Review

Free Wilson Analysis. Theory, Applications and its Relationship to Hansch Analysis

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Dedicated to Prof. Dr. Corwin Hansch on the occasion of his 70th birthday

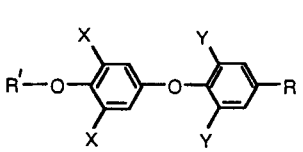
Abstract

The Free Wilson model is a simple and efficient method for the quantitative description of structure activity relationships. It is the only numerical method which directly relates structural features with biological properties, in contrast to Hansch analysis, where physicochemical properties are correlated with biological activity values. Nevertheless both approaches are closely interrelated, not only from a theoretical point of view, but also in their practical applicability. In many cases both models can be combined to a mixed approach which includes Free Wilson type parameters to describe the activity contributions of certain structural modifications and physicochemical parameters to describe the effect of some other substituents on the biological activity. Many successful applications, especially from the work of Hansch and his group on the structure activity relationships of enzyme inhibitors, demonstrate that this combined model is the most powerful tool of classical QSAR.

Key words: Bocek Kopecky model, Free Wilson analysis, Fujita Ban analysis, Hansch analysis, mixed approach, relationship of Free Wilson and Hansch analysis.

1 History

In 1956 Bruice, Kharasch and Winzler [1] investigated the thyromimetic activities of a series of thyroxine analogues (*1*). In an attempt to rationalize the structure activity relationships they formulated Equation (1), where f are empirical substituent constants of the groups X, Y and OR′, derived from biological activity values in a similar manner as Hammett σ constants.



(1)

$$\log \%\ \text{thyroxine-like activity} = k \cdot \sum f + c \qquad (1)$$

$$\sum f = f_X + f_Y + f_{OR'}$$

A close relationship was found between the observed activity values and those calculated from the f values. In addition, Bruice and his coworkers were able to interpret their group contributions f in physicochemical terms: electron attracting groups X, Y and OR′ decreased the biological activity, while the ability of X and Y to form hydrogen bonds increased biological activity.

A similar approach was followed by Fried and Borman to explain the biological potencies of mineralo- and glucocorticoidal steroids [2].

Zahradnik [3–6] tried to apply the concept of the Hammett equation (Equation (2), [7]) directly to biological activity values. He formulated Equation (3), where τ_i is the

$$\log k_{R-X} - \log k_{R-H} = \varrho\sigma_X \qquad (2)$$

$$\log \tau_i - \log \tau_{Et} = \alpha\beta \qquad (3)$$

biological activity value of the i^{th} member of a series, τ_{Et} is the corresponding value of the ethyl compound of the same series, β is a substituent constant (corresponding to σ) and α is a constant characterizing the biological system (corresponding to ϱ). In analogy to the Hammett equation α is supposed to depend only on the system, while the β values are supposed to be independent of the biological system.

Equation (3) is only applicable to unspecific structure activity relationships, most often within homologous series. For more specific structure activity relationships other mathematical models must be used, like Hansch analysis or Free Wilson analysis, which were both published in 1964.

In the extrathermodynamic approach (most often called Hansch analysis to honour the merits of Corwin Hansch in the development of this approach) [8–10] physicochemical properties are correlated with biological activity values, e.g. by Equations (4) or (5) (C is a molar dose, producing a definite biological effect; P, π and σ are physicochemical parameters).

$$\log 1/C = a(\log P)^2 + b\log P + c\sigma + d \qquad (4)$$

$$\log 1/C = a\pi^2 + b\pi + c\sigma + d. \qquad (5)$$

Free and Wilson followed a different strategy. From the observation that in congeneric series the activity contributions (of identical substituents in identical positions of the molecule) to biological activity values are more or less constant, they formulated an additive model [11], which can be presented by Equation (6). In Equation (6), BA are the biological activity values (on a linear scale) and a_i are the

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activity contributions of the substituents X_i which refer to the overall mean of biological activity values, μ.

$$BA = \sum a_i + \mu. \quad (6)$$

In a later version of this model, published by Fujita and Ban [12], μ is not defined as the overall average of biological activity values, but as the calculated biological activity value of the unsubstituted reference compound of the series. This definition resembles more closely the Hammett equation, because the activity contributions a_i now refer to hydrogen in the same position of substitution.

