Prediction of Human Skin Permeability Using a Combination of Molecular Orbital Calculations and Artificial Neural Network

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This study was carried out to develop a novel method for predicting the skin permeability coefficient ($\log K_p$) of compounds from their three-dimensional molecular structure using a combination of molecular orbital (MO) calculation and artificial neural network. Human skin permeability data on 92 structurally diverse compounds were analyzed. The molecular descriptors of each compound, such as the dipole moment, polarizability, sum of charges of nitrogen and oxygen atoms (sum(N,O)), and sum of charges of hydrogen atoms bonding to nitrogen or oxygen atoms (sum(H)) were obtained from MO calculations. The correlation between these molecular descriptors and $\log K_p$ was examined using feed-forward back-propagation neural networks. To improve the generalization capability of a neural network, the network was trained with input patterns given 5% random noise. The neural network model with a configuration of 4–4–1 for input, hidden, and output layers was much superior to the conventional multiple linear regression model in terms of root mean square (RMS) errors (0.528 *vs.* 0.930). A "leave-one-out" cross-validation revealed that the neural network model could predict skin permeability with a reasonable accuracy (predictive RMS error of 0.669).

Key words skin permeability; molecular orbital calculation; artificial neural network; quantitative structure/permeability relationship

In the pharmaceutical, cosmetic and agrochemical fields, it is important to predict the rate at which drug molecules penetrate the skin. To date, several prediction models have been proposed. In many cases, skin permeation was assumed to consist of two processes, *i.e.*, partitioning and diffusion, from a physicochemical point of view. The skin-vehicle partition coefficient of the solute was ascribed using the organic phase-water partition coefficients[1—5] or solvatochromic parameters[6—8] based on a linear free energy relationship, while solute diffusivity through the membrane was described by molecular weight,[2,5] molar volume,[6—9] hydrogen-bonding parameters,[4] and atomic charges.[10] In some cases, heterogeneity in permeation pathway through the skin was also considered to explain the relationship between physicochemical parameters and skin permeation.[11—14] We have previously demonstrated that the percutaneous absorption of drugs having different lipophilicities can be successfully predicted based on a two-layer diffusion model with parallel polar and nonpolar pathways, where partition coefficients between nonpolar pathway and aqueous vehicle is related with octanol/water partition coeffcients.[13,14]

As mentioned above, many studies have been conducted to obtain a relationship between the skin permeability and physicochemical properties of the drug, mainly in order to investigate the mechanisms underlying drug transport through the skin. As far as drug design is concerned, it is also important to be able to predict the skin permeability of drugs from their molecular structures. A fragment substructure method is one of quantitative structure–activity relationship (QSAR) techniques that can be used for this purpose. Pugh and Hadgraft.[15] analyzed the human skin permeability of 91 compounds which had been collected by Flynn,[1] and demonstrated that the fragment substructure approach was fairly satisfactory as far as predicting skin permeability was concerned. Indirect QSAR approaches have also been proposed, where octanol/water partition coefficients,[1,16] and solvatochromic parameters[6,8] were calculated from fragment substructures and then used as descriptors for skin permeation.

A major problem associated with fragment substructure methods is that the effect of the remainder of the molecular environment on fragment properties was not considered. Thus, it may give an inaccurate result, as have been suggested in predicting organic solvent/water partition coefficient.[17] Alternatively, to calculate the physicochemical properties of a drug molecule, molecular mechanics/dynamics or molecular orbital calculation can be used. Using these approaches, the global and local properties of a drug molecule can be obtained from its 3-dimensional structure. Recently, it has been reported that the permeability across biological membranes, such as Caco-2 cells[18,19] and blood-brain barriers,[20] can be successfully predicted based on theoretically computed physicochemical descriptors.

To analyze the relationship between molecular properties and biological effects including skin permeability, linear equations have been used conventionally because of the simplicity of this approach. However, it is not absolutely certain that biological phenomena can be described by such linear equations. Recently, an artificial neural network has been proven to be suitable for processing data on the complicated relationship between causal factors and their results.[21] An artificial neural network is a computer-based system derived from a simplified concept of the brain in which a number of neurons are interconnected in a net-like structure. Topologically, a feed-forward layered neural network consists of an input layer, an output layer, and any number of intermediate layers called hidden layers. Each unit (or neuron) in the layers is influenced by those units in the adjacent layer, the degree of influence by those neurons being dictated by the value of the connections, or their weight. To date, in the pharmaceutical field, a neural network approach has successfully predicted the octanol/water partition coefficient[22] and oral bioavailability[23] of drugs, and it has been used for the analysis of clinical pharmacokinetic data,[24] and the design of pharmaceutical formulations.[25]

