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Ab initio prediction of human skin permeability coefficients

William J. Pugh and Jonathan Hadgraft

The Welsh School of Pharmacy, University of Wales College of Cardiff, Redwood Building, King Edward VII Avenue, Cardiff CF1 3XF (UK)

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Summary

A general linear model was used to fit published human stratum corneum log permeability coefficient (log P) values for 91 diverse compounds to various parameters of their molecular structures. This enabled calculation of additive group contribution values which are useful in predicting log P values. Two sets of predictors are suggested based on the SMILES method of molecular structure description and on an 11-predictor set of empirically determined functional groups. The results were in general agreement with the prediction method based on octanol/water partition and molecular weight proposed by Potts and Guy (*Pharm. Res.*, 9 (1992) 663–669). The method has obvious application in the simple estimation of permeability of compounds for which no data are published, and, where the predicted values for the three methods differ significantly from experimental values, could indicate compounds in which the permeation processs is abnormal.

Introduction

Within the pharmaceutical, cosmetic and agrochemical industries there is a general need to be able to estimate the rate at which molecules penetrate the skin. It is important both from the standpoint of estimating clinical effectiveness and also toxicological risk. When specific drugs are designed to act locally or to be delivered transdermally, it is useful to know what effect different functional groups have on the overall permeability through the skin. In the design of cosmetic agents such as UV filters it is useful to know their intrinsic absorption characteristics so that systemic delivery can be minimised. Equally, in the design of new pesticides, molecules are required which are active but not well absorbed through the skin.

The objective of this work is the prediction of permeability coefficients (P) of compounds for human skin solely from the molecular structure of the penetrant. Recently, Potts and Guy (1992), using values from a collection (Flynn, 1990) of 94 compounds covering a wide range of chemical types, have claimed general success for a universal formula relating log P to molecular weight and log(octanol/water) partition coefficient (log K).

This prediction is, therefore, dependent on a quantity which must be determined experimentally or estimated from a group contribution

Correspondence to: W.J. Pugh, The Welsh School of Pharmacy, University of Wales College of Cardiff, Redwood Building, King Edward VII Avenue, Cardiff CF1 3XF, U.K.

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method such as that used by the Medchem™ program (Pomona College Medicinal Chemistry (MEDCHEM) database, Pomona College, Claremont, CA, 1984). It also uses two parameters which are themselves correlated, and it is axiomatic in multivariate regression analysis that each predictor should be independent (Bolton, 1984; pp. 468–474). For these two reasons it is desirable to have a prediction method based solely on error-free, independent predictors and avoid basing a final prediction on a parameter which may itself be imprecisely known.

Methods

Statistical analysis was conducted mainly using the Minitab™ statistical package (Minitab Release 8.1, Minitab Inc., State College, PA, 1991).

It was assumed that a general linear model would apply of the type:

$$\log P = A + Bb + Cc + \ldots$$

where P is the permeability coefficient, A represents a constant, and B, C, ... are fitted coefficients to the parameters b, c, ... (such as molecular weight, aromaticity, number of amine groups). In order to apply a fitting procedure, a minimum of two examples of each parameter is necessary (much larger numbers are desirable) so that water (no carbon atoms present) and sufentanyl (the only compound containing sulphur) were excluded from the analysis. One of the values for hydrocortisone ($P = 3 \times 10^{-6}$ cm h^{-1}) was also omitted as it was so much at variance with the values for other steroids. The values A, B, C... were calculated as the coefficients in the best fit equation from the multiple regression analysis routine. This gives, amongst other information:

(a) The best fit equation.

(b) The coefficient of determination, r^2, adjusted for the degrees of freedom. This represents the amount of the dependent variable (log P) attributable to the values of the independent (predictor) variables. The residue is unexplained, and should be small for a good model.

(c) The standard deviation about the regression.

(d) The fitted value of log P_C where the log $P_{experimental}$ value for compound C is used in the regression.

(e) The residual. This is log $P_{C.fitted}$ − log $P_{C.experimental}$.

(f) The predicted value of log P_E if the data for compound, E, are omitted from the regression data.

(g) The 95% confidence interval for log P_E.

(h) A warning, X, if the predicted or fitted value is based on predictors well removed form the centre of the data set. XX is printed if the predictor values are extreme outliers (see 'leverage' under Results and Discussion for more detail).

Further details on these statistics are given in the Minitab™ Reference Manual (Minitab Inc., State College, PA, Release 8, 1991, ch. 7).

It is recognised that the choice of predictors is arbitrary, but preliminary examination of the data set suggested a few guidelines:

(a) Halogenation increases permeability and Cl and Br are equally effective (comparison of halogenated and non-halogenated phenols).

(b) Unsaturation of alkyl groups has little effect (styrene and ethyl benzene).

(c) Position of substitution is unimportant (monohalogenated phenols). This assumption is fundamental to the success of the method.

With these points in mind an attempt was made to find general linear relationships between log P and several predictor sets.

Results and Discussion

In an attempt to determine which functional groups might be useful in fitting a multivariate, linear equation for log P, a large number of combinations of groups was tried. The SMILES method (an established convention describing molecular structure) provided a convenient set of possible predictors. In addition, we tried several sets of predictors of our own. To illustrate the selection process, results for two such combinations using 17 and 11 groups are given in Table 1a, together with results based on SMILES pre-

dictors and the approach of Potts and Guy (1992). The coefficients for the results based on the work of Potts and Guy differ slightly from those in their paper because they do not report which of the compounds given by Flynn (1990) were used. We therefore used all of the compounds for which log $K_{octanol}$ values were available. In deciding the usefulness of a model the following statistics, which are listed in Tables 1a, b and 2, should be considered:

(1) r^2: This has been described in the Introduction. In practice it seemed to be of little value in evaluating results.

(2) p: This is the probability of error in concluding that a predictor has a real influence on log P. A value < 0.05 is generally considered acceptable.

(3) Studentized residual (TRESID): The residual is the difference between experimental and predicted values of log P. TRESID is a statistic for the residual when the predicted value is based on the data set from which the compound under test is omitted. It has a t distribution with $(N - v - 1)$ degrees of freedom (N, number of data points; v, number of independent predictors including the constant). Values of TRESID $> t$ ($p = 0.05$) are taken to indicate unusually large differences between experimental and predicted values.

(4) Leverage (HI): High leverage is an indication that the result is based on unusual predictor values, i.e., some predictor values are far removed from the mean values. A value $> 3v/N$ is considered unusual.

(5) DFIT: TRESID measures unusual prediction and leverage measures unusual predictors. The DFIT statistic combines both of these to give an overall measure of the unusualness of an observation. Values $> 2\sqrt{v}/N$ are considered unusual.

Further details of the above statistics, with original references, may be found in the Minitab™ Reference Manual.

