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An Equation for the Prediction of Human Skin Permeability of Neutral Molecules, Ions and Ionic Species

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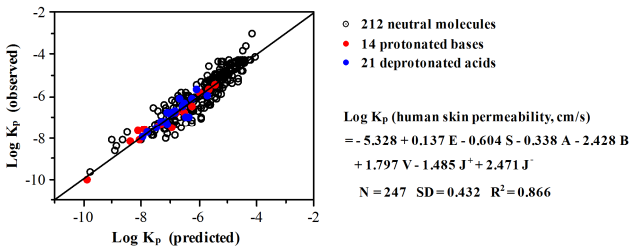

ABSTRACT

Experimental values of permeability coefficients, as log K_p, of chemical compounds across human skin were collected by carefully screening the literature, and adjusted to 37 °C for the effect of temperature. The values of log K_p for partially ionized acids and bases were separated into those for their neutral and ionic species, forming a total data set of 247 compounds and species (including 35 ionic species). The obtained log K_p values have been regressed against Abraham solute descriptors to yield a correlation equation with R^2 = 0.866 and SD = 0.432 log units. The equation can provide valid predictions for log K_p of neutral molecules, ions and ionic species, with predictive R^2 = 0.858 and predictive SD = 0.445 log units calculated by the leave-one-out statistics. The predicted log K_p values for Na^+ and Et_4N^+ are in good agreement with the observed values. We calculated the values of log K_p of ketoprofen as a function of the pH of the donor solution, and found that log K_p markedly varies only when ketoprofen is largely ionized. This explains why models that neglect ionization of permeants still yield reasonable statistical results. The effect of skin thickness on log K_p was investigated by inclusion of two indicator variables, one for intermediate thickness skin and one for full thickness skin, into the above equation. The newly obtained equations were found to be statistically very close to the above equation. Therefore, the thickness of human skin used makes little difference to the experimental values of log K_p.

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Keywords: predictive model; ionic species; ions; human skin; skin permeability; linear free-energy relationship; QSPR ;

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INTRODUCTION

Rapid and accurate prediction of human skin permeability of chemical compounds is very useful for developing dermal and transdermal drug delivery systems and cosmetics, as well as evaluating environmental risks due to contact with skin. Various kinds of empirical and mathematical models for the correlation and prediction of human skin permeability, as log K_p, have been reported (Baba et al., 2015; Mitragotri, 2003), and there have been a number of reviews of these models (Chen et al., 2013; Geinoz et al., 2004; Mitragotri et al., 2011; Moss et al., 2011; Neely et al., 2009). It has been known for years that the permeability of ionizable compounds depends on the pH of the donor solution, attributed to the slower rate of permeation of ionic species compared to the corresponding neutral species (Roy and Flynn, 1990; Swarbrick et al., 1984; Waters and Bhuiyan, 2016). For instance, Waters and Bhuiyan (2016) recently reported that as an in vitro skin mimic, silicone membrane encouraged permeation of the more unionized forms of pharmaceutical compounds rather than the ionized forms. However, the above reviews completely ignore the possibility of ionization and associated factors such as the dependence of permeation on pH for ionizable compounds, and our previous study represents the only attempt to include ionized species in a model for skin permeation (Zhang et al., 2012). Thus one of the most popular models for skin permeation, the Potts and Guy model (Potts and Guy, 1992), uses only the octanol-water partition coefficient (as log $P_{o/w}$) and molecular weight (MW) as compound descriptors (see Eq. 1), with no reference to ionic species.

$$\log K_p = 0.71 \log P_{o/w} - 0.0061 MW - 6.3 \qquad (1)$$

As mentioned, we have previously constructed an equation for predicting skin permeability of neutral molecules, ions and ionic species using the Abraham linear free-energy relationship

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(LFER) model (Zhang et al., 2012). Since then, descriptors for considerably more compounds have been obtained, including those for ionic species (Abraham and Acree, 2016), and it is the purpose of the present work to set out an extended equation for the correlation and prediction of human skin permeability, including neutral molecules and ionic species in the same equation.

METHODS

LFER model

Our method is based on the LFER method of Abraham, firstly applied to the properties of neutral molecules (Abraham, 1993) and subsequently extended to include ions and ionic species by Abraham and Acree (Abraham, 2011; Abraham and Acree, 2010a, b, 2016). The general equation developed by Abraham and Acree is stated as:

$$SP = c + eE + sS + aA + bB + vV + j^{+}J^{+} + j^{-}J^{-} \qquad (2)$$

The dependent variable SP represents an equilibrium coefficient for a series of solutes in a given system, including partition coefficients (as log P) and rate coefficients (as log K), and in the present work permeation coefficients through human skin, as log K_p. The independent variables are the physicochemical properties or descriptors of the solutes as follows. E is the excess molar refraction in units of $(cm^3/mol)/10$, S is the combined dipolarity/polarizability, A and B are the overall solute hydrogen bond acidity and basicity, and V is McGowan's characteristic molecular volume in units of $(cm^3/mol)/100$; J^+ and J^- are the additional descriptors that are specific to ionic species. Note that $J^+ = 0$ for anions, $J^- = 0$ for cations, and both J^+ and $J^- = 0$ for neutral molecules. In the latter case, Eq. 2 reduces to an equation for neutral molecules. We use the term "ions" for permanent ions such as Na^+ and Cl^-, and the term "ionic species" for ions derived from protonation of basic compounds and deprotonation

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of acidic compounds. The compound descriptors for neutral molecules are obtained from a variety of experimental processes, as explained in a number of reviews (Abraham et al., 2004; Clarke and Mallon, 2012; Poole et al., 2013), and Abraham and Acree have reviewed the methods used to obtain descriptors for ions and ionic species (Abraham and Acree, 2016). The coefficients (c, e, s, a, b, v, j^+ and j^-) in Eq. 2 can be obtained by a multiple linear regression of values of SP in a given system against the known solute descriptors, and used to characterize the system of interest.

Effect of Temperature and Ionization

The reliability of the predictive model greatly depends upon the quality of the used database. In this study, we ensured that measurements for the selected K_p data were rigorously conducted through *in vitro* passive diffusion study across excised human skin. As regards the influence of temperature, we corrected values of log K_p at various temperatures to obtain the corresponding value at 37 °C as detailed by Abraham and Martins (2004) (see Table 1). The determination of these corrections was quite coarse and also they should theoretically vary with lipophilicity, but since they are comparatively small little error will be involved in just using the corrections in Table 1.

Table 1. Corrections to log K_p from experimental temperature to 37 □

Adjusted temperatures	Corrections to log K_p
from 20 □ to 37 □	0.69
from 25 □ to 37 □	0.48
from 30 □ to 37 □	0.28
from 32 □ to 37 □	0.20
from 40 □ to 37 □	-0.11

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The effect of ionization on skin permeation of compounds must be taken into consideration, K_p for neutral forms being much larger than that for ionic forms (Zhang et al., 2012). Thus the fractions of neutral and ionic forms (F_n and F_i) for each ionizable compound were carefully calculated according to the pH of the donor solution used. As for the donor solvent containing no buffer salt, the degree of ionization was derived from pK_a and concentration of solute. With compounds that are partially ionized/neutral and have known values of the fraction ionized and neutral, F_i and F_n, we separate the experimental (total) value of $K_p(t)$ into $K_p(n)$ for neutral and $K_p(i)$ for ionic species through the equation

$$K_p(t) = K_p(n) \times F_n + K_p(i) \times F_i \qquad (3)$$

Then we estimate $K_p(n)$ and $K_p(i)$ using our previously established LFER equation (Zhang et al., 2012) and the neutral and ionic descriptors, and can obtain an approximation of the ratio $K_p(n)/K_p(i)$. From $K_p(n)/K_p(i)$ and the accurate values of F_i and F_n, the values of $K_p(n)$ and $K_p(i)$ of partially ionized compounds are deduced. These values are included in Table 2.