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In this article, we have attempted to predict the skin permeability of drugs from their molecular structure using a combination of molecular orbital (MO) calculations and a feed-forward artificial neural network as a modern informatic tool. Human skin permeability data for a number of structurally diverse compounds were taken from the literature[1] and their physicochemical descriptors were calculated from their 3-dimensional molecular structures. The correlation between the skin permeability coefficient and the calculated molecular descriptors was obtained using a neural network. In addition, the predictability of this approach was compared with the results obtained by other methods.

METHODS

Human skin permeability coefficients ($\log K_p$) of 92 structurally diverse compounds were taken from literature.[1] Firstly, the structures of the compounds were built with Chem 3D Pro Ver. 5.0 software (CambridgeSoft Co., Cambridge, MA, U.S.A.) and modeled in their neutral forms. Geometry optimization was performed initially by molecular mechanics (MM2) force field and subsequently using the AM1 Hamiltonian of a semi-empirical MO PACkage (MOPAC97). These descriptors included dipole moment, polarizability, sum of charges of nitrogen and oxygen atoms (sum(N,O)), and sum of charges of hydrogen atoms bonding to nitrogen or oxygen atoms (sum(H)).

Subsequently, the calculated molecular descriptors and skin permeability were correlated using a feed-forward 3-layered neural network (Fig. 1). All the calculation was performed using QwikNet Ver.2.23.[26] The input layer consisted of four molecular descriptor variables (dipole moment, polarizability, sum(N,O), sum(H)), whereas the output layer contained the response variable ($\log K_p$). Before training was started, the input values were scaled between -1 and 1, while the output data were scaled between 0 and 1. An error back-propagation algorithm was used for network training, where the learning rate and momentum parameter were 0.05 and 0.7, respectively. The range of weights was set to be -5 to 5. To avoid "overfitting" to the data, a 5% level of Gaussian noise was added to the input patterns in back-propagation training.[27] The goodness-of-fit was evaluated by the root-mean-square (RMS) error, defined as follows:

$$\text{RMS error} = \sqrt{\frac{(\log K_{p,obs} - \log K_{p,cal})^2}{N}}$$

The predictability of a neural network model was evaluated by a "leave-one-out" cross-validation procedure. This method systematically removed one data point at a time from the training set. A network model was then constructed on the basis of this reduced data set and was subsequently used to predict the removed data. This procedure was repeated for all data so that a complete set of predicted values was obtained.

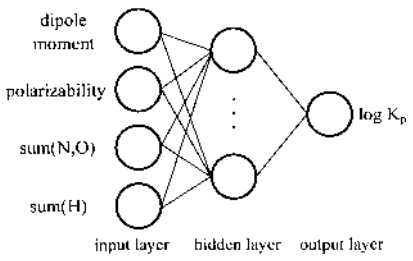

Fig. 1. Schematic Representation of a 3-Layered Neural Network

RESULTS

Table 1 summarized $\log K_p$, the molecular weight (MW), octanol/water partition coefficient ($\log PC_{o/w}$) and results of the MO-calculated molecular descriptors for all the studied compounds. The compounds cover a reasonably broad range of chemical types (hydrocarbons, alcohols, ketones, ethers, esters, carboxylic acids, amines, amides, steroids, and barbiturates), lipophilicity ($-2.25 \leq \log PC_{o/w} \leq 5.49$), and size ($18.0 \leq MW \leq 765.0$). A significant linear correlation between polarizability and MW ($r^2 = 0.976$) was observed. In the case of drugs whose polarizability and dipole moment had been experimentally determined,[28,29] these values were compared with the calculated ones. Linear regression of the calculated *versus* experimental polarizability values yielded a high correlation coefficient ($r^2 = 0.98$). Similarly, the calculated dipole moment also provided a reasonable fit ($r^2 = 0.89$).