2 Theory and Applications of Free Wilson Analysis

2.1 The Classical Free Wilson Model

Due to the limitations caused by the additivity concept, Free Wilson analysis has some shortcomings, especially in its original version. First, all compounds of a series should have the same parent skeleton; otherwise the differences in the skeleton must be considered by an extra parameter. Secondly, at least two positions in the molecule must be varied in order to be able to include more data points than variables. Thirdly, the substituents in the different positions of the molecule should have no influence on the other positions, otherwise the additivity concept may not hold true.

On the other hand, Free Wilson analysis is a simple and effective tool in the very first stages of lead structure optimization. Every medicinal chemist, whether he is familiar with the concept of Free Wilson analysis or not, implicitly follows the general idea that within congeneric series of compounds, having an identical parent structure, all substituents make additive and constant contributions to the biological activity irrespective of all other structural changes in the molecule.

The minimum number of compounds needed for Free Wilson analysis is one for each parameter in the regression equation, i.e. one for the reference compound and one for each different substituent in each position. However, for a statistically meaningful analysis some more compounds are needed. On the other hand, estimations of biological activity values are only possible for new combinations of substituents already included in the analysis. The minimum number of analogs is given by Equation (7), while the maximum number is given by Equation (8) (j = Number of different positions, n_i = number of different substituents in each position.)

$$N_{min} = \sum_j (n_i - 1) + 1 \quad (7)$$

$$N_{max} = n_1 \cdot n_2 \cdot \ldots \cdot n_{j-1} \cdot n_j \quad (8)$$

The actual number of data points needed for a successful Free Wilson analysis will always be a compromise which depends on many different factors. A manual design for test series was proposed by Austel [13] and a quantitative procedure to extract an optimal set out of all possible analogues was developed by Cativiela *et al.* [14, 282].

In early applications of Free Wilson analysis there have been some discussions whether linear activity values (as used by Free and Wilson in their original paper) or logarithmic activity values should be used. Today only logarithmic values, most commonly log 1/C values as in Hansch analysis, are used because so many successful applications prove that the additivity concept applies in the logarithmic scale. In addition, the experimental errors of biological data are (at least as a first approximation) normally distributed in the logarithmic scale and not in the linear scale and last not least, only logarithmic activity values are linear free energy related parameters. As in all quantitative structure activity analyses, the biological activity values should be as accurate as possible. Their standard errors should be known in order to avoid overprediction (often occuring in Free Wilson analyses due to the use of too many variables).

Several reviews on the Free Wilson model have been published [15–22]. In addition, in many QSAR reviews the Free Wilson model is treated together with other approaches [23–40].

The calculation procedure for the classical Free Wilson model suffers from complexity, due to the definition of μ as the overall average of biological activity values. For every compound of the series the biological activity values BA_i (now used in the logarithmic scale) can be expressed as the sum of the biological activity contributions a_{jk} of the substituents R_k in each position j, referring to the overall average μ. In Equation (9), X_{jk} has a value of one when the

$$\log BA_i = \sum_j a_{jk} X_{jk} + \mu \quad (9)$$

substituent R_k is present in the position j, otherwise its value is zero. If the BA values are inverse molar doses, like 1/C, then activity enhancing substituents have positive a_{jk} values, while activity lowering substituents have negative values.

The calculation procedure of the classical Free Wilson model is explained by the data given in Table 1. The antiadrenergic activities of 22 meta- and para-substituted N,N-dimethyl-α-bromo-phenethylamines (*2*) were determined as ED_{50} values [41]. Including hydrogen, six different substituents were tested in each position. Thus n = 22 is a good compromise between the minimum number (n = 11, Equation (7)) and the maximum number (n = 36, Equation (8)) of analogues. The structural matrix given in Table 1 corresponds to a system of 22 equations with 12 unknowns and a constant term (i.e. μ, the overall average of biological activity values). However, this system of equations cannot be solved directly, because there are linear dependences caused by the fact that the sum of substituents (including hydrogen) is one for each position of substitution. Since μ is the mean value of all biological activity values (Equation(10)), the sum

$$\mu = 1/n \cdot \sum_i \log BA_i \quad (10)$$

of all group contributions must be zero. Thus Free and Wilson defined symmetry equations for each position of substitution based on the arbitrary assumption, that the sum of group contributions in each position of substitution be zero. (Equation (11)), leading to Equations (12) and (13) for the data of Table 1 (compare last row of Table 1).