RESULTS AND DISCUSSION

We surveyed the literature and collected *in vitro* log K_p data of compounds recently measured, especially compounds that were ionized under the experimental conditions. As the major data sources, our previous dataset (Zhang et al., 2012) and the dataset of Baba et al. (2015). were combined in the present work. For compounds that exist in both datasets, we took the log K_p values in our previous dataset. This is because most of our log K_p values were derived from Abraham and Martins (2004), who had adjusted log K_p for ionization and temperature dependence, and had used the mean of the values where multiple values exist. Some compounds were omitted in the following cases: a) the compounds are zwitterions under

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original experimental conditions and b) their descriptors cannot be obtained from the experimental data listed in the current literature. We also used compounds whose log K_p had been measured by ourselves under reliable experimental conditions. Descriptors for all the neutral compounds and ionic species that we considered are listed in Table 2, together with the corresponding values of log K_p, corrected to 37 °C. The values of log K_p of the 247 compounds or species in our data set covers both 'highly permeable' and 'poorly permeable' values, varying from -10.01 to -3.00, and meets a normal distribution very well, with a mean of -6.027 and a standard deviation of 1.165, as seen in Figure 1.

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Table 2. Compounds and species used in this work, their solute descriptors, observed log K_p values, and log K_p values calculated from Eq. 6 [a]

No.	Compounds	E	S	A	B	V	J^+	J^-	Inter	Full	log K_p (obs)	log K_p (calc)	Ref. [b]
1	1,1-dichloropropanone	0.395	0.73	0.09	0.35	0.7918	0.0000	0.0000	1.0	0.0	-5.03	-4.83	Baba et al., 2015
2	1-hexyl-2-pyrrolidone	0.407	1.05	0.00	0.75	1.5245	0.0000	0.0000	1.0	0.0	-5.21	-4.99	Baba et al., 2015
3	1-methoxy-2-propanol	0.218	0.53	0.33	0.81	0.7896	0.0000	0.0000	1.0	0.0	-6.20	-6.28	Baba et al., 2015
4	1-octyl-2-pyrrolidone	0.390	1.05	0.00	0.75	1.8063	0.0000	0.0000	1.0	0.0	-4.83	-4.48	Baba et al., 2015
5	2,4,6-trichlorophenol	1.010	0.80	0.60	0.15	1.1423	0.0000	0.0000	1.0	0.0	-4.30	-4.19	Baba et al., 2015
6	2,4-dichlorophenol	0.960	0.82	0.54	0.17	1.0199	0.0000	0.0000	1.0	0.0	-4.30	-4.45	Baba et al., 2015
7	2-amino-4-nitrophenol	1.415	1.95	1.01	0.43	1.0491	0.0000	0.0000	1.0	0.0	-6.54	-5.81	Baba et al., 2015
8	2-chlorophenol	0.853	0.88	0.32	0.31	0.8975	0.0000	0.0000	1.0	0.0	-4.56	-4.99	Zhang et al., 2012
9	2-ethoxyethanol	0.237	0.55	0.29	0.82	0.7896	0.0000	0.0000	1.0	0.0	-6.68	-6.30	Zhang et al., 2012
10	2-hydroxypropyl nicotinate	0.840	1.38	0.35	1.19	1.3720	0.0000	0.0000	1.0	0.0	-7.55	-6.59	Zhang et al., 2012
11	2-naphthol	1.520	1.08	0.61	0.40	1.1441	0.0000	0.0000	1.0	0.0	-4.65	-4.89	Zhang et al., 2012
12	2-nitro-p-phenylenediamine	1.525	2.05	0.35	0.70	1.0902	0.0000	0.0000	1.0	0.0	-6.66	-6.21	Baba et al., 2015
13	2-phenylethanol	0.811	0.82	0.31	0.66	1.0569	0.0000	0.0000	1.0	0.0	-5.20	-5.52	Zhang et al., 2012
14	3,4-xylenol	0.830	0.90	0.55	0.38	1.0569	0.0000	0.0000	1.0	0.0	-4.52	-4.97	Zhang et al., 2012
15	3-methylphenol	0.822	0.88	0.57	0.34	0.9160	0.0000	0.0000	1.0	0.0	-4.89	-5.12	Zhang et al., 2012
16	3-nitrophenol	1.050	1.57	0.79	0.23	0.9493	0.0000	0.0000	1.0	0.0	-5.33	-5.25	Baba et al., 2015

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17	4-amino-2-nitrophenol	1.360	1.50	0.30	0.66	1.0491	0.0000	0.0000	1.0	0.0	-5.91	-5.87	Baba et al., 2015
18	4-bromophenol	1.080	1.17	0.67	0.20	0.9501	0.0000	0.0000	1.0	0.0	-4.52	-4.89	Zhang et al., 2012
19	4-butylphenol	0.796	0.88	0.55	0.37	1.3387	0.0000	0.0000	1.0	0.0	-4.47	-4.43	Baba et al., 2015
20	4-chloro-3,5-dimethylphenol	0.925	0.96	0.64	0.21	1.1793	0.0000	0.0000	1.0	0.0	-4.31	-4.39	Zhang et al., 2012
21	4-chloro-3-methylphenol	0.920	1.02	0.67	0.22	1.0384	0.0000	0.0000	1.0	0.0	-4.34	-4.71	Zhang et al., 2012
22	4-chloro-m-phenylenediamine	1.358	1.50	0.23	0.69	1.0384	0.0000	0.0000	1.0	0.0	-6.54	-5.93	Zhang et al., 2012
23	4-chlorophenol	0.915	1.08	0.67	0.20	0.8975	0.0000	0.0000	1.0	0.0	-4.52	-4.95	Zhang et al., 2012
24	4-cyanophenol	0.940	1.63	0.80	0.29	0.9298	0.0000	0.0000	1.0	0.0	-5.53	-5.49	Baba et al., 2015
25	4-ethylphenol	0.800	0.90	0.55	0.36	1.0569	0.0000	0.0000	1.0	0.0	-4.53	-4.92	Zhang et al., 2012
26	4-hydroxybenzyl alcohol	0.998	1.30	0.86	0.79	0.9747	0.0000	0.0000	0.0	0.0	-6.26	-6.43	Zhang et al., 2012
27	4-hydroxy-methylphenylacetate	0.908	1.46	0.59	0.68	1.2722	0.0000	0.0000	1.0	0.0	-5.26	-5.65	Zhang et al., 2012
28	4-hydroxyphenylacetamide	1.180	2.08	0.84	0.94	1.1724	0.0000	0.0000	0.0	0.0	-6.89	-6.88	Zhang et al., 2012
29	4-hydroxyphenylacetic acid	1.030	1.45	0.94	0.74	1.1313	0.0000	0.0000	0.0	0.0	-6.16	-6.14	Baba et al., 2015
30	4-MeC6H4CH2NH(CH2)4Me, cation	0.610	2.60	1.34	0.00	1.8240	1.3136	0.0000	1.0	0.0	-5.80	-5.94	Zhang et al., 2012
31	4-MeC6H4CH2NH(CH2)5Me, cation	0.600	2.60	1.36	0.00	1.9649	1.2956	0.0000	1.0	0.0	-5.67	-5.67	Zhang et al., 2012
32	4-MeC6H4CH2NH(CH2)6Me, cation	0.590	2.63	1.36	0.00	2.1058	1.2969	0.0000	1.0	0.0	-5.50	-5.43	Zhang et al., 2012
33	4-MeC6H4CH2NHBu, cation	0.620	2.62	1.34	0.00	1.6831	1.3349	0.0000	1.0	0.0	-6.52	-6.23	Zhang et al., 2012
34	4-MeC6H4CH2NHEt, cation	0.640	2.66	1.44	0.00	1.4013	1.2994	0.0000	1.0	0.0	-6.77	-6.74	Zhang et al., 2012