When a multiple linear regression analysis of $\log K_p$ was performed, the following equation was obtained:

$$\log K_p = -5.016 - 0.197\mu + 2.059 \times 10^{-3}\alpha + 0.395\,\text{sum(N,O)} - 1.668\,\text{sum(H)}$$
$$n = 92,\quad R^2 = 0.418,\quad \text{S.D.} = 0.957,\quad F_{4,87} = 15.6\ (P = 1.17\text{E-}8)$$

where μ and α are the dipole moment and polarizability, respectively. Basic information on the multiple linear regression analysis was shown in Table 2. The same data were subjected to neural network analysis. A preliminary study indicated that the neural network model with a configuration of 4–4–1 was optimal in terms of RMS error. Figure 2 shows the relationship between observed and calculated $\log K_p$, based on both multiple linear regression and neural network analyses. The RMS error obtained for linear regression analysis was 0.930, which was much larger than that for neural network analysis (RMS error = 0.528).

In Fig. 3, the optimal model was used to predict values for unknown compounds using a "leave-one-out" cross-validation procedure. The predictive RMS error for the "leave-one-out" prediction analysis was 0.669. Thus, a neural network model can predict skin permeability with a reasonable accuracy from calculated molecular descriptors of compounds.

DISCUSSION

Percutaneous absorption is a complex phenomenon that fundamentally involves diffusion and partitioning processes. Solute partitioning from an aqueous solution is determined by solute–solvent interactions that involve dipole–dipole interactions. The permanent dipole moment of a molecule is directly related to these interactions. The polarizability of the molecule is also responsible for solubility phenomena, since it determines inducible dipole moments.[30] Hydrogen bonding is another important force to determine solute–solvent interactions. Early studies have suggested that the free energy of solute transfer into stratum corneum lipids is a function of the hydrogen bonding ability of the permeant.[4] This energy would reflect the process of 'stripping' a molecule from its

Table 1. Skin Permeability (K_p), Molecular Weight (MW), Octanol/Water Partition Coefficient ($PC_{oct/w}$), Dipole Moment (μ), Polarizability (α), Sum of Charges of Nitrogen and Oxygen Atoms (sum(N,O)), and Sum of Charges of Hydrogen Atoms Bonding to Nitrogen or Oxygen Atoms (sum(H))