Numerous preliminary attempts at fitting led us initially to propose the use of 17 functional groups. No distinction could be seen between single- and double-bonded alkyl C atoms, so all C atoms not involved in C = O groups were designated -C-. For a new compound log P may then

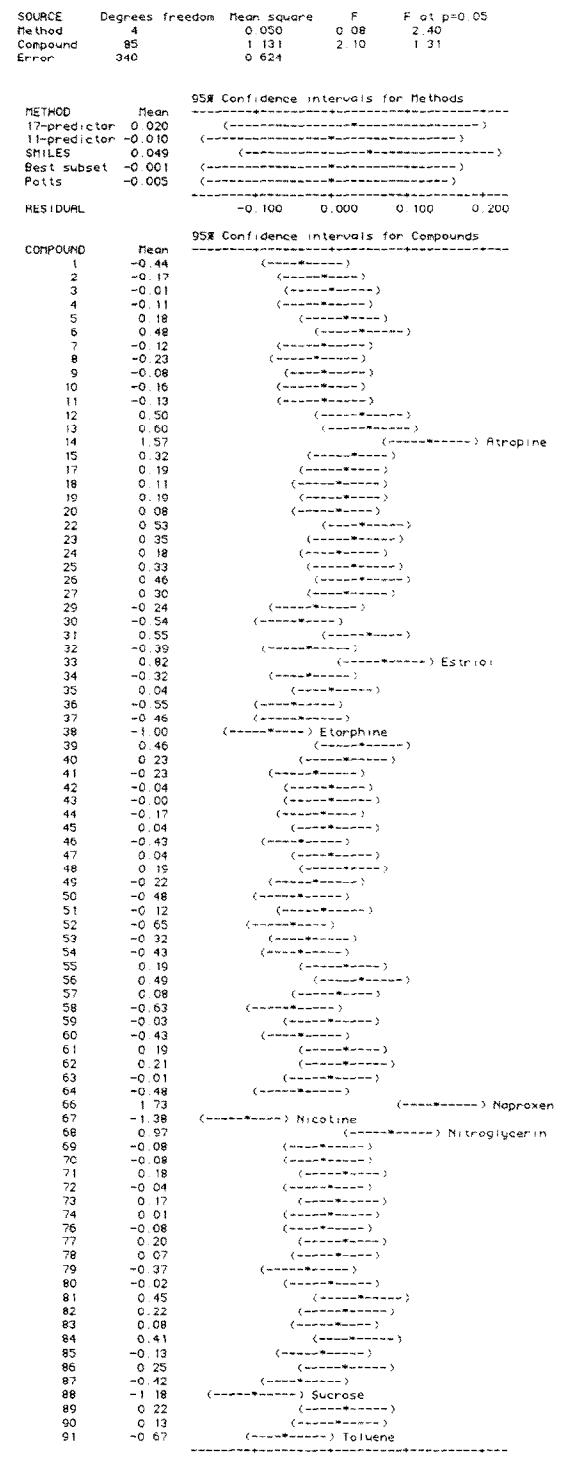

Fig. 1. Two-way ANOVA of residuals for 86 compounds by five methods.

be predicted by counting how many of each group are present and substituting in the appropriate equation based on Table 1a.

For example, nitrazepam has values: 14 -C-, 2 aromatic rings, 1 N (amine), 1 N (amide), 1 N (to O), 2 O (to N), 1 CO (amide), Mol. Wt 281.3. All other variable predictors are zero.

Log P is predicted as $-2.696 + 14(0.251) + 2(-0.679) + 1(-0.955) + 1(-0.502) + 1(-1.742) + 1(-0.174) + 2(0.613) + 281.3(-0.00084) = -3.71$.

The 95% confidence interval is -4.64 to -3.71.

Examination of the p values in Table 1a shows that many are well above the generally acceptable value of 0.05, indicating that these predictor coefficients are not significantly different from zero. This is probably because too few compounds with these groups are in the data set. Removal of functional attributes with low confidence levels resulted in an 11-predictor model. Here all, except the predictors based on N-O (for which only four compounds were available), had very low p values. Similarly, the SMILES convention suggested use of the predictors listed under SMILES 1 in Table 1b. Again the high p values for several of the predictors show that they have little individual value and they were combined and eliminated to give the statistically significant predictors in SMILES 3, which were used for the rest of this work. In the Potts-Guy equation, both predictors are highly significant, as expected for a relatively simple bivariate system. The molecular weight term of their equation is insignificant in

TABLE 1

Coefficients for (a) various predictor groups and (b) SMILES groups

(a) Predictor	17-predictor		11-predictor		Potts-Guy	
	Coefficient	p	Coefficient	p	Coefficient	p
Constant	−2.696	0.00	2.709	0.00	−2.722	0.00
-C-	0.251	0.08	0.233	0.00	–	–
Aromaticity	−0.679	0.01	−0.467	0.02	–	–
Alcohol	−0.494	0.01	–	–	–	–
Phenol	−0.094	0.77	–	–	–	–
Ketone/aldehyde	−0.194	0.56	–	–	–	–
Acid	−0.606	0.23	–	–	–	–
Ether	−0.151	0.54	–	–	–	–
Ester	−0.106	0.84	–	–	–	–
Halide	0.351	0.23	0.446	0.01	–	–
N (amine)	−0.955	0.01	−1.177	0.00	–	–
N (amide)	−0.502	0.37	–	–	–	–
CO (amide)	−0.174	0.74	–	–	–	–
O (to N)	0.613	0.14	0.503	0.16	–	–
N (to O)	−1.742	0.09	−1.445	0.14	–	–
Non-aromatic ring	−0.791	0.00	−0.657	0.00	–	–
Steroid	−0.935	0.12	−1.136	0.01	–	–
Mol. Wt	−0.00084	0.93	–	–	−0.00555	0.00
Log K	–	–	–	–	0.663	0.00
OH	–	–	−0.452	0.00	–	–
'O'	–	–	−0.316	0.01	–	–
Amide	–	–	−0.352	0.00	–	–
Number of compounds		91		91		87
r^2 (adjusted)		0.671		0.676		0.636

-C-, all C atoms not in C = O (phenobarbital has -C- value 9); -OH, alcohol, phenol; 'O', ether, aldehyde, acid, ester (butanoic acid has 'O' value 1); Amide, C = O, N in amides (phenobarbital has Amide value 5). Coefficients significantly different from zero ($p < 0.05$) underlined.

the 17- and 11-predictor models as it is assimilated into the group contributions.

The Studentised residual values (Table 2) showed some interesting features. The 11-predictor model gave six outliers, the 17-predictor gave nine, the Potts-Guy model 11 and SMILES 12. In many cases, e.g., diethylcarbamazine, digitoxin and isoquinoline, there is no consistency amongst the methods and the unusual predictions are probably due to inadequacy of the model. Others have predicted values which are consistently lower (ethylbenzene, toluene) or higher (naproxen) than experimental. This could indicate that: (a) all four models are inadequate; (b) the experimental value is wrong; or (c) a different absorption mechanism applies, this really being an extension of (a).

The leverage statistic showed that sucrose had unusual predictor values in all three methods. The 17- and 11-predictor models were poor at fitting N-O compounds; this is probably the result of using N (to O) and O (to N) groups as predictors ($p = 0.16$ and 0.14) when only a small number of such compounds were available. The 11-predictor model has four outliers, the 17-predictor has five and the Potts-Guy model four.