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35	4-MeC6H4CH2NHMe, cation	0.650	2.58	1.42	0.00	1.2604	1.2835	0.0000	1.0	0.0	-7.51	-6.92	Zhang et al., 2012
36	4-MeC6H4CH2NHPr, cation	0.630	2.63	1.37	0.00	1.5422	1.3290	0.0000	1.0	0.0	-6.77	-6.49	Zhang et al., 2012
37	4-nitrophenol	1.070	1.72	0.82	0.26	0.9493	0.0000	0.0000	1.0	0.0	-5.33	-5.42	Baba et al., 2015
38	4-propoxyphenol	0.840	1.17	0.57	0.52	1.2565	0.0000	0.0000	1.0	0.0	-5.18	-5.12	Baba et al., 2015
39	5,5-diethylbarbituric acid	1.030	1.14	0.47	1.18	1.3739	0.0000	0.0000	1.0	0.0	-7.29	-6.43	Zhang et al., 2012
40	5-ethyl-5-(3-methylbutyl)barbital	1.030	1.11	0.47	1.23	1.7966	0.0000	0.0000	1.0	0.0	-5.98	-5.77	Zhang et al., 2012
41	5-ethyl-5-butylbarbituric acid	1.030	1.14	0.47	1.18	1.6557	0.0000	0.0000	1.0	0.0	-7.05	-5.92	Zhang et al., 2012
42	5-ethyl-5-phenylbarbital	1.630	1.80	0.73	1.15	1.6999	0.0000	0.0000	1.0	0.0	-6.68	-6.17	Zhang et al., 2012
43	5-fluorouracil	0.720	0.84	0.57	1.02	0.7693	0.0000	0.0000	1.0	0.0	-6.82	-7.02	Zhang et al., 2012
44	8-methoxypsoralen	1.611	1.70	0.00	0.80	1.4504	0.0000	0.0000	1.0	0.0	-5.12	-5.47	Zhang et al., 2012
45	acetic acid	0.265	0.64	0.62	0.44	0.4648	0.0000	0.0000	1.0	0.0	-6.08	-6.12	Baba et al., 2015
46	acetylsalicylic acid	0.781	1.69	0.71	0.67	1.2879	0.0000	0.0000	0.0	1.0	-5.50	-5.79	Baba et al., 2015
47	aldosterone	2.010	3.47	0.40	1.90	2.6890	0.0000	0.0000	1.0	0.0	-7.45	-7.06	Zhang et al., 2012
48	alprenolol, neutral, F_n = 0.02, log K_p(t) = -6.90	1.250	1.09	0.15	1.44	2.16	0.0000	0.0000	1.0	0.0	-5.30	-5.48	Zhang et al., 2012
49	alprenolol, cation, F_i = 0.98, log K_p(t) =-6.90	1.100	4.46	1.78	0.00	2.1802	2.2574	0.0000	1.0	0.0	-7.59	-7.90	Zhang et al., 2012
50	aminopyrine	1.680	1.74	0.00	1.60	1.8662	0.0000	0.0000	0.0	1.0	-6.55	-6.68	Baba et al., 2015
51	amylobarbital	1.030	1.10	0.59	1.22	1.7966	0.0000	0.0000	0.0	1.0	-6.00	-5.78	Baba et al., 2015
52	aniline	0.955	0.96	0.26	0.41	0.8162	0.0000	0.0000	1.0	0.0	-4.94	-5.39	Baba et al., 2015

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53	anisole	0.708	0.75	0.00	0.29	0.9160	0.0000	0.0000	1.0	0.0	-4.41	-4.74	Baba et al., 2015
54	atenolol	1.450	1.90	0.62	2.03	2.1763	0.0000	0.0000	1.0	0.0	-7.35	-7.50	Baba et al., 2015
55	barbital	1.030	1.00	0.58	1.12	1.3739	0.0000	0.0000	0.0	1.0	-7.31	-6.24	Baba et al., 2015
56	benzaldehyde	0.820	1.00	0.00	0.39	0.8730	0.0000	0.0000	1.0	0.0	-4.51	-5.20	Baba et al., 2015
57	benzene	0.610	0.52	0.00	0.14	0.7164	0.0000	0.0000	1.0	0.0	-4.27	-4.61	Zhang et al., 2012
58	benzenetriol	1.180	1.37	1.40	0.68	0.8925	0.0000	0.0000	1.0	0.0	-6.98	-6.51	Baba et al., 2015
59	benzoic acid	0.730	0.90	0.59	0.40	0.9317	0.0000	0.0000	1.0	0.0	-5.68	-5.27	Baba et al., 2015
60	benzyl alcohol	0.803	0.87	0.39	0.56	0.9160	0.0000	0.0000	1.0	0.0	-5.30	-5.59	Zhang et al., 2012
61	benzyl nicotinate	1.262	1.60	0.00	0.80	1.6393	0.0000	0.0000	1.0	0.0	-4.87	-5.12	Zhang et al., 2012
62	betamethasone	2.040	3.51	0.71	1.92	2.9132	0.0000	0.0000	1.0	0.0	-7.15	-6.83	Baba et al., 2015
63	betamethasone-17-valerate	1.970	3.10	0.56	2.40	3.6334	0.0000	0.0000	1.0	0.0	-6.50	-6.42	Baba et al., 2015
64	bromoacetic acid F_i = 0.70, log K_p(t) = -6.52	0.706	3.66	0.00	0.82	0.6183	0.0000	0.1469	1.0	0.0	-8.01	-7.96	Baba et al., 2015
65	bromoacetic acid F_n = 0.30 log K_p(t) = -6.52	0.556	1.06	0.77	0.38	0.6398	0.0000	0.0000	1.0	0.0	-6.01	-5.92	Baba et al., 2015
66	bromochloroacetic acid F_i =0.90, log K_p(t) =-6.46	0.790	3.18	0.10	2.48	0.7407	0.0000	1.9889	1.0	0.0	-6.82	-6.95	Baba et al., 2015
67	bromochloroacetic acid F_n = 0.10, log K_p(t) = -6.46	0.640	1.24	0.92	0.28	0.7622	0.0000	0.0000	1.0	0.0	-5.67	-5.61	Baba et al., 2015
68	bromochloroacetonitrile	0.597	1.10	0.22	0.21	0.7016	0.0000	0.0000	1.0	0.0	-4.35	-5.23	Baba et al., 2015
69	bromodichloromethane	0.593	0.69	0.10	0.04	0.6693	0.0000	0.0000	1.0	0.0	-4.41	-4.59	Baba et al., 2015
70	butan-1-ol	0.224	0.42	0.37	0.48	0.7309	0.0000	0.0000	1.0	0.0	-5.70	-5.53	Zhang et al., 2012

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71	butan-2,3-diol	0.341	0.93	0.61	0.88	0.7896	0.0000	0.0000	1.0	0.0	-7.38	-6.77	Zhang et al., 2012
72	butan-2-one	0.166	0.70	0.00	0.51	0.6879	0.0000	0.0000	1.0	0.0	-5.42	-5.73	Zhang et al., 2012
73	butanoic acid	0.210	0.64	0.61	0.45	0.7466	0.0000	0.0000	0.0	0.0	-6.41	-5.64	Baba et al., 2015
74	butobarbital	1.030	1.14	0.47	1.18	1.6557	0.0000	0.0000	0.0	1.0	-7.07	-5.92	Baba et al., 2015
75	butoxyethanol	0.201	0.53	0.26	0.83	1.0714	0.0000	0.0000	1.0	0.0	-6.00	-5.80	Baba et al., 2015
76	butyl nicotinate	0.658	1.07	0.00	0.73	1.4542	0.0000	0.0000	1.0	0.0	-4.86	-5.04	Zhang et al., 2012
77	butyl p-aminobenzoate	1.010	1.35	0.30	0.68	1.5951	0.0000	0.0000	1.0	0.0	-4.41	-4.89	Baba et al., 2015
78	butyl paraben	0.900	1.47	0.74	0.43	1.5540	0.0000	0.0000	1.0	0.0	-4.34	-4.59	Akomeah et al., 2007
79	$C_6H_5(CH_2)_2COOH$	0.750	1.18	0.60	0.60	1.2135	0.0000	0.0000	1.0	0.0	-4.93	-5.42	Zhang et al., 2012
80	$C_6H_5(CH_2)_2COOH$, anion	0.900	3.43	0.03	3.02	1.1920	0.0000	2.1879	1.0	0.0	-6.78	-7.07	Zhang et al., 2012
81	$C_6H_5(CH_2)_3COOH$	0.760	1.29	0.61	0.57	1.3544	0.0000	0.0000	1.0	0.0	-4.85	-5.16	Zhang et al., 2012
82	$C_6H_5(CH_2)_3COOH$, anion	0.910	3.59	0.04	3.01	1.3329	0.0000	2.2184	1.0	0.0	-6.70	-6.82	Zhang et al., 2012
83	$C_6H_5(CH_2)_4COOH$	0.770	1.24	0.57	0.60	1.4933	0.0000	0.0000	1.0	0.0	-4.30	-4.94	Zhang et al., 2012
84	$C_6H_5(CH_2)_4COOH$, anion	0.920	3.63	0.04	3.10	1.4718	0.0000	2.2794	1.0	0.0	-6.15	-6.66	Zhang et al., 2012
85	$C_6H_5(CH_2)_7COOH$	0.790	1.27	0.57	0.62	1.7771	0.0000	0.0000	1.0	0.0	-3.86	-4.49	Zhang et al., 2012
86	$C_6H_5(CH_2)_7COOH$, anion	0.940	3.87	0.07	3.26	1.8965	0.0000	2.4256	1.0	0.0	-5.71	-6.07	Zhang et al., 2012
87	C_6H_5COOH	0.730	0.90	0.59	0.40	0.9317	0.0000	0.0000	1.0	0.0	-4.91	-5.27	Zhang et al., 2012
88	C_6H_5COOH, anion	0.880	3.05	0.02	2.75	0.9102	0.0000	2.1385	1.0	0.0	-6.76	-6.81	Zhang et al., 2012