$$\sum_i a_{jk} X_{jk} = 0 \quad \text{(for each value of j)} \quad (11)$$

meta-position: (12)

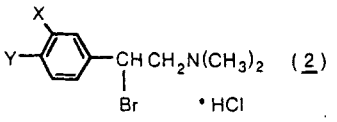
$$6 \cdot a_H + a_F + 4 \cdot a_{Cl} + 5 \cdot a_{Br} + a_I + 5 \cdot a_{Me} = 0$$

para-position (13)

$$6 \cdot a_H + 4 \cdot a_F + 4 \cdot a_{Cl} + 4 \cdot a_{Br} + a_I + 3 \cdot a_{Me} = 0$$

From such equations any one of the a_i values can be expressed as a function of the other a_i values, e.g. Equations (14) and (15).

Table 1. Antiadrenergic Activities of N,N-Dimethyl-α-bromophenethylamines (2) [41, 42]. Structures, Structural Matrix and Log1/C Values (C = ED_{50} in mol · kg^{-1})



(2)

No.	Structure X	Y	Meta-substituents X H	F	Cl	Br	I	Me	Para-substituents Y H	F	Cl	Br	I	Me	Log1/C values observed	calculated[a]	Residuals[a] $y_{obs} - y_{calc}$
1	H	F	1							1					8.16	8.161	−0.001
2	H	Cl	1								1				8.68	8.589	0.091
3	H	Br	1									1			8.89	8.841	0.049
4	H	I	1										1		9.25	9.250	0.000
5	H	Me	1											1	9.30	9.077	0.223
6	F	H		1					1						7.52	7.520	0.000
7	Cl	H			1				1						8.16	8.028	0.132
8	Br	H				1			1						8.30	8.255	0.045
9	I	H					1		1						8.40	8.400	0.000
10	Me	H						1	1						8.46	8.275	0.185
11	Cl	F			1					1					8.19	8.368	−0.178
12	Br	F				1				1					8.57	8.595	−0.025
13	Me	F						1		1					8.82	8.615	0.205
14	Cl	Cl			1						1				8.89	8.796	0.094
15	Br	Cl				1					1				8.92	9.023	−0.103
16	Me	Cl						1			1				8.96	9.043	−0.083
17	Cl	Br			1							1			9.00	9.048	−0.048
18	Br	Br				1						1			9.35	9.275	0.075
19	Me	Br						1				1			9.22	9.295	−0.075
20	Me	Me						1						1	9.30	9.531	−0.231
21	Br	Me				1								1	9.52	9.511	0.009
22	H	H	1						1						7.46	7.821	−0.361
Sums:			6	1	4	5	1	5	6	4	4	4	1	3			

[a] From Equations (16), (18) and (19); deviations of ±0.001 due to rounding errors.

meta-position

$$a_H = -1/6 \cdot a_F - 2/3 \cdot a_{Cl} - 5/6 \cdot a_{Br} - 1/6 \cdot a_I - 5/6 \cdot a_{Me} \quad (14)$$

para-position:

$$a_H = -2/3 \cdot a_F - 2/3 \cdot a_{Cl} - 2/3 \cdot a_{Br} - 1/6 \cdot a_I - 1/2 \cdot a_{Me} \quad (15)$$

Insertion of these equations into the structural matrix leads to an elimination of the two hydrogen columns and to a change of all rows for compounds bearing hydrogen in one or both positions [42]. The new matrix corresponds to a system of 22 equations with only 10 variables and a constant term, now readily solvable by linear multiple regression analysis [43–45]. From the resulting a_i values of F, Cl, Br, I and Me, the a_H values can be calculated for each position by Equations (14) and (15) and the overall result is presented by Equation (16) [42]. 95% Confidence intervals are given for each term; it should be noted that no confidence intervals are given for the [meta-H] and [para-H] terms because these terms were not included in the regression analysis.