The DFIT values show that the 17-predictor model has nine suspect compounds, the 11-predictor has 10 and that of Potts and Guy 11. Again some compounds show consistently high (etorphine, sucrose) or low (atropine, naproxen) fitted values.

Prediction of log P

To test the validity of a prediction method it is necessary to apply the equation to 'unknown' compounds and compare predicted and true values. We are forced to accept experimental values as being true values. The coefficients in Tables 1a and b can be used for this. The success of each method can also be assessed by omitting the experimental value for each compound in turn from the data set and predicting its log P from the regression equation based on the remaining data. The 95% confidence interval and leverage can be calculated at the same time. This was done for all the compounds by all four methods and the results are listed in Tables 3a and b. Note that it is not possible to calculate confidence intervals for predicted values from the Potts-Guy

(b) Predictor	SMILES 1		SMILES 2		SMILES 3	
	Coefficient	p	Coefficient	p	Coefficient	p
Constant	−2.614	0.00	−2.654	0.00	−2.674	0.00
C	1.75	0.09	–	–	–	–
C=	0.264	0.14	–	–	–	–
c	0.291	0.00	0.299	0.00	0.253	0.00
O	−0.114	0.32	–	–	–	–
O=	0.016	0.92	–	–	–	–
Ring close	−0.849	0.00	−0.881	0.00	−0.866	0.00
Halide	0.416	0.15	0.479	0.07	0.376	0.05
N	0.526	0.01	–	–	–	–
n	0.053	0.92	–	–	–	–
Mol. Wt	−0.00316	0.64	−0.00348	0.57	–	–
[C]	–	–	0.205	0.03	0.155	0.00
[O]	–	–	−0.102	0.35	−0.157	0.04
[N]	–	–	−0.369	0.02	−0.409	0.00
Number	91		91		91	
r^2 (adjusted)	0.54		0.54		0.52	

Coefficients significantly different from zero ($p < 0.05$) underlined. C, single bonded carbon; C=, double bonded carbon; c, aromatic carbon; N, aliphatic nitrogen; n, aromatic nitrogen; [C], any aliphatic carbon; [O], any oxygen; [N], any nitrogen. The predictors listed under SMILES 1 follow the original SMILES convention. The others are modifications made to improve the p values of the predictors. SMILES 3 was used for the remainder of this work.

method as one of the predictors (log $K_{octanol}$) is subject to error, so the 95% prediction intervals were calculated (Bolton, 1984; pp. 198–202).

Use of a 'best subset' for prediction

In some cases, it seems at first sight that use of the whole data set is not the best way of predic-

TABLE 2

Compounds shown to be unusual by regression analysis

		17-predictor	11-predictor	Potts-Guy	SMILES
Studentised residuals	(+)	diethylcarbamazine	–	–	–
		–	–	digitoxin	digitoxin
		ethylbenzene	ethylbenzene	ethylbenzene	ethylbenzene
		–	–	etorphine	etorphine
		isoquinoline	–	–	–
		nicotine	nicotine	–	nicotine
		–	–	–	nitroglycerine
		styrene	–	–	styrene
		toluene	toluene	toluene	toluene
	(−)	–	–	aldosterone	–
		–	atropine	atropine	atropine
		–	–	–	chlorpheniramine
		–	–	cortisone	cortisone
		–	–	estriol	–
		2-ethoxyethanol	–	–	–
		–	–	hydromorphone	–
		–	*N*-nitrosodiethanolamine	–	*N*-nitrosodiethanolamine
		naproxen	naproxen	naproxen	naproxen
		resorcinol	–	–	–
		–	–	testosterone	–
Leverage		diethylcarbamazine	–	–	–
		digitoxin	–	digitoxin	digitoxin
		–	–	–	estradiol 2
		–	–	–	ethylbenzene
		–	–	–	etorphine
		–	–	–	H-21-hexanoate
		–	–	H-21-octanoate	H-21-octanoate
		–	–	methanol	–
		–	–	–	nicotine
		nitroglycerine	nitroglycerine	–	nitroglycerine
		N-nitrosodiethanolamine	*N*-nitrosodiethanolamine	–	–
		–	–	–	styrene
		sucrose	sucrose	sucrose	–
		–	–	–	toluene
		–	2,4,6-trichlorophenol	–	–
DFITS	(+)	diethylcarbamazine	–	–	–
		–	–	digitoxin	digitoxin
		–	–	ethylbenzene	–
		etorphine	etorphine	etorphine	etorphine
		–	–	H-pimelamate	–
		–	–	Me-H-21-pimelamate	–
		nicotine	nicotine	–	nicotine
		–	–	–	nitroglycerine
		–	–	–	styrene
		sucrose	sucrose	sucrose	sucrose
		–	–	toluene	–

TABLE 2 (continued)

	17-predictor	11-predictor	Potts-Guy	SMILES
(–)	–	–	aldosterone	–
	atropine	atropine	atropine	atropine
	chlorpheniramine	chlorpheniramine	–	–
	–	–	cortisone	–
	–	fentanyl	–	–
	naproxen	naproxen	naproxen	naproxen
	nitroglycerine	nitroglycerine	–	–
	N-nitrosodiethanolamine	*N*-nitrosodiethanolamine	–	*N*-nitrosodiethanolamine
	resorcinol	–	–	–

H, hydrocortisone; Me, methyl.

tion. For instance, log P values are given for the series methanol to decanol. Prediction of log P for a higher monohydric alcohol would seem to be best achieved by using the equation for this subset:

$$\log P = -3.59 + 0.269(\text{-C-});\ (N = 10,\ r^2 = 0.976)$$

To check this, each alcohol in turn was omitted from the subset and its log P value predicted from the remaining nine alcohols. The values are given in Table 3a. A two-way analysis of variance (ANOVA) of residual against alcohol name and method gave an F value for method of 3.6 indicating significant difference between the best subset and the 17- and 11-predictor methods ($p = 0.01$). The best subset method gave predicted values with a significantly smaller mean residual than the 17- and 11-predictor models (0.237, 0.243). It must, however, be borne in mind that values for such series of similar compounds are often the product of a single laboratory and hence liable to systematic error.

Similar families of closely related compounds can be identified: aliphatic acids, halogenated phenols, hydrocortisone esters, non-aromatic non-esterified steroids. Two-way ANOVA results are given in Table 4, and it can be seen that the best subset method often gives predicted values significantly closer to the experimental values than at least one of the other methods. Unfortunately, most drugs do not fall into such simple subsets. In some cases, it is possible to produce a logical mixed subset, e.g., the aromatic steroids (estradiol, estriol, estrone) can be combined with non-aromatic steroids (cortexolone, cortexone, corticosterone, hydrocortisone, hydroxyprogesterone, pregnenolone, progesterone, testosterone, cortisone) with the same functional groups (ketone, alcohol). Again the mixed subset gives a significantly better result. Formation of a mixed subset is usually more complicated. The non-halogenated phenols (3,4-xylenol, 4-ethyl phenol, *m*-, *o*- and *p*-cresol, phenol, resorcinol, thymol) must be combined with the hydrocarbons (ethylbenzene, styrene, toluene) to give a sufficient mixture of -C- and phenol values to make predictions possible. Although the best subset method gives the smallest mean residual, the F value, 2.86, is just below the $p = 0.05$ value of 2.92, so it is unsafe to claim significant advantage. The remainder of the compounds required fitting into ever more compex subsets, often with compounds of widely differing structure being included to give the requisite mix of functional groups. For example, the amines and alkaloids (10 compounds) had to be combined with 37 other compounds. Here, comparison with the Potts-Guy method was not possible as log K values were missing for some compounds, but the best subset result was significantly better than the 17- and 11-predictor methods. For all other compounds the choice of subset becomes almost a matter of personal taste and the best subset method is no improvement. Friedman's test (Bolton, 1984; pp. 402–403), the non-parametric equivalent of two-way ANOVA, gave similar results for significant differences amongst the median residuals.