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89	caffeine	1.500	1.82	0.08	1.25	1.3632	0.0000	0.0000	1.0	0.0	-6.85	-6.83	Akomeah et al., 2007
90	catechol	0.970	1.10	0.88	0.47	0.8338	0.0000	0.0000	1.0	0.0	-5.87	-5.80	Baba et al., 2015
91	chloral hydrate	0.814	0.96	0.59	0.56	0.8750	0.0000	0.0000	1.0	0.0	-5.97	-5.78	Baba et al., 2015
92	chloroacetic acid, F_i = 0.90, log K_p(t) = -6.62	0.577	2.94	0.00	1.10	0.5657	0.0000	0.3680	1.0	0.0	-7.78	-7.77	Baba et al., 2015
93	chloroacetic acid, F_n = 0.1, log K_p(t) = -6.62	0.427	1.03	0.79	0.35	0.5872	0.0000	0.0000	1.0	0.0	-5.97	-5.95	Baba et al., 2015
94	chloroacetonitrile	0.372	0.89	0.38	0.26	0.5266	0.0000	0.0000	1.0	0.0	-4.56	-5.63	Baba et al., 2015
95	chlorodibromomethane	0.775	0.68	0.12	0.10	0.7219	0.0000	0.0000	1.0	0.0	-4.37	-4.62	Baba et al., 2015
96	chlorpheniramine	1.465	1.41	0.00	1.33	2.2098	0.0000	0.0000	0.0	1.0	-5.93	-5.24	Baba et al., 2015
97	codeine	2.220	2.15	0.15	1.80	2.2057	0.0000	0.0000	1.0	0.0	-6.57	-6.78	Zhang et al., 2012
98	codeine cation	2.070	5.83	2.68	0.00	2.2272	2.9847	0.0000	0.0	0.0	-10.01	-9.90	Roy and Flynn, 1989
99	cortexolone	1.910	3.45	0.36	1.60	2.7389	0.0000	0.0000	1.0	0.0	-7.20	-6.23	Baba et al., 2015
100	cortexone	1.740	3.50	0.14	1.31	2.6802	0.0000	0.0000	1.0	0.0	-6.42	-5.61	Baba et al., 2015
101	corticosterone	1.860	3.43	0.40	1.63	2.7389	0.0000	0.0000	1.0	0.0	-6.84	-6.31	Zhang et al., 2012
102	cortisone	1.960	3.50	0.36	1.87	2.7546	0.0000	0.0000	1.0	0.0	-7.38	-6.88	Baba et al., 2015
103	coumarin	1.230	1.68	0.00	0.52	1.0619	0.0000	0.0000	0.0	1.0	-5.60	-5.53	Baba et al., 2015
104	cyclobarbitone	1.440	1.35	0.49	1.45	1.7859	0.0000	0.0000	0.0	1.0	-6.65	-6.42	Baba et al., 2015
105	cytarabine	2.090	2.25	0.87	2.12	1.6234	0.0000	0.0000	1.0	0.0	-8.66	-8.92	Baba et al., 2015
106	decan-1-ol	0.191	0.42	0.37	0.48	1.5763	0.0000	0.0000	1.0	0.0	-4.15	-4.01	Zhang et al., 2012

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107	dexamethasone	2.040	3.51	0.71	1.92	2.9132	0.0000	0.0000	0.0	0.0	-7.27	-6.83	Zhang et al., 2012
108	diazinon	1.310	1.55	0.00	1.40	2.3056	0.0000	0.0000	1.0	0.0	-5.62	-5.34	Baba et al., 2015
109	dibromoacetic acid, F_i = 0.85, log K_p(t) = -6.25	0.948	3.34	0.11	2.53	0.7955	0.0000	2.0502	1.0	0.0	-6.76	-6.90	Baba et al., 2015
110	dibromoacetic acid, F_n = 0.15, log K_p(t) =-6.25	0.798	1.24	0.92	0.31	0.8147	0.0000	0.0000	1.0	0.0	-5.57	-5.57	Baba et al., 2015
111	dibromoacetonitrile	0.766	1.24	0.25	0.26	0.7542	0.0000	0.0000	1.0	0.0	-4.33	-5.33	Baba et al., 2015
112	dichloroacetic acid, F_i = 0.80, log K_p(t) = -6.39	0.632	2.53	0.00	2.18	0.6881	0.0000	1.4260	1.0	0.0	-7.21	-7.30	Baba et al., 2015
113	dichloroacetic acid, F_n = 0.20, log K_p(t) = -6.39	0.482	1.20	0.92	0.26	0.7096	0.0000	0.0000	1.0	0.0	-5.75	-5.65	Baba et al., 2015
114	dichloroacetonitrile	0.428	0.96	0.20	0.17	0.6490	0.0000	0.0000	1.0	0.0	-4.38	-5.16	Baba et al., 2015
115	diclofenac	1.810	1.85	0.55	0.77	2.0250	0.0000	0.0000	1.0	0.0	-5.30	-4.61	Zhang et al., 2012
116	diclofenac, anion	1.960	5.31	0.03	3.35	2.0035	0.0000	2.6243	1.0	0.0	-7.00	-6.32	Zhang et al., 2012
117	diethylcarbamazine	0.645	1.30	0.00	1.55	1.7241	0.0000	0.0000	1.0	0.0	-6.15	-6.69	Zhang et al., 2012
118	diethylether	0.041	0.25	0.00	0.45	0.7309	0.0000	0.0000	1.0	0.0	-5.37	-5.25	Zhang et al., 2012
119	digitoxin	3.460	5.63	1.33	4.35	5.6938	0.0000	0.0000	1.0	0.0	-8.15	-9.03	Zhang et al., 2012
120	dihydrocodeine	2.060	2.32	0.26	1.74	2.2487	0.0000	0.0000	1.0	0.0	-6.00	-6.72	Zhang et al., 2012
121	dihydromorphine	2.080	1.35	0.42	2.04	2.1078	0.0000	0.0000	1.0	0.0	-7.58	-7.16	Zhang et al., 2012
122	dimethylethylamine	0.094	0.18	0.00	0.64	0.7720	0.0000	0.0000	1.0	0.0	-5.80	-5.59	Baba et al., 2015
123	ephedrine	0.916	0.74	0.21	1.21	1.4385	0.0000	0.0000	0.0	1.0	-5.50	-6.07	Baba et al., 2015
124	estradiol	1.800	1.77	0.86	1.10	2.1988	0.0000	0.0000	1.0	0.0	-5.61	-5.16	Zhang et al., 2012

