC_t values using eq 6 vs experimental logPC_t values for 49 data points in the testing set.

different partition coefficients in different chemical composition; therefore, distinguishing a tissue according to its composition and considering ionized forms of compounds are obviously reasonable.

Similar to eq 5.1, eq 5.4 describes the distribution situation for entering into the lipid of the tissues, whereas it is for the prediction of the cationic compounds. It shows that the volumes of the cationic molecules give positive contribution to the drug's distribution into the lipid. It is considered that for entering into the lipid the molecules had better be more lipophilic; thus, the charge on the cation may become an adverse factor for entering the lipid so that enough molecular volume may take part in decentralizing the molecule charges, and then, it may be easier to come closer to the lipid molecules.

Eq 5.5 shows that the dipole moment and log*P* values of the cationic molecule are positively relative with the distribution in the protein part of the tissues. Because protein molecules are dipolar molecules, the molecules that bear a larger dipole moment may get larger dipole−dipole interactions with the protein molecules. Meanwhile, the positive relationship of the log*P* values suggests that compounds that bear more lipophilic properties will be in favor of the protein distribution, which is similar to that of the neutral compounds.

Eq 5.6 shows a similar case with the neutral molecules, the ratio of the distribution concentration in water and in blood approximately equal to 1, and the logarithm value turns out to be zero.

Eqs 5.7, 5.8, and 5.9 give the models for the anionic compounds. Eq 5.7 suggests that the ratio of the distribution in the lipid and blood of the anionic molecules seems to be constant, and the negative value suggests that the anions may not be able to easily get into the lipid composition of the tissues.

Eq 5.8 has two parameters for the protein/blood distribution, E_{homo} and log*P*. Here, E_{homo} also shows a negative correlation with the distribution into the protein, which is similar to the equation for the neutral compounds. It is noticeable that it is different with the neutral and cationic compounds, and in this equation, the log*P* value shows negative contribution to the distribution into the protein. It offers some possible interaction mechanism with protein molecules of the compounds. The interaction of the protein molecules and the compounds is usually considered to be the electrostatic effect. When the interaction sites are fixed, the relative location of the protein molecules and the candidate drug molecules are simultaneously fixed. The positive relationship of the log*P* values and the partition coefficient for the neutral and cationic ones probably suggests that after their locations are fixed, the lipophilic parts of the drug molecule seem to be approaching the nonpolar regions of the protein molecules. Thus, the lipophilicity of the structure may benefit the distribution in the protein. However, for the anionic ones, it seems that their lipophilic parts are adjacent to the polar regions of the protein molecules, and consequently, their lipophilic properties result in a negative effect on the distribution of the molecules, and also, their log*P* values show a negative relationship with the protein/blood partition coefficient.

Eq 5.9 suggests that if the anionic compounds have lower molar refraction, they may easily enter into the water in the tissues.

At the present time, there have been lots of studies on the relationship between the solvation free energies (ΔG_w) and the log *BB* values.[11] In this work, we also introduced the ΔG_w values of all of the compounds to the correlation equations and then built eq 6. It can be seen that ΔG_w can take part in the descriptions of all three states, neutral, cationic, or anionic states of the compounds. For the neutral and anionic compounds, it is significant in the protein part of the tissues, and for the cationic compounds, ΔG_w shows significance in the part of the lipid. For the neutral molecules, the correlation relationship between the distribution into protein and the descriptor ΔG_w is negative, which suggests that if one compound can easily dissolve in water, which has a lower ΔG_w value, then it will easily express distribution behavior into the protein. Similarly, the distribution of the anionic states into the protein is also negatively correlated to the ΔG_w value but with a lower coefficient, which means less contribution to the equation. For the cationic one, the distribution into lipid is also negatively correlated to the ΔG_w value. It suggests that for the neutral molecules, they may mainly interact with the amido terminal and the carboxyl group of the protein molecules. For the cationic compounds, they may mainly interact with the phosphate group of the lipid. And for the anionic ones, they may mainly interact with the amido terminal of the protein molecules.

In our previous work,[21,22] the structures of the molecules in the dataset were a little simple and unitary. Though it gave excellent relativity results, it still needs more types of molecules to reinforce our research and conclusion. Compared with the

previous work, the molecule dataset in this work contains more series of compounds of all kinds of types. Also, it is noticeable that the compounds selected in this work were mostly clinical drugs, such as Alfentanil, a common anodyne, Dicloxacillin, Penicilin, antibiotic drugs, Chlorpromazine, Promethazine, and Haloperidol, the drugs for psychiatric disorders and so on, which made the model for predicting the absorption and distribution of drugs more convincible. From the research set forth above, it can be seen that the models certainly show strong predictive power. Both training and testing sets have excellent relativities between the tissue/blood partition coefficients and the physicochemical parameters. Therefore, these models can be used to predict the absorption and the distribution of the structurally diverse compounds in the seven tissues, which is a useful and effective method for drug design.

Meanwhile, these models also help us to understand the in vivo absorption mechanism of the compounds. The differences among all of the equations indicate that neutral and ionic forms of a compound have different mechanisms of action in vivo. From the equations, we can clearly see the distribution into the main compositions of the tissues: lipid, protein, and water. Furthermore, we may draw the conclusion that though the constitution of the three tissue compositions (lipid, protein, water) is not the same in different tissues, the partition coefficient of a compound into the same tissue composition seems to be constant. In another words, the equilibrium distribution in the human body may follow such a rule that the same state (neutral, cation, and anion) of a compound has essentially identical partition coefficients between the same tissue composition and the blood in these tissues. Only the different content of the three compositions lead to the different partition coefficients in different tissues, that is, if the content of a composition is fixed, the distribution of one compound is also fixed, even in different tissues. Therefore, if we can only obtain the three tissue composition/blood partition coefficients of the three states (neutral, cationic, and anionic form) of a candidate compound using theoretical or experimental methods, we can easily obtain its tissue/blood partition coefficients of many tissues from eq 4.

Obviously, eq 4 can also be used to calculate the partition coefficients of a single tissue, and this will result in a more accurate prediction for tissue/blood partition coefficients than the result of the linear equations.[21] Further work should be done to collect more molecules to validate the present models, yet we can try to obtain more detailed equations for every tissue such as that in our previous work.[21] We are also screening some more appropriate descriptors for the model equations so that they can perform a more accurate calculation and/or faster calculation for different purposes.

Conclusion

This work brings forward a model that can simultaneously give the prediction of drug distribution into seven tissues, not only nonexcretory tissues (brain, heart, lung, muscle, and fat) but also excretory tissues (kidney and liver). The compounds dataset in this research contains more series of compounds of all types. The models show strong predictive power. Both training and testing sets give good relativity between the tissue/blood partition coefficients and the physicochemical parameters. It means that for structurally diverse molecules the model shows good relativity and excellent predicting power. The equilibrium distribution in the human body may follow such a rule that the same state (neutral, cation and anion) of a compound has essentially identical partition coefficients between the same tissue composition and the blood in these tissues. Only the different content of the three compositions lead to the different partition coefficients in different tissues, that is, if the content of a composition is decided, the distribution of one compound is also fixed, even in different tissues. In this way, it gives a very convenient method for the prediction of drug absorption not only in tissues but also in further predictions of the distribution situations in the main compositions of the tissues. Thus, this work offers an advanced and suggestive methodology for the research of the drug's absorption and partition in drug design.

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