Equation (16) is only one possible result. If two other substituents are removed from the original matrix, a different matrix for regression analysis but an identical equation result, now giving values of −0.252 (±0.16) for [meta-H] and −0.623 (±0.17) for [para-H].

$$\begin{aligned} \log 1/C = {} & -0.252[\text{meta-H}] \\ & -0.553(\pm 0.45)[\text{meta-F}] \\ & -0.045(\pm 0.20)[\text{meta-Cl}] \\ & +0.182(\pm 0.17)[\text{meta-Br}] \\ & +0.327(\pm 0.45)[\text{meta-I}] \\ & +0.202(\pm 0.17)[\text{meta-Me}] \\ & -0.623[\text{para-H}] \\ & -0.283(\pm 0.20)[\text{para-F}] \\ & +0.144(\pm 0.20)[\text{para-Cl}] \\ & +0.397(\pm 0.20)[\text{para-Br}] \\ & +0.806(\pm 0.45)[\text{para-I}] \\ & +0.633(\pm 0.24)[\text{para-Me}] \\ & +8.696(\pm 0.09) \end{aligned}$$

$$(n = 22;\ r = 0.969;\ s = 0.194;\ F = 16.99) \quad (16)$$

The theory of linear equations and the problem of linear dependences as applied to Free Wilson analysis have been discussed in the literature [42, 46, 47].

A comparison of observed log 1/C values with those calculated from Equation (16) (Table 1) demonstrates the good fit by the additive model. Values of activity contributions for substituents occuring only once in the matrix (meta-F, meta-I and para-I), called single point determinations, lead to calculated log 1/C values which are identical to the observed values. In such cases the values of the group contributions include the experimental error of a single compound.

The log 1/C values of compounds not included in the original analysis can be estimated from Equation (16). For the 3,4-diiodo-analogue Equation (16) predicts an even higher biological activity than for the most active compound included in the original set (log $1/C_{calc}$ = 8.696 + 0.327 + 0.806 ≈ 9.8).

The definition of the symmetry equations leads to several disadvantages. The calculation procedure is complex and each addition or elimination of a compound changes the symmetry equations and the value of μ. Consequently the values of all group contributions are changed more or less, making the comparison of different Free Wilson analyses in the same data set very difficult.

2.2 The Fujita Ban Model

In the modification of Free Wilson analysis proposed by Fujita and Ban in 1971 [12], symmetry equations are no longer needed. Fujita and Ban interpret μ as the theoretical biological activity value of the unsubstituted reference compound of a series and they relate all group contributions to hydrogen in the same position of substitution (Equation (17); b_{jk} = activity contributions relative to hydrogen, μ = calculated biological activity value of the unsubstituted compound).

$$\log BA_i = \sum_j b_{jk} X_{jk} + \mu \qquad (17)$$

A much simpler calculation procedure results from this version. Only the columns of the reference substituents need to be eliminated from the original matrix (by doing this the activity contributions of the reference substituents, i.e. meta-H and para-H in the case of Table 1, are forced to zero). Regression analysis of the resulting matrix directly leads to Equation (18) [42, 48].

$$\begin{aligned}\log 1/C = {} & -0.301(\pm 0.50)[\text{meta-F}] \\ & +0.207(\pm 0.29)[\text{meta-Cl}] \\ & +0.434(\pm 0.27)[\text{meta-Br}] \\ & +0.579(\pm 0.50)[\text{meta-I}] \\ & +0.454(\pm 0.27)[\text{meta-Me}] \\ & +0.340(\pm 0.30)[\text{para-F}] \\ & +0.768(\pm 0.30)[\text{para-Cl}] \\ & +1.020(\pm 0.30)[\text{para-Br}] \\ & +1.429(\pm 0.50)[\text{para-I}] \\ & +1.256(\pm 0.33)[\text{para-Me}] \\ & +7.821(\pm 0.27)\end{aligned}$$

$$(n = 22;\ r = 0.969;\ s = 0.194;\ F = 16.99) \qquad (18)$$

The constant term μ = 7.821 is the calculated biological activity value of compound 22, the unsubstituted compound. Of course the statistical parameters r, s and F are identical with those of Equation (16) and all calculated log 1/C values are identical from both equations.