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125	estrone	1.730	2.05	0.50	1.08	2.1558	0.0000	0.0000	1.0	0.0	-5.52	-5.24	Baba et al., 2015
126	ethacrynic acid anion	1.500	4.91	0.07	3.65	2.0318	0.0000	2.5114	1.0	0.0	-7.38	-7.12	Baba et al., 2015
127	ethanol	0.246	0.42	0.37	0.48	0.4491	0.0000	0.0000	1.0	0.0	-6.08	-6.03	Zhang et al., 2012
128	ethyl nicotinate	0.667	1.10	0.00	0.73	1.1724	0.0000	0.0000	1.0	0.0	-5.28	-5.57	Zhang et al., 2012
129	ethyl p-aminobenzoate	1.030	1.31	0.31	0.69	1.3133	0.0000	0.0000	1.0	0.0	-5.06	-5.40	Baba et al., 2015
130	ethylbenzene	0.613	0.51	0.00	0.15	0.9982	0.0000	0.0000	1.0	0.0	-3.00	-4.12	Zhang et al., 2012
131	ethylene glycol mono isopropyl ether	0.196	0.48	0.21	0.91	0.9305	0.0000	0.0000	1.0	0.0	-6.71	-6.20	Baba et al., 2015
132	ethylene glycol mono methyl ether acetate	0.166	0.79	0.00	0.81	0.9462	0.0000	0.0000	1.0	0.0	-6.10	-6.05	Baba et al., 2015
133	ethylene glycol mono propyl ether	0.212	0.50	0.30	0.83	0.9305	0.0000	0.0000	1.0	0.0	-6.34	-6.05	Baba et al., 2015
134	etodolac	1.803	2.17	1.05	1.15	2.2390	0.0000	0.0000	0.0	1.0	-5.48	-5.51	Baba et al., 2015
135	famotidine	2.690	2.14	1.20	2.50	2.2617	0.0000	0.0000	0.0	1.0	-8.15	-8.66	Baba et al., 2015
136	fentanyl	1.830	1.75	0.00	1.81	2.8399	0.0000	0.0000	1.0	0.0	-5.81	-5.42	Baba et al., 2015
137	fentanyl cation	1.680	5.67	2.22	0.00	2.8615	2.8615	0.0000	0.0	0.0	-8.21	-8.38	Roy and Flynn, 1990
138	fluocinonide	1.950	2.48	0.31	2.51	3.4603	0.0000	0.0000	1.0	0.0	-6.33	-6.54	Zhang et al., 2012
139	flurbiprofen, neutral, F_n = 0.01, log K_p(t) = -6.20	1.440	1.45	0.62	0.76	1.84	0.0000	0.0000	1.0	0.0	-4.72	-4.75	Zhang et al., 2012
140	flurbiprofen, anion, F_i = 0.99, log K_p(t) = -6.20	1.590	4.56	0.07	3.36	1.8174	0.0000	2.5383	1.0	0.0	-6.36	-6.51	Zhang et al., 2012
141	flurbiprofen glucoside	2.321	3.80	0.85	1.80	2.8693	0.0000	0.0000	1.0	0.0	-6.28	-6.80	Swart et al., 2005
142	flurbiprofen mannoside	2.321	3.73	0.85	1.95	2.8693	0.0000	0.0000	1.0	0.0	-6.74	-7.13	Swart et al., 2005

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143	glycerol trinitrate	0.586	2.11	0.00	0.35	1.2300	0.0000	0.0000	1.0	0.0	-5.21	-5.16	Zhang et al., 2012
144	griseofulvin	1.750	2.64	0.00	1.44	2.3947	0.0000	0.0000	0.0	1.0	-6.44	-5.87	Baba et al., 2015
145	heptan-1-ol	0.211	0.42	0.37	0.48	1.1536	0.0000	0.0000	0.0	0.0	-4.57	-4.77	Zhang et al., 2012
146	heptanoic acid	0.149	0.64	0.62	0.44	1.1693	0.0000	0.0000	0.0	0.0	-5.26	-4.87	Baba et al., 2015
147	hexan-1-ol	0.210	0.42	0.37	0.48	1.0127	0.0000	0.0000	1.0	0.0	-4.92	-5.02	Zhang et al., 2012
148	hexanoic acid	0.174	0.63	0.62	0.44	1.0284	0.0000	0.0000	0.0	0.0	-5.48	-5.11	Baba et al., 2015
149	hexyl nicotinate	0.628	1.07	0.00	0.73	1.7360	0.0000	0.0000	1.0	0.0	-4.83	-4.54	Zhang et al., 2012
150	hydrocodone	2.030	1.81	0.00	1.85	2.2057	0.0000	0.0000	1.0	0.0	-6.26	-6.67	Zhang et al., 2012
151	hydrocortisone	2.030	3.49	0.71	1.90	2.7976	0.0000	0.0000	1.0	0.0	-7.22	-6.98	Zhang et al., 2012
152	hydrocortisone hemipimelate	2.020	3.58	1.06	2.61	3.8740	0.0000	0.0000	0.0	0.0	-6.24	-6.94	Zhang et al., 2012
153	hydrocortisone hemisuccinate	2.100	3.15	1.06	2.61	3.4513	0.0000	0.0000	0.0	0.0	-6.69	-7.43	Zhang et al., 2012
154	hydrocortisone hexanoate	1.810	3.02	0.46	2.16	3.6587	0.0000	0.0000	0.0	0.0	-5.30	-5.73	Zhang et al., 2012
155	hydrocortisone hydroxyhexanoate	2.020	3.49	0.83	2.64	3.7174	0.0000	0.0000	0.0	0.0	-6.60	-7.17	Zhang et al., 2012
156	hydrocortisone methylpimelate	1.930	3.49	0.46	2.61	4.0149	0.0000	0.0000	0.0	0.0	-5.82	-6.45	Zhang et al., 2012
157	hydrocortisone methylsuccinate	1.990	3.11	0.46	2.61	3.5922	0.0000	0.0000	0.0	0.0	-7.23	-6.97	Zhang et al., 2012
158	hydrocortisone N,N-dimethylsuccinate	2.210	3.77	0.46	2.86	3.7742	0.0000	0.0000	0.0	0.0	-7.73	-7.62	Zhang et al., 2012
159	hydrocortisone octanoate	1.770	3.05	0.46	2.16	3.9405	0.0000	0.0000	0.0	0.0	-4.76	-5.24	Zhang et al., 2012
160	hydrocortisone pimelamate	2.210	4.15	0.96	2.78	3.9151	0.0000	0.0000	0.0	0.0	-6.61	-7.57	Zhang et al., 2012
161	hydrocortisone propionate	1.870	2.90	0.46	2.16	3.2360	0.0000	0.0000	0.0	0.0	-6.02	-6.41	Zhang et al., 2012

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162	hydrocortisone succinamate	2.310	3.32	1.01	2.84	3.4924	0.0000	0.0000	0.0	0.0	-8.14	-7.98	Zhang et al., 2012
163	hydromorphone	2.040	1.60	0.16	1.95	2.0648	0.0000	0.0000	1.0	0.0	-7.83	-7.09	Zhang et al., 2012
164	hydroquinone	1.063	1.27	1.06	0.57	0.8338	0.0000	0.0000	1.0	0.0	-6.31	-6.19	Baba et al., 2015
165	hydroxypregnenolone	1.550	3.35	0.57	1.35	2.7232	0.0000	0.0000	1.0	0.0	-6.30	-5.71	Baba et al., 2015
166	hydroxyprogesterone	1.640	3.35	0.25	1.31	2.6802	0.0000	0.0000	1.0	0.0	-6.30	-5.57	Baba et al., 2015
167	ibuprofen, neutral, F_n = 0.03, log K_p(t) = -5.83	0.730	0.70	0.57	0.79	1.7771	0.0000	0.0000	1.0	0.0	-4.58	-4.57	Zhang et al., 2012
168	ibuprofen, anion , F_i = 0.97, log K_p(t) = -5.83	0.880	3.50	0.08	3.31	1.7556	0.0000	2.4188	1.0	0.0	-6.15	-6.25	Zhang et al., 2012
169	ibuprofen glucoside	1.826	3.11	0.85	2.00	2.8075	0.0000	0.0000	1.0	0.0	-6.94	-7.05	Swart et al., 2005
170	ibuprofen mannoside	1.826	2.79	0.85	2.00	2.8075	0.0000	0.0000	1.0	0.0	-6.55	-6.86	Swart et al., 2005
171	indomethacin	2.240	1.47	0.58	1.43	2.5299	0.0000	0.0000	1.0	0.0	-5.39	-5.03	Zhang et al., 2012
172	indomethacin anion	2.390	5.62	0.10	4.38	2.5084	0.0000	2.9899	1.0	0.0	-7.22	-7.17	Zhang et al., 2012
173	isoquinoline	1.211	1.00	0.00	0.54	1.0443	0.0000	0.0000	0.0	1.0	-5.11	-5.20	Zhang et al., 2012
174	iso-thymol	0.824	0.81	0.56	0.43	1.3387	0.0000	0.0000	1.0	0.0	-4.84	-4.53	Baba et al., 2015
175	ketoprofen, neutral, F_n = 0.50, logK_p(t) = -5.51	1.650	2.26	0.55	0.89	1.9779	0.0000	0.0000	1.0	0.0	-5.22	-5.26	Zhang et al., 2012
176	ketoprofen, anion, F_i = 0.50, logK_p(t) = -5.51	1.800	5.49	0.01	3.39	1.9564	0.0000	2.4851	1.0	0.0	-6.84	-6.97	Zhang et al., 2012
177	ketoprofen glucoside	2.628	4.22	0.85	2.20	3.0082	0.0000	0.0000	1.0	0.0	-7.73	-7.74	Swart et al., 2005
178	ketoprofen mannoside	2.628	4.07	0.85	2.20	3.0082	0.0000	0.0000	1.0	0.0	-7.59	-7.65	Swart et al., 2005
179	ketorolac	1.600	2.03	0.65	1.05	1.8712	0.0000	0.0000	1.0	0.0	-5.60	-5.74	Baba et al., 2015
180	levosimendan	2.100	1.76	0.70	1.60	2.0915	0.0000	0.0000	1.0	0.0	-6.00	-6.46	Baba et al., 2015