TABLE 3

(a) Experimental and predicted values of log P and (b) 95% confidence and prediction intervals of log P values in (a)

(a)	Experiment	17-predictor	11-predictor	Best subset	Potts-Guy	SMILES
1 2-butanone	−2.36	−2.18	−2.32	−3.94	−2.96	−2.20
2 2-chlorophenol	−1.48	−1.74	−1.80	−1.43	−2.02	−1.66
3 2-naphthol	−1.55	−1.79	−1.79	−1.46	−1.64	−2.07
4 2,4-dichlorophenol	−1.22	−1.42	−1.36	−1.33	−1.39	−1.28
5 2,4,6-trichlorophenol	−1.23	−0.91	−0.67	−1.00	−1.17	−0.67
6 2-ethoxyethanol	−3.60	−2.27	−2.48	−2.51	−3.58	−2.31
7 3,4-xylenol	−1.44	−1.57	−1.78	−1.60	−1.85	−1.88
8 4-bromophenol	−1.44	−2.14	−1.81	−1.42	−1.97	−1.66
9 4-chlorocresol	−1.26	−1.50	−1.57	−1.36	−1.46	−1.67
10 4-chlorophenol	−1.44	−1.74	−1.81	−1.42	−1.86	−1.66
11 4-ethyl phenol	−1.46	−1.57	−1.77	−1.60	−1.82	−1.72
12 aldosterone	−5.52	−4.51	−4.46	−5.73	−3.95	−4.59
13 amobarbital 1	−2.64	−3.38	−3.43	1.32	−2.68	−3.18
14 atropine	−5.07	−2.24	−2.54	−2.57	−3.10	−2.85
15 barbital	−3.95	−3.90	−2.97	−3.74	−3.29	−3.55
16 benzyl alcohol	−2.22	−2.20	−1.99	–	−2.60	−2.02
17 butanoic acid	−3.00	−2.56	−2.28	−2.83	−2.68	−2.34
18 butanol	−2.60	−2.23	−2.21	−2.50	−2.55	−2.19
19 butobarbital	−3.71	−3.34	−3.44	−3.98	−2.79	−3.23
20 chloroxylenol	−1.28	−1.24	−1.32	−1.08	−1.34	−1.51
21 chlorpheniramine	−2.66	−1.23	−1.38	−1.15	–	−0.96
22 codeine	−4.31	−3.95	−3.78	−3.37	−3.78	−4.53
23 cortexolone	−4.13	−3.65	−3.56	−3.88	−2.95	−3.48
24 cortexone	−3.35	−3.16	−3.12	−3.48	−2.63	−3.35
25 corticosterone	−4.22	−3.64	−3.55	−3.86	−3.34	−3.48
26 cortisone	−5.00	−3.91	−4.07	−4.40	−3.74	−3.62
27 decanol	−1.10	−0.76	−0.79	−0.78	−0.94	−1.29
28 diethylcarbamazine	−3.00	−6.21	−3.60	−6.96	–	−2.53
29 digitoxin	−3.89	−4.38	−4.44	−3.78	−6.15	−5.81
30 ephedrine	−2.22	−2.48	−2.50	−3.56	−2.97	−1.96
31 estradiol 1	−3.52	−2.84	−2.92	−2.84	−2.43	−3.05
32 estradiol 2	−2.28	−3.15	−3.10	−3.31	−2.45	−3.12
33 estriol	−4.40	−3.25	−3.28	−3.28	−2.66	−3.17
34 estrone	−2.44	−3.01	−3.16	−3.43	−2.39	−3.11
35 ethanol	−3.10	−2.70	−2.67	−3.04	−3.19	−2.49
36 ethylbenzene	0.08	−1.61	−1.37	0.02	−1.27	−1.77
37 ethyl ether	−1.80	−1.92	−2.11	−3.36	−2.54	−2.23
38 etorphine	−2.44	−3.68	−3.72	−4.72	−3.82	−3.62
39 fentanyl 1	−2.25	−1.25	−1.05	−1.98	−1.66	−1.06
40 fentanyl 2	−2.00	−1.33	−1.11	−2.22	−1.68	−1.11
41 fluocinonide	−2.77	−2.83	−2.98	−3.29	−3.38	−3.49
42 heptanoic acid	−1.70	−1.93	−1.62	−1.83	−1.79	−1.91
43 heptanol	−1.50	−1.53	−1.53	−1.74	−1.56	−1.76
44 hexanoic acid	−1.85	−2.19	−1.86	−2.25	−2.11	−2.06
45 hexanol	−1.89	−1.76	−1.76	−1.98	−1.94	−1.90
46 H-pimelamate	−3.05	−3.38	−3.48	−3.55	−4.04	−3.15
47 H-succinamate	−4.59	−3.99	−4.10	−4.72	−4.32	−3.56
48 H-*N,N*-diMe-succinamate	−4.17	−3.51	−3.63	−3.60	−4.09	−3.24
49 H-21-hemipimelate	−2.75	−3.39	−3.08	−2.25	−3.39	−2.90

TABLE 3 (continued)