Although it is convenient to use the unsubstituted analogue, any other compound may be taken as reference compound, even with a substituent combination not included in the original data set, e.g. a 3-F,4-I-analogue. In doing so, the activity contributions of these substituents are forced to zero, the corresponding columns are removed from the structural matrix and Equation (19) results [42].

$$\begin{aligned}\log 1/C = {} & 0.301(\pm 0.50)[\text{meta-H}] \\ & +0.508(\pm 0.51)[\text{meta-Cl}] \\ & +0.735(\pm 0.50)[\text{meta-Br}] \\ & +0.880(\pm 0.60)[\text{meta-I}] \\ & +0.755(\pm 0.50)[\text{meta-Me}] \\ & -1.429(\pm 0.50)[\text{para-H}] \\ & -1.089(\pm 0.50)[\text{para-F}] \\ & -0.661(\pm 0.50)[\text{para-Cl}] \\ & -0.409(\pm 0.50)[\text{para-Br}] \\ & -0.173(\pm 0.52)[\text{para-Me}] \\ & +8.949(\pm 0.66)\end{aligned}$$

$$(n = 22;\ r = 0.969;\ s = 0.194;\ F = 16.99) \qquad (19)$$

Again r, s and F and all calculated log 1/C values are identical with those from Equations (16) and (18). Now the constant term μ = 8.949 is the calculated biological activity value of the 3-F,4-I-analogue and all activity contributions refer to this pattern of substitution. The activity contributions and μ values from Fujita Ban analyses and Free Wilson analyses are interrelated by Equations (20) and (21) (a_{jZ} = activity contribution of the reference substituent R_Z in position j) (Table 2) [42].

$$b_{jk} = a_{jk} - a_{jZ} \qquad (20)$$

$$\mu_{FB} = \mu_{FW} + \sum_j a_{jZ} \qquad (21)$$

Thus the relationships between different Fujita Ban analyses and classical Free Wilson analysis are as simple as the relationship between the temperature scales of Celsius and Kelvin. Only the choice of the reference point determines the magnitude of all values.

A slightly different modification of Free Wilson analysis was formulated by Cammarata, where μ in Equation (17) is defined as the observed biological activity value of the unsubstituted compound (instead of the theoretical value) [49, 50]. However, this procedure is inadequate from a statistical point of view [20, 42, 47, 48] and should not be used.

2.3 Problems in Free Wilson and Fujita Ban Analyses

2.3.1 Biological Activity Values

Only logarithmic values of molar doses producing a certain effect, logarithms of rate constants and logarithms of binding or inhibition constants should be used as activity parameters in quantitative structure activity analyses. Linear values or % values of effect produced by a fixed dose sometimes lead to significant relationships; however, such results are only a reflection of the close interrelationship between such values and the same values in one of the above mentioned scales. Early comparisons of linear vs. logarithmic values [51, 52] came to wrong conclusions, because standard deviations were compared in different scales. The use of linear and logarithmic biological activity values in Free Wilson analyses has been reviewed [18].

2.3.2 Single Point Determinations

Single point determinations do not cause problems, when there are not too many of them included in the analysis. In each case they give a first measure of the effect of a certain substituent on the biological activity, without any statistical

Table 2. Antiadrenergic Activities of N,N-Dimethyl-α-bromophenethylamines (Table 1). Comparison of Activity Contributions from Different Free Wilson Analyses [42]

Substituent	Classical Free Wilson model	Fujita Ban modification			
		Equation (18)		Equation (19)	
	a_{jk}	b_{jk}	$b_{jk} - a_{jk}$	b_{jk}	$b_{jk} - a_{jk}$
Meta-H	−0.252	0[a]	0.252	0.301	0.553
Meta-F	−0.553	−0.301	0.252	0[a]	0.553
Meta-Cl	−0.045	0.207	0.252	0.508	0.553
Meta-Br	0.182	0.434	0.252	0.735	0.553
Meta-I	0.327	0.579	0.252	0.880	0.553
Meta-Me	0.202	0.454	0.252	0.755	0.553
Para-H	−0.623	0[a]	0.623	−1.429	−0.806
Para-F	−0.283	0.340	0.623	−1.089	−0.806
Para-Cl	0.144	0.768	0.624[b]	−0.661	−0.805[b]
Para-Br	0.397	1.020	0.623	−0.409	−0.806
Para-I	0.806	1.429	0.623	0[a]	−0.806
Para-Me	0.633	1.256	0.623	−0.173	−0.806
μ	8.696 ·	7.821	0.875[c]	8.949	−0.253[d]