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181	lidocaine	1.110	1.51	0.07	1.24	2.0589	0.0000	0.0000	1.0	0.0	-5.51	-5.42	Baba et al., 2015
182	lidocaine cation	0.960	4.18	2.12	0.00	2.0804	1.7490	0.0000	1.0	0.0	-7.42	-7.29	Baba et al., 2015
183	linolenic acid anion	0.698	3.59	0.14	3.90	2.5687	0.0000	2.6821	1.0	0.0	-5.99	-5.67	Baba et al., 2015
184	mannitol	0.836	2.33	0.87	1.77	1.3062	0.0000	0.0000	1.0	0.0	-8.42	-8.86	Zhang et al., 2012
185	m-cresol	0.822	0.88	0.57	0.34	0.9160	0.0000	0.0000	1.0	0.0	-4.89	-5.12	Zhang et al., 2012
186	meperidine cation	0.840	4.25	1.93	0.00	2.0716	1.8235	0.0000	1.0	0.0	-7.43	-7.41	Baba et al., 2015
187	methanol	0.278	0.44	0.43	0.47	0.3082	0.0000	0.0000	1.0	0.0	-6.38	-6.29	Zhang et al., 2012
188	methyl 4-hydroxyphenylacetate	0.908	1.36	0.59	0.70	1.2722	0.0000	0.0000	0.0	0.0	-5.26	-5.64	Baba et al., 2015
189	methyl nicotinate	0.710	1.13	0.00	0.71	1.0315	0.0000	0.0000	1.0	0.0	-5.77	-5.78	Zhang et al., 2012
190	methyl p-aminobenzoate	1.030	1.25	0.30	0.72	1.1724	0.0000	0.0000	1.0	0.0	-4.99	-5.68	Baba et al., 2015
191	methyl paraben	0.930	1.46	0.71	0.46	1.1313	0.0000	0.0000	1.0	0.0	-5.03	-5.41	Akomeah et al., 2007
192	methyl salicylate	0.850	0.84	0.02	0.47	1.1313	0.0000	0.0000	1.0	0.0	-4.80	-4.83	Baba et al., 2015
193	methylphenylether	0.708	0.75	0.00	0.29	0.9160	0.0000	0.0000	1.0	0.0	-4.68	-4.74	Zhang et al., 2012
194	methyltriglycol nicotinate	0.730	1.42	0.00	1.79	2.0530	0.0000	0.0000	1.0	0.0	-6.83	-6.74	Zhang et al., 2012
195	morphine	2.230	1.30	0.39	2.01	2.0648	0.0000	0.0000	1.0	0.0	-7.24	-7.11	Zhang et al., 2012
196	naproxen	1.510	2.02	0.60	0.67	1.7821	0.0000	0.0000	1.0	0.0	-4.97	-4.97	Zhang et al., 2012
197	naproxen, anion	1.660	5.07	0.02	3.11	1.7606	0.0000	2.4260	1.0	0.0	-6.53	-6.56	Zhang et al., 2012
198	naproxen glucoside	2.818	3.81	0.85	2.10	2.8124	0.0000	0.0000	1.0	0.0	-7.89	-7.57	Swart et al., 2005
199	naproxen mannoside	2.818	3.73	0.85	2.10	2.8124	0.0000	0.0000	1.0	0.0	-7.70	-7.52	Swart et al., 2005

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200	nicorandil	1.100	2.60	0.39	1.28	1.4464	0.0000	0.0000	0.0	1.0	-7.30	-7.39	Baba et al., 2015
201	nicotine	0.865	0.88	0.00	1.09	1.3710	0.0000	0.0000	1.0	0.0	-5.34	-5.92	Baba et al., 2015
202	nimesulide	2.109	2.70	0.31	1.09	2.0787	0.0000	0.0000	0.0	1.0	-6.35	-5.68	Baba et al., 2015
203	nizatidine	1.910	2.92	0.64	2.41	2.4622	0.0000	0.0000	0.0	1.0	-7.78	-8.47	Baba et al., 2015
204	nonan-1-ol	0.193	0.42	0.37	0.48	1.4354	0.0000	0.0000	1.0	0.0	-4.30	-4.27	Zhang et al., 2012
205	o-cresol	0.840	0.86	0.52	0.30	0.9160	0.0000	0.0000	1.0	0.0	-4.88	-4.99	Zhang et al., 2012
206	octan-1-ol	0.199	0.42	0.37	0.48	1.2945	0.0000	0.0000	1.0	0.0	-4.30	-4.52	Zhang et al., 2012
207	octanoic acid	0.150	0.65	0.62	0.45	1.3102	0.0000	0.0000	0.0	0.0	-5.18	-4.65	Baba et al., 2015
208	o-phenylenediamine	1.260	1.40	0.24	0.73	0.9160	0.0000	0.0000	1.0	0.0	-6.70	-6.21	Zhang et al., 2012
209	o-tert-butylphenol	0.823	0.92	0.52	0.40	1.3387	0.0000	0.0000	1.0	0.0	-4.48	-4.51	Baba et al., 2015
210	ouabain	4.010	6.20	0.90	3.46	4.1615	0.0000	0.0000	1.0	0.0	-9.66	-9.75	Zhang et al., 2012
211	oxycodone	2.320	2.50	0.29	1.91	2.2644	0.0000	0.0000	1.0	0.0	-6.43	-7.18	Zhang et al., 2012
212	oxymorphone	2.320	2.10	0.39	1.90	2.1235	0.0000	0.0000	1.0	0.0	-7.60	-7.21	Zhang et al., 2012
213	p-cresol	0.820	0.87	0.57	0.31	0.9160	0.0000	0.0000	1.0	0.0	-4.83	-5.04	Zhang et al., 2012
214	pentan-1-ol	0.219	0.42	0.37	0.48	0.8718	0.0000	0.0000	0.0	0.0	-5.30	-5.28	Zhang et al., 2012
215	pentanoic acid	0.205	0.63	0.62	0.45	0.8875	0.0000	0.0000	0.0	0.0	-6.11	-5.39	Baba et al., 2015
216	phenobarbital	1.630	1.72	0.71	1.18	1.6999	0.0000	0.0000	0.0	1.0	-6.70	-6.19	Baba et al., 2015
217	phenol	0.805	0.89	0.60	0.30	0.7751	0.0000	0.0000	1.0	0.0	-5.27	-5.29	Zhang et al., 2012
218	phloroglucinol	1.360	1.39	1.40	0.73	0.8925	0.0000	0.0000	1.0	0.0	-5.87	-6.62	Baba et al., 2015