(a)	Experiment	17-predictor	11-predictor	Best subset	Potts-Guy	SMILES
50 H-21-hemisuccinate	−3.20	−4.16	−3.80	−3.67	−3.50	−3.37
51 H-21-hexanoate	−1.75	−2.70	−1.79	−1.70	−2.34	−2.80
52 H-21-hexanoate-6-OH	−3.04	−3.15	−3.20	−5.32	−3.54	−2.88
53 H-21-octanoate	−1.21	−2.28	−2.37	−1.11	−1.86	−2.54
54 H-21-proprionate	−2.47	−3.41	−3.48	−2.69	−3.07	−3.23
55 hydrocortisone 2	−3.93	−4.22	−4.04	−2.30	−3.73	−3.49
56 hydromorphone	−4.82	−5.03	−5.09	−3.26	−3.45	−4.63
57 hydroxyprogesterone	−3.22	−3.17	−3.12	−3.50	−2.73	−3.36
58 isoquinoline	−1.78	−3.12	−2.89	−2.43	−2.10	−2.59
59 *m*-cresol	−1.82	−1.80	−2.00	−1.77	−2.03	−2.03
60 Me-H-21-pimelate	−2.27	−2.60	−2.87	−3.01	−3.20	−2.96
61 Me-H-21-succinate	−3.68	−3.14	−3.50	−2.94	−3.65	−3.34
62 meperidine	−2.43	−2.08	−2.54	−2.24	−2.29	−2.56
63 methanol	−3.30	−2.93	−2.90	−3.33	−3.42	−2.64
64 methyl-4-hydroxybenzoate	−2.04	−1.93	−2.33	−4.06	−2.27	−2.19
65 *N*-nitrosodiethanolamine	−5.22	−3.99	−3.76	−5.24	–	−3.11
66 naproxen	−3.40	−0.87	−0.63	0.16	−1.86	−1.53
67 nicotine	−1.71	−4.80	−4.74	−2.55	−2.87	−3.38
68 nitroglycerine	−1.96	1.72	−2.42	−2.30	−2.66	−6.46
69 3-nitrophenol	−2.25	−2.69	−2.78	−2.25	−2.17	−2.94
70 4-nitrophenol	−2.25	−2.69	−2.78	−2.25	−2.19	−2.94
71 nonanol	−1.22	−1.03	−1.05	−1.14	−1.12	−1.45
72 *o*-cresol	−1.80	−1.80	−2.00	−1.78	−2.03	−2.03
73 octanoic acid	−1.60	−1.67	−1.38	−1.13	−1.53	−1.75
74 octanol	−1.28	−1.29	−1.30	−1.46	−1.48	−1.61
75 ouabain	−6.11	−6.62	−5.69	−4.93	–	−5.07
76 *p*-cresol	−1.75	−1.80	−2.01	−1.78	−2.03	−2.03
77 pentanoic acid	−2.70	−2.33	−2.05	−2.46	−2.42	−2.19
78 pentanol	−2.22	−2.00	−1.98	−2.25	−2.18	−2.05
79 phenobarbital	−3.34	−3.73	−3.55	−4.00	−3.03	−2.73
80 phenol	−2.09	−2.04	−2.24	−1.94	−2.28	−2.18
81 pregnenolone	−2.82	−2.71	−2.55	−2.22	−1.95	−3.22
82 progesterone	−2.82	−2.65	−2.66	−3.18	−1.94	−3.22
83 propanol	−2.85	−2.46	−2.44	−2.77	−2.89	−2.34
84 resorcinol	−3.62	−1.63	−2.63	−3.57	−3.26	−2.28
85 salicylic acid	−2.20	−2.78	−2.57	−2.12	−1.99	−2.35
86 scopolamine (hyoscine)	−4.30	−3.54	−3.61	−5.04	−3.57	−3.93
87 styrene	−0.19	−1.58	−1.36	0.12	−1.38	−1.77
88 sucrose	−5.28	−6.86	−6.29	−6.79	−6.33	−3.93
89 testosterone	−3.40	−3.17	−3.01	−4.31	−2.10	−3.51
90 thymol	−1.25	−1.07	−1.30	−1.01	−1.34	−1.57
91 toluene	0.00	−1.87	−1.61	−0.25	−1.45	−1.93

(continued overleaf)

Identification of unusual predictions

An assessment of whether each method individually involves unusual predictors and predictions has already been made. Two-way ANOVA of the residuals from the five methods enables us to see if the mean residual for each compound is significantly different from zero. Such a consensus would give a fair degree of confidence in concluding that either the experimental value is wrong or that absorption is occurring by an abnormal method. Fig. 1 shows the relationship between predicted and experimental permeability coefficients for the different approaches. Note that Fig. 1 does not include all 91 compounds as the best subset and Potts-Guy method are not applicable to all compounds. The results show

TABLE 3 (continued)

(b)	17-predictor	11-predictor	Best subset	Potts-Guy	SMILES
1 2-butanone	0.50	0.38	1.78	1.48	0.35
2 2-chlorophenol	0.41	0.36	0.07	1.46	0.41
3 2-naphthol	0.54	0.51	0.87	1.46	0.46
4 2,4-dichlorophenol	0.83	0.68	0.11	1.47	0.79
5 2,4,6-trichlorophenol	1.28	1.20	0.37	1.48	1.39
6 2-ethoxyethanol	0.49	0.33	0.22	1.50	0.34
7 3,4-xylenol	0.36	0.27	0.12	1.46	0.31
8 4-bromophenol	1.60	0.36	0.17	1.46	0.41
9 4-chlorocresol	0.40	0.35	0.12	1.47	0.41
10 4-chlorophenol	0.40	0.36	0.17	1.46	0.41
11 4-ethyl phenol	0.36	0.27	0.12	1.47	0.31
12 aldosterone	0.54	0.45	1.94	1.44	0.58
13 amobarbital 1	0.84	0.73	53.0	1.46	0.56
14 atropine	0.61	0.36	0.81	1.89	0.30
15 barbital	0.86	0.77	1.96	1.47	0.57
16 benzyl alcohol	0.47	0.27	–	1.47	0.31
17 butanoic acid	0.58	0.38	1.48	1.47	0.35
18 butanol	0.34	0.31	0.12	1.47	0.35
19 butobarbital	0.83	0.74	3.07	1.45	0.56
20 chloroxylenol	0.42	0.37	0.42	1.48	0.41
21 chlorpheniramine	1.20	1.04	1.30	–	0.82
22 codeine	0.70	0.65	0.94	1.47	0.65
23 cortexolone	0.43	0.32	0.43	1.44	0.34
24 cortexone	0.43	0.36	0.46	1.46	0.39
25 corticosterone	0.43	0.32	0.41	1.45	0.34
26 cortisone	0.74	0.39	1.14	1.45	0.32
27 decanol	0.58	0.55	0.17	1.49	0.47
28 diethylcarbamazine	3.21	0.61	54.00	–	0.40
29 digitoxin	2.26	1.02	3.06	1.53	0.81
30 ephedrine	0.52	0.46	0.66	1.46	0.34
31 estradiol 1	0.73	0.55	0.78	1.45	0.39
32 estradiol 2	0.73	0.55	0.70	1.46	0.39
33 estriol	0.73	0.60	0.93	1.41	0.37
34 estrone	0.59	0.48	1.47	1.46	0.39
35 ethanol	0.40	0.35	0.19	1.50	0.39
36 ethylbenzene	0.44	0.30	0.20	1.45	0.31
37 ethyl ether	0.58	0.35	0.43	1.46	0.35
38 etorphine	1.08	0.90	1.21	1.45	0.54
39 fentanyl 1	0.79	0.71	1.76	1.48	0.75
40 fentanyl 2	0.79	0.71	2.26	1.49	0.75
41 fluocinonide	1.17	0.98	1.19	1.48	0.97
42 heptanoic acid	0.57	0.35	0.81	1.47	0.35
43 heptanol	0.40	0.38	0.10	1.47	0.36
44 hexanoic acid	0.56	0.34	0.33	1.46	0.34
45 hexanol	0.36	0.35	0.11	1.46	0.35
46 H-pimelamate	0.52	0.43	1.12	1.48	0.50
47 H-succinamate	0.52	0.43	1.29	1.49	0.38
48 H-*N,N*-diMe-succinamate	0.51	0.42	0.97	1.49	0.45
49 H-21-hemipimelate	0.68	0.43	1.51	1.49	0.49

that overall there is no difference between the five methods ($F = 0.08$), but several compounds have mean residuals significantly different from zero. These are listed in Table 5. Noteable are naproxen and atropine, with predicted values much higher than predicted, and nicotine with a