[a] By definition.
[b] Deviations due to rounding errors.
[c] $\mu_{FW} - \mu_{FB} = 8.696 - 7.821 = 0.252 + 0.623 = 0.875$.
[d] $\mu_{FW} - \mu_{FB} = 8.696 - 8.949 = 0.553 - 0.806 = -0.253$.

significance. If single point determinations are removed from a Fujita Ban analysis (e.g. compounds 4, 6 and 9 from Equation (18)), the other regression coefficients do not change their values and the standard deviation s does not change its value (because the number of degrees of freedom remains constant). The correlation coefficient r decreases more or less, while the F value either decreases due to the worse fit, or it increases due to the fact that F values are much more influenced by the number of variables than by the quality of fit (which applies to this example).

Analyses with only few degrees of freedom may be suited to sort substituents according to their effects on biological activity. Their statistical parameters are, however, without any significance. Many published Free Wilson analyses suffer from such problems (e.g. [50, 53]).

2.3.3 Complex Linear Dependences

Complex linear dependences, often called singularities, arise when substituents in different positions only occur together [16, 17, 42, 46]. Early problems, where data sets were called "ill-conditioned" because no unique solution could be obtained from different Free Wilson analyses [54], were later recognized to be caused by such linear dependences [16].

While there is no easy way to eliminate such linear dependences in the classical model, in the Fujita Ban model those substituents can be combined to a new pseudosubstituent [42]. Its activity contribution is a measure for the combined effect of all substituents which are included in the pseudosubstituent. Linear dependences are often hidden. They cause computational errors (division by zero during the matrix inversion) but they can be detected by looking at the matrix determinant [46]. If the matrix determinant is zero or close to zero, no unique solution can be obtained. The value of the matrix determinant does not depend on the choice of reference substituents nor does it depend on the inclusion or deletion of compounds leading to single point determinations [55].

In cases, where different positions in a molecule are assumed to be equivalent, the number of identical substituents in the equivalent positions can be used as a parameter in Free Wilson and Fujita Ban analyses [46, 48, 56, 57]. In homologous series even the number of CH_2 groups may be used as a Free Wilson type parameter, as long as the additivity concept applies.

Optically active compounds can be treated in two different ways. First, both configurations (leading to R- and S-enantiomers) can be treated separately and values of 0.5 are given to each position for racemates or diastereomeric mixtures [51]. On the other hand, additional Free Wilson type parameters can be used to indicate whether a compound is a (+)-entantiomer or a (−)-enantiomer [58]. This second approach looks less reliable because the well-known variability of the activity differences between enantiomers (Pfeiffer's rule) [59] is not taken into account by this method.

2.3.4 Regression Analysis and Statistical Parameters

Calculation procedures have been described step by step for classical Free Wilson analysis [16, 17, 19, 20, 22] as well as for Fujita Ban analysis [60]. Although computer programs for both models [17, 61, 62], a simplified algorithm for Fujita Ban analysis [60] and a calculation procedure for an approximative solution to the Free Wilson model [20, 63, 64] are described in the literature, any standard program of linear multiple regression analysis can be used.

As proposed for the extrathermodynamic approach [65], the statistical parameters presented with the results should include r, s and F values and the 95% confidence intervals of the regression coefficients (not standard errors which are lower by a factor of 2–3).

In contrast to Hansch analysis, where only few variables are needed to describe a data set, the correlation coefficient r is of limited value in most Free Wilson analyses, due to the large number of variables usually included. A much better measure for the quality of fit are the standard deviation s and the F value.

No partial F test (usually called sequential F test) should be applied to Free Wilson analyses, because the significance of individual parameters has not the same meaning as in the Hansch model [66]. Even the information that the activity contribution of a certain substituent is not significantly different from that of the reference substituent, is a useful information. In each case the significance depends on the choice of the reference substituents.