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219	piroxicam, anion	2.710	6.81	0.00	3.78	2.2285	0.0000	2.7356	1.0	0.0	-7.50	-7.48	Zhang et al., 2012
220	piroxicam, neutral	2.560	2.90	0.17	1.49	2.2500	0.0000	0.0000	1.0	0.0	-6.02	-6.36	Zhang et al., 2012
221	p-phenylenediamine	1.300	1.66	0.44	0.83	0.9160	0.0000	0.0000	1.0	0.0	-6.98	-6.67	Zhang et al., 2012
222	prednisolone	2.210	3.10	0.71	1.92	2.7546	0.0000	0.0000	1.0	0.0	-7.91	-6.85	Baba et al., 2015
223	pregnenolone	1.360	3.29	0.32	1.18	2.6645	0.0000	0.0000	1.0	0.0	-5.90	-5.31	Baba et al., 2015
224	progesterone	1.450	3.29	0.00	1.14	2.6215	0.0000	0.0000	1.0	0.0	-4.90	-5.17	Zhang et al., 2012
225	propan-1-ol	0.236	0.42	0.37	0.48	0.5900	0.0000	0.0000	1.0	0.0	-5.93	-5.78	Zhang et al., 2012
226	propranolol (F_n larger than 0.85)	1.840	1.43	0.44	1.31	2.1480	0.0000	0.0000	1.0	0.0	-6.05	-5.41	Baba et al., 2015
227	propranolol, cation (F_i larger than 0.995)	1.690	4.31	2.07	0.00	2.1695	2.4319	0.0000	1.0	0.0	-7.70	-8.11	Zhang et al., 2012
228	propylparaben	0.900	1.45	0.74	0.43	1.4131	0.0000	0.0000	1.0	0.0	-5.41	-4.83	Baba et al., 2015
229	pyrogallol	1.165	1.26	1.35	0.64	0.8925	0.0000	0.0000	1.0	0.0	-6.17	-6.33	Baba et al., 2015
230	ranitidine	1.600	1.63	0.25	2.33	2.3985	0.0000	0.0000	0.0	1.0	-7.41	-7.52	Baba et al., 2015
231	resorcinol	0.980	1.11	1.09	0.52	0.8338	0.0000	0.0000	1.0	0.0	-6.70	-6.00	Zhang et al., 2012
232	salicylic acid	0.900	0.85	0.73	0.37	0.9904	0.0000	0.0000	1.0	0.0	-5.07	-5.08	Zhang et al., 2012
233	salicylic acid, anion	1.050	3.19	0.08	2.74	0.9689	0.0000	2.2641	1.0	0.0	-7.04	-6.45	Zhang et al., 2012
234	scopolamine	1.686	1.32	0.09	2.17	2.2321	0.0000	0.0000	0.0	1.0	-7.58	-7.18	Baba et al., 2015
235	sufentanil	1.800	2.28	0.00	1.91	3.1051	0.0000	0.0000	1.0	0.0	-5.53	-5.51	Baba et al., 2015
236	sufentanil cation	1.650	6.16	3.02	0.00	3.1266	2.5848	0.0000	1.0	0.0	-8.11	-8.06	Baba et al., 2015
237	testosterone	1.540	2.56	0.32	1.17	2.3827	0.0000	0.0000	1.0	0.0	-5.54	-5.33	Zhang et al., 2012

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238	theophylline	1.500	1.60	0.54	1.34	1.2223	0.0000	0.0000	1.0	0.0	-6.92	-7.33	Baba et al., 2015
239	thymol	0.822	0.80	0.43	0.44	1.3387	0.0000	0.0000	1.0	0.0	-4.35	-4.51	Zhang et al., 2012
240	toluene	0.601	0.52	0.00	0.14	0.8573	0.0000	0.0000	0.0	0.0	-3.64	-4.36	Zhang et al., 2012
241	tribromomethane	0.974	0.68	0.15	0.06	0.7745	0.0000	0.0000	1.0	0.0	-4.34	-4.41	Baba et al., 2015
242	trichloroacetic acid, F_i = 0.90, log K_p(t) = -6.39	0.674	3.08	0.14	2.48	0.8105	0.0000	1.9882	1.0	0.0	-6.75	-6.80	Baba et al., 2015
243	trichloroacetic acid, F_n= 0.10, log K_p(t) = -6.39	0.524	1.21	1.01	0.26	0.8320	0.0000	0.0000	1.0	0.0	-5.60	-5.46	Baba et al., 2015
244	trichloromethane	0.425	0.49	0.15	0.02	0.6167	0.0000	0.0000	1.0	0.0	-4.46	-4.56	Baba et al., 2015
245	triglycol nicotinate	0.950	1.58	0.37	1.78	1.9121	0.0000	0.0000	1.0	0.0	-8.08	-7.16	Zhang et al., 2012
246	urea	0.501	1.49	0.83	0.84	0.4646	0.0000	0.0000	1.0	0.0	-7.93	-7.64	Zhang et al., 2012
247	water	0.000	0.45	0.82	0.35	0.1673	0.0000	0.0000	1.0	0.0	-6.28	-6.43	Zhang et al., 2012

[a] K_p in units of cm/s; values of solute descriptors of neutral compounds taken from Abraham et al. (2009), Abraham et al. (2007), Abraham et al. (2008), Stephens et al. (2012) and Zhang et al. (2012) or obtained as described before (Abraham et al., 2015a; Abraham et al., 2015b; Clarke and Mallon, 2012); ionic descriptors obtained as described before (Abraham and Acree, 2016). [b] Cited studies where log K_p (obs) was obtained.

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We made a distinction between skin permeation through *stratum corneum* or through full thickness skin or through intermediate thickness skin, by the use of indicator variables. For permeation through the *stratum corneum*, the indicator variable is zero because this is our 'standard system'. In column 'Inter', Table 2, all values are zero except for permeation through intermediate thickness where the indicator value = 1. In column 'Full' all values are zero except for permeation through full thickness skin where the indicator value = 1.

Regression of the values of log K_p against the descriptors in Eq. 2 and the two indicator variables 'Inter' and 'Full' leads to Eq. 4.

$$\log K_p = - 5.182(0.126) + 0.185(0.085)\,E - 0.617(0.057)\,S - 0.373(0.095)\,A - 2.412\,(0.091)\,B + 1.763(0.081)\,V - 1.440(0.122)\,J^{+} + 2.461(0.113)\,J^{-} - 0.121(0.099)\,\text{Inter} - 0.299(0.139)\,\text{Full}$$

$$N = 247 \quad SD = 0.430 \quad R^2 = 0.869 \quad F = 174.70 \quad PRESS = 47.550 \quad Q^2 = 0.858 \quad PSD = 0.448 \qquad (4)$$

Here and elsewhere, N is the number of compounds or species studied, R^2 is the squared correlation coefficient, SD is the standard deviation, and F is the Fisher F-statistic. PRESS and Q^2 are the leave-one-out statistics and PSD is the predicted standard deviation (Abraham et al., 2009). The SD values for the coefficients are in parentheses. The coefficient 0.121 for the indicator variable 'inter' is very small, only just larger than the SD value, and exclusion of this term results in Eq. 5.

$$\log K_p = - 5.311(0.071) + 0.159(0.082)\,E - 0.617(0.057)\,S - 0.352(0.094)\,A - 2.401(0.091)\,B + 1.782\,(0.079)\,V - 1.448(0.123)\,J^{+} + 2.450(0.113)\,J^{-} - 0.190(0.108)\,\text{Full}$$

$$N = 247 \quad SD = 0.430 \quad R^2 = 0.868 \quad F = 195.92 \quad PRESS = 47.317 \quad Q^2 = 0.858 \quad PSD = 0.446 \qquad (5)$$

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If both of the terms in the indicator variables are left out, Eq. 6 is obtained.

$\log K_p = - 5.328(0.071) + 0.137(0.082) E - 0.604(0.057) S - 0.338(0.094) A - 2.428(0.090) B + 1.797(0.079) V - 1.485(0.121) J^+ + 2.471(0.113) J^-$

$N = 247 \quad SD = 0.432 \quad R^2 = 0.866 \quad F = 221.48 \quad PRESS = 47.335 \quad Q^2 = 0.858 \quad PSD = 0.445$

(6)

From a comparison of Eqs. 4, 5 and 6, it can be seen that the inclusion of the 'Inter' variable makes no difference to the statistics of the LFER equation. The effect of the 'Full' indicator variable is very small, and we suggest that Eq. 6 be used in the prediction of further values of log K_p. What our analysis indicates is that differences in the thickness of skin used make very little difference to the actual experimental value of K_p.