TABLE 3 (continued)

(b)	17-predictor	11-predictor	Best subset	Potts-Guy	SMILES
50 H-21-hemisuccinate	0.66	0.44	1.50	1.48	0.38
51 H-21-hexanoate	0.41	0.35	1.08	1.50	0.43
52 H-21-hexanoate-6-OH	0.46	0.36	1.03	1.48	0.42
53 H-21-octanoate	0.52	0.45	1.79	1.53	0.53
54 H-21-proprionate	0.37	0.30	2.05	1.46	0.32
55 hydrocortisone 2	0.51	0.36	1.66	1.47	0.34
56 hydromorphone	1.25	1.04	1.78	1.44	0.70
57 hydroxyprogesterone	0.43	0.36	0.43	1.46	0.39
58 isoquinoline	0.71	0.59	0.75	1.46	0.44
59 *m*-cresol	0.35	0.27	0.12	1.47	0.31
60 Me-H-21-pimelate	0.73	0.45	0.70	1.48	0.57
61 Me-H-21-succinate	0.76	0.43	0.70	1.48	0.46
62 meperidine	1.36	0.50	1.57	1.46	0.36
63 methanol	0.46	0.39	0.24	1.51	0.43
64 Me-4-hydroxybenzoate	0.65	0.36	0.98	1.46	0.40
65 *N*-nitrosodiethanolamine	2.31	2.25	0.61	–	0.58
66 naproxen	0.99	0.72	2.63	1.43	0.57
67 nicotine	0.99	0.84	1.22	1.44	0.60
68 nitroglycerine	8.04	7.88	1.84	1.45	1.13
69 nitrophenol 3	0.77	0.75	0.20	1.47	0.40
70 nitrophenol 4	0.77	0.75	0.20	1.46	0.40
71 nonanol	0.51	0.49	0.19	1.48	0.43
72 *o*-cresol	0.35	0.27	0.12	1.47	0.31
73 octanoic acid	0.59	0.37	1.08	1.47	0.38
74 octanol	0.45	0.43	0.13	1.47	0.39
75 ouabain	1.37	1.03	0.70	–	0.78
76 *p*-cresol	0.35	0.27	0.12	1.47	0.31
77 pentanoic acid	0.56	0.35	0.75	1.47	0.34
78 pentanol	0.34	0.32	0.11	1.46	0.34
79 phenobarbital	0.89	0.79	7.45	1.46	0.53
80 phenol	0.35	0.28	0.18	1.47	0.33
81 pregnenolone	0.55	0.51	1.13	1.46	0.47
82 progesterone	0.52	0.45	1.03	1.46	0.47
83 propanol	0.37	0.32	0.15	1.49	0.37
84 resorcinol	0.84	0.34	0.35	1.49	0.36
85 salicylic acid	0.66	0.39	0.23	1.47	0.41
86 scopolamine (hyoscine)	0.72	0.49	0.93	1.45	0.43
87 styrene	0.45	0.30	0.15	1.77	0.31
88 sucrose	1.66	1.41	1.35	1.61	0.98
89 testosterone	0.54	0.48	0.76	1.44	0.50
90 thymol	0.44	0.33	0.48	1.48	0.34
91 toluene	0.45	0.29	0.20	1.44	0.31

The 95% confidence interval (prediction interval for Potts-Guy method) for a compound is given by the predicted value (part a) $\pm$ the corresponding value in part (b). For example, 95% CI for testosterone by 11-predictor method is -3.01 ± 0.48.

correspondingly low prediction. Two-way ANOVA on the 17-, 11-predictor, SMILES and best subset results showed that the mean residual for diethylcarbamazine was higher than predicted.

Comparison of residuals from the five methods

The distribution of the residuals for the 11-predictor method is shown in Fig. 2. Those for the other methods are similar. Table 6 gives the basic statistics for the residuals. The trimmed

mean is the mean after removal of the upper and lower 5% of data. Mean and median values are close to zero for all methods, and the balance between the upper and lower quartiles for individual methods indicates symmetrical distribution about zero. Two-way ANOVA shows that there is no difference amongst the means for the five methods (see above). Overall there seems no reason to prefer any particular method.

Success rate of predicted values

It must be borne in mind that deviation of the predicted from the experimental values might be because the absorption involves more than simple passive diffusion. For example, protein binding would be expected to hinder diffusion while fluidisation of the hydrocarbon chains in the lipid barrier should enhance absorption. In these cases, the deviation of the residual should be significantly large and of the same sign for all methods. We have already identified cases where this is so. Secondly, the deviation might be large because the experimental value is wrong. The reliability of the experimental values in Flynn's table can only be estimated from the three compounds which have duplicated values. Log P values for these are: -3.52, -2.28 (estradiol), -2.25, -2.00 (fentanyl) and -5.52, -3.93 (hydrocortisone). Differences are 1.24, 0.25 and 1.59; mean 1.03. On the basis of this tiny amount of data, we could record a result with an absolute residual less than 1 as a success (code 1), a borderline result as an absolute residual between 1 and 2 (code 2), and an outlier as greater than 2 (code 3). These limits represent ratios between log $P_{\text{experimental}}$ and log $P_{\text{predicted}}$ of < 10, < 100 and > 100, respectively. Taking a more optimistic view of the experimental results we also coded $|\log P|$ differences

TABLE 4

Use of 'best subset' to predict log P

Two-way ANOVA		Mean residual values					F	p
Set	N	17 [a]	11 [b]	SMILES	Potts-Guy	Best [c]		
A	10	0.237	0.243	−0.054	−0.021	0.007	3.60	0.01
B	5	0.034	0.332	−0.157	0.064	0.070	3.01	0.32
C	7	−0.191	−0.141	0.202	−0.266	0.044	4.53	0.00
D	6	−0.511	−0.460	0.360	−0.423	0.260	2.60	0.07
E	9	0.290	0.360	0.330	0.860	0.200	5.35	0.00
F	4 (+9)	0.098	0.045	0.07	0.677	−0.055	0.47	0.76
G	11	−0.273	−0.430	0.483	−0.491	0.017	2.95	0.03
H	10 (+37)	−0.041	−0.105	−0.021	–	0.085	0.03	0.99
Friedman's test		Estimated median residuals					S [d]	p
Set	N	17 [a]	11 [b]	SMILES	Potts-Guy	Best [c]		
A	10	0.241	0.250	0.047	0.041	0.039	16.6	0.00
B	5	0.006	0.312	0.091	0.070	0.078	5.6	0.25
C	7	−0.240	−0.302	0.225	−0.350	−0.046	13.8	0.01
D	6	−0.741	−0.651	0.582	−0.590	−0.011	5.7	0.22
E	9	0.313	0.390	0.019	0.860	0.094	20.7	0.00
F	4 (+9)	0.040	−0.010	0.212	0.630	−0.100	6.0	0.21
G	11	−0.054	−0.256	0.245	−0.284	−0.026	22.2	0.00
H	10 (+37)	−0.001	−0.121	0.225	–	−0.034	1.6	0.67

A, alkanols; B, alkacids; C, chlorophenols; D, hydrocortisone esters; E, non-aromatic, non-esterified steroids; F, aromatic steroids (+9 non-aromatic); G, amines and alkaloids (+37 other compounds); H, hydrocarbons and phenols.