Compound	log K_p (cm/s)	log $PC_{oct/w}$	MW	MO-calculated molecular descriptors			
				μ	α	sum(H)	sum(N,O)
Aldosterone	−7.79	1.08	360.4	5.884	179.6	0.418	−1.541
Amobarbital	−6.20	1.96	226.3	1.614	109.9	0.543	−1.721
Atropine	−8.63	1.81	289.4	2.433	154.2	0.205	−1.184
Barbital	−7.51	0.65	184.2	1.441	86.0	0.542	−1.687
Benzyl alcohol	−5.78	1.10	108.1	1.739	61.2	0.199	−0.321
4-Bromophenol	−5.00	2.59	173.0	1.593	64.3	0.221	−0.247
Butane-2-one	−5.91	0.03	72.1	2.810	35.2	0.000	−0.290
Butanoic acid	−6.56	0.79	88.1	1.854	38.3	0.242	−0.683
Butanol	−6.16	0.88	74.1	1.522	36.7	0.197	−0.329
Butobarbital	−7.27	1.65	212.2	1.570	102.9	0.543	−1.720
4-Chloro-*m*-cresol	−4.82	3.10	142.6	1.787	70.9	0.222	−0.250
2-Chlorophenol	−5.04	2.15	128.6	0.937	60.8	0.229	−0.245
4-Chlorophenol	−5.00	2.39	128.6	1.477	61.5	0.220	−0.248
Chloroxylenol	−4.84	3.39	156.6	1.225	80.1	0.219	−0.250
Codeine	−7.87	0.89	299.4	1.944	163.8	0.213	−1.020
Cortexolone	−7.69	2.52	346.5	2.534	178.9	0.221	−1.212
Cortexone	−6.91	2.88	330.5	2.467	175.7	0.220	−0.908
Corticosterone	−7.08	1.94	346.5	3.357	178.2	0.422	−1.223
Cortisone	−8.56	1.42	360.4	3.525	181.2	0.442	−1.503
o-Cresol	−5.36	1.95	108.1	1.418	63.2	0.219	−0.254
m-Cresol	−5.38	1.96	108.1	1.526	63.5	0.217	−0.253
p-Cresol	−5.31	1.95	108.1	1.360	64.0	0.217	−0.253
Decanol	−4.66	4.00	158.3	1.513	85.1	0.197	−0.329
2,4-Dichlorophenol	−4.78	3.08	163.0	0.402	68.7	0.231	−0.241
Diethyl ether	−5.36	0.83	74.1	1.246	38.3	0.000	−0.283
Digitoxin	−8.45	1.86	764.9	7.494	367.8	1.054	−3.850
Ephedrine	−5.78	1.03	165.2	2.521	92.4	0.356	−0.619
β-Estradiol 1	−7.08	2.69	272.4	2.703	153.8	0.414	−0.572
β-Estradiol 2	−5.84	2.69	272.4	2.703	153.8	0.414	−0.572
Estriol	−7.96	2.47	288.4	1.708	157.5	0.603	−0.887
Estrone	−6.00	2.76	270.4	3.375	153.1	0.217	−0.532
Ethanol	−6.66	−0.31	46.1	1.551	20.5	0.197	−0.330
2-Ethoxyethanol	−7.16	−0.54	90.1	2.010	41.5	0.196	−0.602
Ethylbenzene	−3.48	3.15	106.2	0.243	66.5	0.000	0.000
4-Ethylphenol	−5.02	2.40	122.2	1.300	72.2	0.217	−0.253
Etorphine	−6.00	1.86	411.5	3.198	220.5	0.426	−1.267
Fentanyl 1	−5.81	4.37	336.5	3.825	204.1	0.000	−0.923
Fentanyl 2	−5.56	4.37	336.5	3.825	204.1	0.000	−0.923
Fluocinonide	−6.33	3.19	494.5	5.907	233.6	0.000	−2.069
Heptanoic acid	−5.26	2.50	130.2	1.859	62.6	0.242	−0.683
Heptanol	−5.06	2.72	116.2	1.521	60.8	0.197	−0.329
Hexanoic acid	−5.41	1.90	116.2	1.862	54.5	0.242	−0.683
Hexanol	−5.45	2.03	102.2	1.516	52.8	0.197	−0.329
H-Pimelamate[a)]	−6.61	2.31	503.6	5.446	253.3	0.862	−2.269
H-Succinamate[a)]	−8.15	1.43	461.6	6.983	228.3	0.873	−2.655
H-*N*,*N*-diMe-Succinamate[a)]	−7.73	2.03	489.6	4.255	246.4	0.412	−2.542
H-21-Hemipimelate[a)]	−6.31	3.26	504.6	4.148	250.0	0.661	−2.519
H-21-Hemisuccinate[a)]	−6.76	2.11	462.5	3.503	225.7	0.666	−2.506
H-21-Hexanoate[a)]	−5.31	4.48	460.6	1.581	235.4	0.409	−1.831
H-21-Hexanoate-6-hydroxy[a)]	−6.60	2.79	476.6	5.868	240.6	0.618	−2.166
H-21-Octanoate[a)]	−4.77	5.49	488.7	4.143	251.7	0.426	−1.863
H-21-Proprionate[a)]	−6.03	3.00	418.5	5.267	211.9	0.419	−1.838
Hydrocortisone 1	−9.08	1.53	362.5	2.885	181.3	0.641	−1.538
Hydrocortisone 2	−7.49	1.53	362.5	2.885	181.3	0.641	−1.538
Hydromorphone	−8.38	1.25	285.3	4.820	156.3	0.216	−0.902
Hydroxypregnenolone	−6.78	2.74	330.5	1.968	173.1	0.397	−0.931
17α-Hydroxyprogesterone	−6.78	3.00	332.5	5.759	175.5	0.198	−0.868
Isoquinoline	−5.34	2.03	129.2	2.224	85.3	0.000	−0.138
Me-H-21-Pimelate[a)]	−5.83	3.70	518.6	6.298	259.3	0.414	−2.476
Me-H-21-Succinate[a)]	−7.24	2.58	476.6	4.388	234.8	0.422	−2.468
Meperidine	−5.99	2.72	247.3	2.289	137.2	0.000	−0.888
Methanol	−6.86	−0.77	32.0	1.621	12.3	0.195	−0.326
Methyl-4-hydroxybenzoate	−5.60	1.96	152.1	2.903	81.8	0.224	−0.883
Morphine	−8.59	0.62	285.3	3.654	154.5	0.436	−1.024
2-Naphtol	−5.11	2.84	144.2	1.460	95.8	0.217	−0.252
Naproxen	−6.96	3.18	230.3	1.160	140.2	0.243	−0.887

Table 1. (Continued.)