Eq. 6 shows reasonably similar coefficients to our previous equation deduced from only 118 compounds, but with better values of SD (0.432) and R^2 (0.866). To prevent overfitting, the predicted R^2 (Q^2) was calculated by the leave-one-out statistics, which may indicate how well the model predicts new observations. Q^2 of Eq. 6 is 0.858, very close to the R^2 value of 0.866. This indicates that Eq. 6 can provide valid predictions for new observations without overfitting. The predictive standard deviation (PSD) can also be obtained using the same statistics; this gives the predictive accuracy of regression models (Abraham et al., 2009). The PSD value of Eq. 6 is 0.445, which indicates that Eq. 6 is a good predicting model for log K_p, especially for the cases including ions and ionic species. In Figure 2, a plot of observed log K_p versus predicted log K_p is shown for all the compounds and species involved into the calculation of Eq. 6. The data points for cationic and anionic species are found to scatter randomly around the line of identity, implying that no systematic bias for ionic species exists through Eq. 6.

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In the construction of Eq. 6, we made an approximation of the ratio $K_p(n)/K_p(i)$, which is deduced from our previous model (Zhang et al., 2012) and the known descriptors, to estimate the values of $K_p(n)$ and $K_p(i)$ of partially ionized compounds in Table 2. Now we use Eq. 6 to calculate the values of $K_p(n)/K_p(i)$, as shown in Table 3. Table 3 reveals that neutral acids and bases permeate across the human skin very much faster than their ionic species, but the actual ratio depends on their structures.

Table 3. Calculated values of $K_p(n)/K_p(i)$ using Eq.6

Acids	$K_p(n)/K_p(i)$	Bases	$K_p(n)/K_p(i)$
C_6H_5COOH	35	4-$MeC_6H_4CH_2NHMe$	40
$C_6H_5(CH_2)_2COOH$	45	4-$MeC_6H_4CH_2NHEt$	43
$C_6H_5(CH_2)_3COOH$	45	4-$MeC_6H_4CH_2NHPr$	44
$C_6H_5(CH_2)_4COOH$	52	4-$MeC_6H_4CH_2NHBu$	43
$C_6H_5(CH_2)_7COOH$	38	4-$MeC_6H_4CH_2NH(CH_2)_4Me$	41
chloroacetic acid	66	4-$MeC_6H_4CH_2NH(CH_2)_5Me$	65
bromoacetic acid	108	4-$MeC_6H_4CH_2NH(CH_2)_6Me$	58
dichloroacetic acid	45	alprenolol	266
dibromoacetic acid	22	propranolol	505
bromochloroacetic acid	22	sufentanil	352
trichloroacetic acid	21	lidocaine	75
piroxicam	13	meperidine	121
salicylic acid	24	fentanyl	900
naproxen	39	codeine	1323
indomethacin	137		
ibuprofen	48		
ketoprofen	52		
flurbiprofen	57		
diclofenac	51		
ethacrynic acid	71		
linolenic acid	229		

We have shown that Eq. 6 can be used to predict skin permeation of a wide range of cationic and anionic species, but it can also be used to predict values for permanent ions. In

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our previous paper (Zhang et al., 2012), we used our constructed equation to predict values of log K_p for skin permeation for the sodium and tetraethylammonium ions, and we can do the same through Eq. 6. Values are for Na^+: -8.12 (obs) (Zhang et al., 2012), -7.41 (calc) (Zhang et al., 2012) and -7.55 (this work), and for Et_4N^+: -7.84 (obs) (Zhang et al., 2012), -6.48 (calc) (Zhang et al., 2012) and -6.38 (this work), so that it is possible to predict log K_p for permanent ions with no more than a set of simple descriptors (Abraham and Acree, 2016).

We illustrate the prediction of log K_p with the examples shown in Table 4, for species that have never been studied in terms of skin permeation. We can extend our predictions as follows. In Eq. 3, values of the fraction ionized and neutral, F_i and F_n, depend on the pK_a of the solute and the pH of the donor solution. Eq. 3 can then be used in reverse, and a total value of log K_p can be calculated for any set of F_i and F_n values. Since these depend on the pH of the donor solution, this amounts to a calculation of log K_p as a function of pH. We illustrate this in Figure 3 for ketoprofen, an acid with a pK_a of 4.30; experimental data for the neutral and ionized forms from Zhang et al. (2012).

Table 4. Prediction of log K_p for some neutral and ionic species

Species	E	S	A	B	V	J^+	J^-	log K_p (pred)
3,4-dimethoxybenzoic acid	0.95	1.65	0.57	0.75	1.3309	0.000	0.000	-5.82
3,4-dimethoxybenzoic acid, anion	1.04	3.93	0.00	3.17	1.3094	0.000	2.190	-7.49
bupivacaine	1.32	2.10	0.34	1.33	2.5139	0.000	0.000	-5.24
bupivacaine, cation	1.17	4.67	2.92	0.00	2.5354	1.592	0.000	-6.78

Eq. 3 and Figure 3 can be used to explain why models that do not distinguish between neutral and ionic species, still yield reasonable statistical results. Because K_p(n) is very much larger than K_p(i), partial ionization results in only a small diminution in the observed K_p value. Thus for ketoprofen, at pH = 4.3, when it is 50% neutral, our calculated log K_p is -5.55 as compared to our calculated value at 100 % neutral of -5.26. Even at pH 4.67 when ketoprofen

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is only 30% in the neutral form, our calculated log K_p is -5.76, only 0.50 log units less than for the 100 % neutral species. Unless a particular compound is largely in the ionized form, use of neutral descriptors and neglect of ionization will lead to calculated log K_p values that are not too far out-of-line.

We cannot compare the result shown in Figure 3 with any previous such results, because this appears to be the first time that log K_p values have been predicted as a function of pH in this way. Indeed, we cannot compare our equation for permeation of neutral molecules and ionic species, Eq. 6, with any previous equation that includes ionic species other than our own equation (Zhang et al., 2012). What we can say is that our statistics for Eq. 6 compare favorably with those reported for equations that deal only with neutral species. One of the most recent, and successful, models for skin permeation is that of Baba et al. (2015) who used an SVM-Gaussian method in which 2732 descriptors per compound were initially computed. Reduction to 11 descriptors yielded an equation for 169 compounds with R^2 = 0.867 and a root mean square error, RMSE = 0.423 log units. This can be compared to Eq. 6 where we use only 7 descriptors from the beginning, and for 247 species find that R^2 = 0.866 and RMSE = 0.425 log units.

CONCLUSION

The LFER method provides a very useful tool to construct a predictive model for human skin permeability of neutral molecules, ions and ionic species. In this study, an equation has been constructed using the experimental log K_p of a large and varied set of compounds and species. The equation can be used to predict the values of log K_p for neutral molecules, ions and ionic species. The PSD value of the equation is 0.432, which shows that log K_p can be predicted

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quite accurately. An advantage of our method over previous methods is that it provides valid predictions of log K_p for partially ionized compounds, in terms of the fractions of neutral and ionic species that exist at some given pH of the donor solution. We found that for ionizable compounds at low degrees of ionization (that is, less than 50%), the experimental values of log K_p do not deviate markedly from that for the neutral molecules. By a critical analysis via LEERs, it was confirmed that the thickness of skin exerts very little influence on the experimental value of log K_p.

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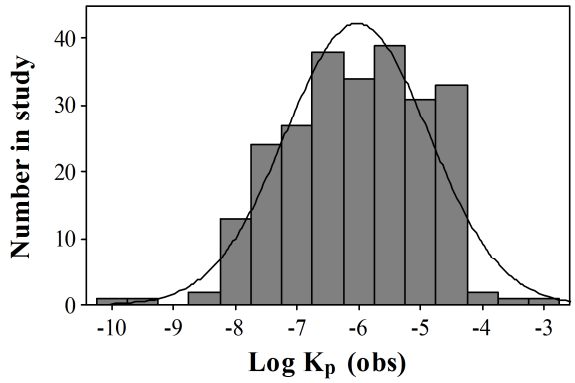
Legend to Figures

Figure 1. Distribution of log K_p (cm/s) of the compounds and species in our data set.

Figure 2. A plot of observed log K_p (cm/s) versus calculated log K_p (cm/s) for all the compounds and species involved in the calculation of Eq. 6. The solid line corresponds to ideal agreement. Markers: ○, neutral molecules; ■, cations from protonated bases; ♦, anions from deprotonated acids.

Figure 3. A plot of values of log K_p (cm/s) for ketoprofen as a function of the pH of the donor solution. The value of Fi at the top axis corresponds to the ionic fraction of ketoprofen at given pH. ● calculated values, ○ observed values for the neutral and fully ionized forms.



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