[a] 17-predictor method. [b] 11-predictor method. [c] Best subset method. [d] Friedman's test statistic – approximates to chi-squared. Significantly different results ($p < 0.05$) are underlined. The 'best subset' method does not give significantly better results.

TABLE 5

Compounds with mean residuals significantly different from zero ($p < 0.05$)

High predicted values (P_{pred}/P_{exp})		Low predicted values (P_{exp}/P_{pred})	
Based on all five methods			
naproxen	53.7	nicotine	24.4
atropine	37.2	sucrose	15.1
nitroglycerine	9.3	etorphine	10.0
estriol	6.6		
Based on 17-, 11-predictor, best subset and SMILES			
		diethylcarbamazine	97.7

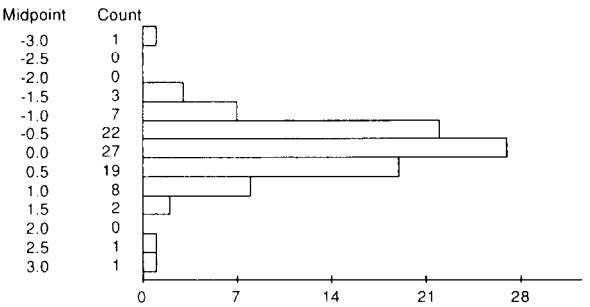

Fig. 2. Histogram of residuals from the 11-predictor method.

of < 0.301, < 0.602 and > 0.602, representing ratios of < 2, < 4 and > 4, as 1A, 2A, 3A. The results are given in Table 7. Again there is little to choose between the methods. The best subset method seems to perform slightly better if one takes the optimistic view of experimental data. As mentioned above this might be misleading because the subsets are not comprised of independent data, being largely the results of single laboratories.

Relationship between experimental and predicted values of log P

For compounds with the same absorption process (assumed to be simple, passive diffusion for most compounds) a linear relationship with intercept 0 and gradient 1 would be expected. A typical plot – for the 11-predictor method – is shown in Fig. 3 and the regression data for all methods are listed in Table 8. It appears from Table 8 that the Potts-Guy method is best, although it must be remembered that the regression analysis assumes zero error in the predictor values. This is is not the case for the Potts-Guy method as one of the predictors is log K. To test whether the intercepts and gradients are significantly different from their target values of 0 and 1, a t-test was performed on the output of the regression analysis (Bolton, 1984; pp. 191–193). To justify the conclusion that these parameters are different, the t values should exceed t at $(N-1)$ degrees of freedom and $p = 0.05$. The results in Table 8 show the superiority of the Potts-Guy method, although the 11-predictor method

TABLE 6

Basic statistics for residuals from the four methods

Statistic	Method				
	17 [a]	11 [b]	Best [c]	SMILES	Potts-Guy
Number of points	91	91	90	91	87
Mean	0.0070	0.0212	−0.0160	0.0000	−0.0089
Trimmed mean [d]	−0.0050	0.0152	−0.0310	−0.0145	−0.0146
Median	0.02	−0.04	0.01	0.07	−0.06
S.D.	0.997	0.810	1.041	0.806	0.750
S.E.	0.104	0.085	0.110	0.085	0.080
Minimum	−3.21	−3.03	−3.96	−1.96	−2.26
Maximum	3.68	2.77	3.96	2.66	1.97
Lower quartile [e]	−0.39	−0.37	−0.30	−0.53	−0.42
Upper quartile	0.37	0.43	0.24	0.41	0.32

[a] 17-predictor; [b] 11-predictor; [c] best subset methods; [d] trimmed mean is mean after discarding the upper 5% and lower 5% of data; [e] a quarter of data points are below the lower quartile value.

TABLE 7

Codings for the residuals from the four prediction methods

Method	N	Code					
f031	2	3	1A	2A	3A		
17-predictor	91	72	14	5	35	25	31
11-predictor	91	74	14	3	32	30	28
SMILES	91	74	15	2	34	26	31
Best subset	90	72	11	7	49	13	28
Potts-Guy	87	71	15	1	38	18	31

Codes for $|\log P_{exp} - \log P_{pred}|$: 1 ($< 1$), 1A ($< 0.301$), 2 ($> 1$; < 2), 2A (> 0.301; < 0.602), 3 (> 2), 3A (> 0.602).

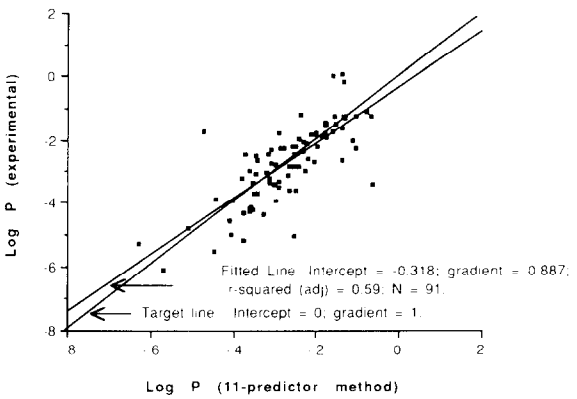

Fig. 3. Plot of log P experimental values against values predicted by the 11-predictor method.

also gave intercept and gradient not significantly different from 0 and 1, respectively. An apparent drawback is that the analysis includes atypical data as predictors. If these atypical points are omitted we should get a better prediction of the log P of 'typical' compounds, i.e., those whose absorption is not complicated by additional factors such as protein binding or self-enhancement. To check this the test was repeated omitting compounds coded 3, i.e., $|\log P|$ difference > 2.

It can be seen (Table 8) that the omission of these few compounds resulted in a great improvement in the intercept and gradient values. If one accepts that the prediction of outliers is in any case unlikely to be successful, then the prediction might best be performed omitting compounds coded 3 from the equations, with the understand-

TABLE 8

Regression statistics for log P_{exp} against log P_{pred}

Method	N	Intercept	Gradient	r^2_{adj}	t_{int}	t_{grad}	$t_{(p=0.05)}$	Difference [a]
Using all available values								
17-predictor	91	−0.860	0.678	0.48	3.95	4.36	1.66	Int., Grad.
11-predictor	91	−0.318	0.887	0.59	1.45	1.46	1.66	
SMILES	91	−0.489	0.810	0.43	1.74	1.93	1.66	Int., Grad.
Best subset	90	0.999	0.620	0.51	5.16	5.92	1.66	Int., Grad.
Potts-Guy [b]	87	−0.121	0.950	0.61	0.53	0.61	1.66	
Omitting values with code 3								
17-predictor	86	−0.190	0.919	0.69	1.00	1.23	1.66	
11-predictor	88	0.001	0.999	0.73	0.01	0.02	1.66	
SMILES	89	0.150	1.078	0.57	0.58	0.79	1.66	
Best subset	83	−0.309	0.878	0.78	2.04	2.36	1.66	Int., Grad.
Potts-Guy [b]	85	0.122	1.055	0.64	0.53	0.65	1.66	
Omitting values with code 3A								
17-predictor	60	−0.098	0.967	0.92	0.95	0.87	1.67	
11-predictor	63	0.050	1.007	0.90	0.42	0.16	1.67	
SMILES	62	0.084	1.018	0.74	0.41	0.23	1.67	
Best subset	65	−0.159	0.937	0.91	1.62	1.69	1.67	Grad.
Potts-Guy [b]	56	0.169	1.045	0.89	1.40	0.93	1.67	

[a] Difference column shows if intercept and/or gradient are significantly different from their target values of 0 and 1 ($p = 0.05$; d.f. $= N - 2$).