Compound	$\log K_p$ (cm/s)	$\log PC_{oct/w}$	MW	MO-calculated molecular descriptors			
				μ	α	sum(H)	sum(N,O)
Nicotine	−5.27	1.17	158.2	3.078	94.0	0.000	−0.398
Nitroglycerin	−5.52	2.00	227.1	5.508	75.5	0.000	−0.746
3-Nitrophenol	−5.81	2.00	139.1	4.007	70.6	0.228	−0.242
4-Nitrophenol	−5.81	1.96	139.1	5.265	71.6	0.229	−0.237
Nonanol	−4.78	3.62	144.3	1.729	76.7	0.195	−0.326
Octanoic acid	−5.16	3.00	144.2	1.866	70.6	0.242	−0.683
Octanol	−4.84	2.97	130.2	1.483	68.6	0.197	−0.329
Pentanoic acid	−6.26	1.30	102.1	1.849	46.4	0.242	−0.683
Pentanol	−5.78	1.56	88.1	1.718	44.3	0.195	−0.327
Phenobarbital	−6.90	1.47	232.2	1.757	120.3	0.544	−1.715
Phenol	−5.65	1.46	94.1	1.233	53.9	0.217	−0.253
Pregnenolone	−6.38	3.13	316.5	3.745	169.3	0.197	−0.627
Progesterone	−4.92	3.77	314.5	4.578	171.9	0.000	−0.596
Propanol	−6.41	0.25	60.1	1.689	28.4	0.195	−0.326
Resorcinol	−7.18	0.80	110.1	1.586	58.9	0.437	−0.497
Salicylic acid	−5.76	2.26	138.1	1.240	70.7	0.508	−0.960
Scopolamine	−7.86	1.24	303.4	5.462	154.0	0.204	−1.036
Styrene	−3.75	2.95	104.2	0.010	71.6	0.000	0.000
Sucrose	−8.84	−2.25	342.3	2.960	149.6	1.733	−3.433
Sufentanyl	−5.48	4.59	386.6	3.821	216.8	0.000	−1.207
Testosterone	−6.21	3.31	288.4	3.840	157.8	0.198	−0.616
Thymol	−4.81	3.34	150.2	1.261	89.6	0.217	−0.255
Toluene	−3.56	2.75	92.1	0.264	58.4	0.000	0.000
2,4,6-Trichlorophenol	−4.79	3.69	197.4	1.073	76.6	0.235	−0.226
3,4-Xylenol	−5.00	2.35	122.2	1.646	73.1	0.216	−0.253
Water	−6.86	−1.38	18.0	1.861	3.4	0.383	−0.383

a) Hydrocortisone derivatives.

Table 2. Results of Multiple Linear Regression Analysis of Skin Permeability against MO-Calculated Descriptors

	Coefficient	95% confidence interval		*t*-test (*P*-value)
		Lower limit	Upper limit	
Intercept	−5.016	−5.504	−4.529	5.4E-35
μ	−0.197	−0.380	−0.0137	0.035
α	0.002059	−0.003345	0.007463	0.451
sum(N,O)	0.395	−0.247	1.037	0.228
sum(H)	−1.668	−2.983	−0.352	0.014

water of hydration. Thus, the dipole moment, polarizability, sum(N,O) and sum(H) were considered to be good measures to describe partitioning into the skin.

Diffusivity of the solute is also an important factor, primarily determined by its molecular size. The polarizability has a dimension of volume; if the molecule contains large atoms with electrons some distance from the nucleus, the nuclear control is less, the electron distribution is less rigid, and, hence, the polarizability is greater.[31] Thus, the polarizability of a molecule is a good measure of its volume. In fact, the calculated polarizability of the compounds investigated was correlated closely with its molecular weight (r^2=0.976). Therefore, when the polarizability was used as a molecular descriptor, it would not be necessary to incorporate the molecular volume (or weight) of the compound.

The skin permeation of a drug molecule has been correlated with a linear combination of the physicochemical parameters or the group contributions of the corresponding drug in predicting skin permeability. This approach allows us to evaluate the contribution of each descriptor to determining skin permeability. However, this simple additivity-based method is not particularly impressive from the stochastic point of view, since the interrelations among factors governing the permeation of a drug molecule may be convoluted. In multiple linear regression models, the problem could be solved by the use of interrelation terms between the descriptors. However, it should be noted that multicollinearity of the descriptors decreases the robustness of a multiple linear regression model and makes the contribution of the descriptors unclear. In this study, we applied a neural network for its simplicity. In addition, the nonlinearity of a neural network model is able to deal with the effects of the heterogeneous structure of the skin on drug permeation. That is, it is considered that some neurons in the hidden layer may contribute mainly to permeation of hydrophilic drugs through polar pathway, whereas others to lipophilic ones through nonpolar pathway. Thus, a neural network analysis is clearly well suited to meet this need.