[b] The Potts-Guy method is not strictly amenable to this regression analysis since one of the predictors (log K) is subject to error.

ing that the predicted value is based on simple, passive diffusion. The suggested coefficients would then be those in Table 9.

Effect of number of data points on predicted value

It seems axiomatic that better predictions will be obtained from large data sets. It was of interest to see whether there were sufficient compounds in Flynn's table to give stable predictions. Ephedrine was chosen as an example with a low residual. Predictions were made as described on the data set from which ephedrine had been omitted. A second compound chosen at random was then omitted and the prediction made on this smaller subset. This was repeated until the predicted value became unstable. The procedure was repeated using naproxen (high residual) as a test compound omitting the same sequence of compounds as for ephedrine. Plots of the predicted values using the 17-predictor method are shown in Fig. 4a. It can be seen that the predictions are reaching limiting values well before 90 compounds are used, so that the size of Flynn's data set is adequate for the prediction. Similar plots are given by the 11-predictor and Potts-Guy methods. The results of the best subset method (Fig. 4b) show that ephedrine has a sufficient number of compounds in its subset to give a stable result, but naproxen does not. While a data set sufficiently large to give a stable result is

TABLE 9

Coefficients for predictor groups omitting predicted values code 3

Predictor	17-predictor		11-predictor		SMILES		Potts-Guy	
	Coefficient	p	Coefficient	p	Coefficient	p	Coefficient	p
Constant	−3.090	0.00	−2.896	0.00	−0.262	0.00	−2.650	0.00
-C-	0.178	0.09	0.264	0.00	–	–	–	–
Aromaticity	0.047	0.83	−0.257	0.02	–	–	–	–
Alcohol	−0.623	0.00	–	–	–	–	–	–
Phenol	−0.841	0.00	–	–	–	–	–	–
Ketone/aldehyde	−0.392	0.10	–	–	–	–	–	–
Acid	−0.732	0.04	–	–	–	–	–	–
Ether	−0.475	0.01	–	–	–	–	–	–
Ester	−0.355	0.34	–	–	–	–	–	–
Halide	0.178	0.39	0.370	0.01	0.335	0.00	–	–
N (amine)	−2.240	0.00	−1.738	0.00	–	–	–	–
N (amide)	−3.260	0.00	–	–	–	–	–	–
CO (amide)	1.302	0.05	–	–	–	–	–	–
O (to N)	−0.117	0.87	0.299	0.16	–	–	–	–
N (to O)	−0.264	0.83	−0.839	0.14	–	–	–	–
Non-aromatic ring	−0.643	0.00	−0.690	0.00	–	–	–	–
Steroid	−2.070	0.00	−1.621	0.01	–	–	–	–
Mol. Wt	−0.00766	0.28	–	–	–	–	−0.00628	0.00
Log K	–	–	–	–	–	–	0.696	0.00
OH	–	–	−0.513	0.00	–	–	–	–
'O'	–	–	−0.221	0.01	–	–	–	–
Amide	–	–	−0.361	0.00	–	–	–	–
[C]	–	–	–	–	0.187	0.00	–	–
[O]	–	–	–	–	−0.297	0.00	–	–
[N]	–	–	–	–	−0.639	0.00	–	–
c	–	–	–	–	0.275	0.00	–	–
Compounds	86		88		89		85	
r^2 (adjusted)	0.840		0.810		0.668		0.666	

Coefficients significantly different from zero ($p < 0.05$) underlined.

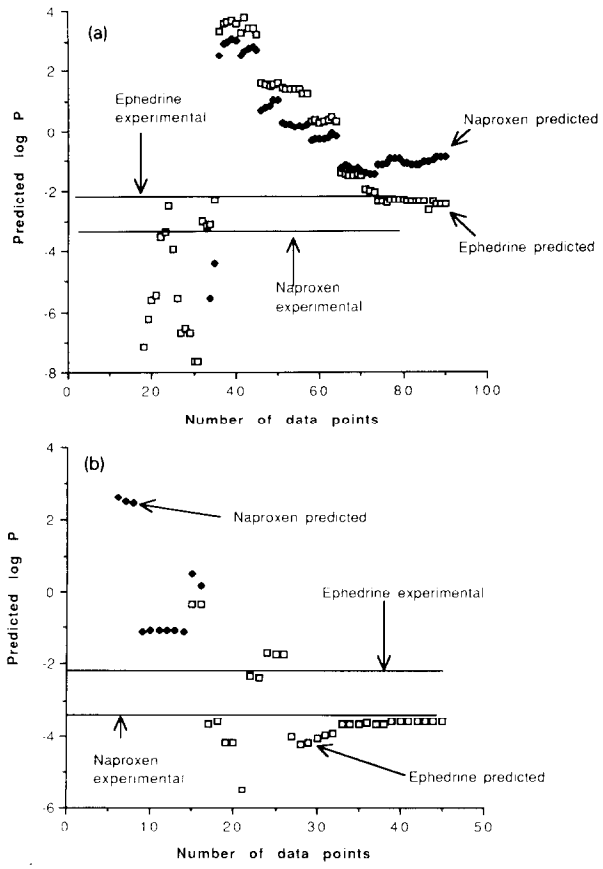

Fig. 4. (a) Dependence of predicted log P on number of data points; 17-predictor method. (b) Dependence of predicted log P on number of data points; best subset method.

essential, this does not, of course, imply that the predicted value will be correct.

Conclusion

The permeability coefficient of a compound can be predicted by assigning additive numerical values to its functional groups. This is simpler than the approach of Potts and Guy which requires a value for log K which must be found experimentally or itself estimated by a similar group addition method. Neither method is able to predict compounds which are absorbed by a process involving complications such as protein binding or self-enhancement which are not simply and directly related to the presence of amenable molecular features. For this reason it is probably best to accept that 'atypical' compounds cannot be predicted accurately and use the coefficients in Table 9 which are based on the data set from which atypical compounds have been excluded as predictors. We recommend that both the 11-predictor and SMILES method should be used to check that the predictions agree, and this should be supplemented by the Potts-Guy method whenever log K values are known with some confidence. The method has an obvious use in the approximate prediction of permeability in the absence of experimental values. It also highlights compounds which have unusual absorption mechanisms, where significant differences can be seen between the predicted and experimental values, and thus should be useful in targetting research into the processes underlying the transdermal penetration of drugs.

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