Goodness-of-fit to the experimental data is not a good criterion to evaluate the acceptability of neural network models, because it depends on the range of weights, the amount of input noises, and other parameter settings. Alternatively, a predictive RMS error obtained by a leave-one-out prediction method is useful for this purpose. In a preliminary study, we calculated predictive RMS errors for neural network models with a configuration of 4–*x*–1 (x=2, 3, ..., 7), in order to find the optimal one. Since the predictive RMS errors were 0.821, 0.717, 0.669, 0.700, 0.693, and 0.771 for x=2—7, respectively, we selected a neural network model with a 4–4–1 configuration as the optimal. The predictive RMS error (0.669 for 92 compounds) was smaller than the standard deviation of residuals from regression ($SD_{residual}$) of 0.712 obtained by

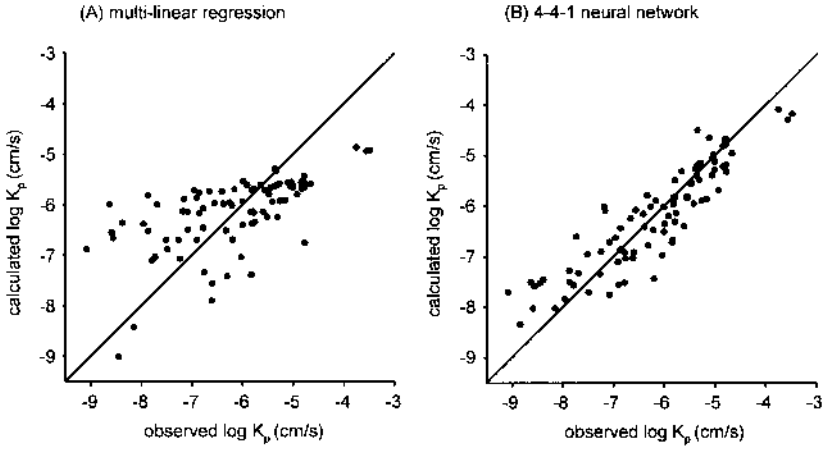

Fig. 2. Relationship between Experimental and Calculated Skin Permeability Coefficients

Figures (A) and (B) were obtained from the analyses using multiple linear regression and 4–4–1 neural network, respectively.

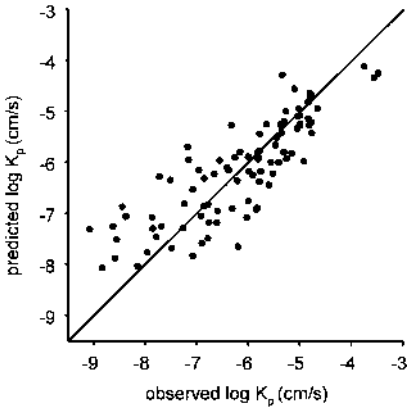

Fig. 3. Leave-One-Out Cross-Validation of 4–4–1 Neural Network for Prediction of Skin Permeability Coefficient

the Potts and Guy's approach,[3] in which the $\log K_p$ was predicted from $\log PC_{oct/w}$ and molecular weight. As a computational method, the fragment approach of Pugh and Hadgraft gave a $SD_{residual}$ of 0.810 for 91 compounds.[15] It has been shown that the solvatochromic approaches are useful for predicting skin permeability. The $SD_{residual}$ obtained using the equations of Potts and Guy[7] and Abraham *et al.*[8] were 0.236 (n=23) and 0.197 (n=47), respectively. Recently, Pugh *et al.*[4,10] proposed a combination of the solvatochromic approach and solubility/diffusion model. Although the approach of Pugh *et al.*[4,10] would gave a mechanistic insight into skin permeation, its predictability was not so good as simple solvatochromic approaches, taking the estimation errors for both partition and diffusion coefficients into consideration. Considering that our dataset has much wider structural diversity than that of Abraham *et al.*,[8] our present approach offers satisfactory predictability. It should also be noted that we used a Flynn's dataset[1] for a direct comparison between the previous[3,15] and present models, in spite that the dataset includes permeability coefficients measured under different conditions (temperature, pH, skin preparation).

In conclusion, combination of MO calculations and neural networks allows us to predict the skin permeability of drugs from their molecular formula. We believe that application of this prediction method should be of significant help in future drug design.

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