While in classical Free Wilson analysis the values of the confidence intervals do not depend on the choice of the symmetry equations, different results are obtained from different Fujita Ban analyses (compare Equations (18) and (19)) [42]. Thus no firm conclusions can be drawn from such confidence intervals, with the only exception that the selection of well represented reference substituents leads to much smaller confidence intervals than the choice of less well represented substituents (no confidence intervals are assigned to the reference substituents because their values are forced to zero).

2.4 Applications of Free Wilson Analysis

The Free Wilson model has never become as popular as Hansch analysis because of its limitations: it applies only as long as the additivity concept holds true and secondly, predictions of biological activity values can be made only for new substituent combinations. However, there are numerous applications in medicinal chemistry, most of them listed in Table 3.

Table 3. Applications of Free Wilson Analysis in Medicinal Chemistry. In Vitro and In Vivo Models.

Biological activity and references
Acetylcholinesterase inhibition [67–69]
Adrenergic α-receptor binding [70]
Albumin binding [71]
Anabolic activity [72]
Analgesic activity [11, 29, 58, 73–75]
Androgenic activity [72]
Anthelmintic activity [76]
Antiadrenergic activity [42, 48, 49, 60, 63, 77–81]
Antiallergic activity [82, 83]
Antibacterial activity [11, 15, 17, 21, 22, 28, 50, 57, 60, 63, 84–91]
Anticholinergic activity [92]
Anticonvulsant activity [93, 94]
Antifungal activity [46, 48, 57, 95]
Antihypertensive activity [96, 97]
Antiinflammatory activity [56, 98–101]
Antilipemic activity [102]
Antimalarial activity [27, 54, 103, 104]
Antimicrobial activity [105–107]
Antimitotic activity [108, 109]
Antimycoplasmal activity [110]
Antitumor activity [52, 111–117]
Antiulcer activity [118]
Antiviral activity [119–122]
ATPase inhibition [123]
Benzodiazepine receptor binding [124–126]
Bradykinin potentiation [127]
Butyrylcholinesterase inhibition [48, 67, 128–131]
Carboxylesterase inhibition [67]
Dihydrofolate reductase inhibition [132, 133]
Diuretic activity [134, 135]
Dopamine β-hydroxylase substrate properties [12, 79]
Dopamine receptor binding [70, 136]
Estrogenic activity [137]
Glucocorticoid activity [2, 138]
Hallucinogenic activity [53]
Hypnotic activity [48]
Hypoglycemic activity [17, 23, 139]
Inhibition of brain oxidative metabolism [73]
Inhibition of oxytocin contraction [140–143]
Learning and behaviour [144, 145]
Local anesthetic activity [146]
Microsomal oxidation [147]
Mineralocorticoid activity [2]
Mitochondrial uncoupling activity [148, 149]
Monoamine oxidase inhibition [150–152]
Muscarine receptor binding [70]
Muscle relaxant activity [93]
Neuroleptic activity [70]
Norepinephrine uptake inhibition [51, 78, 79, 153]
Opiate receptor binding [154, 155]
Ovicidal activity [156]
Pharmacokinetic properties [157–160]
Phenylethanolamine-N-methyltransferase inhibition [79]
Phenylethanolamine-N-methyltransferase substrate properties [12, 78, 79]
Plasmin inhibition [161]
Progestational activity [162]
Prostaglandin synthetase inhibition [163]
Psychostimulant activity [164]
Radioprotective activity [67, 165–168]
Renin inhibition [169]
Ribosomal erythromycin binding [170]
Saluretic activity [135]
Sedative activity [93]
Serotonin receptor binding [70]
Serotonin uptake inhibition [171]
Spasmolytic activity [37, 38, 172–174]
Thrombin inhibition [161]
Thyromimetic activity [1, 48]
Toxicity [11, 29, 67, 100, 102, 156, 166, 175–187]
Tranquilizing activity [180, 188]
Trypsin inhibition [161]
Tuberculostatic activity [189]
Vermicidal activity [156]

In agrochemistry the Free Wilson model has been used for the quantitative description of antifungal activity [190–192], herbicidal activity [193–195], Hill reaction inhibition [21, 196], inhibition of cell division [108, 197], insecticidal activity [198–200] and plant growth stimulation [105, 106, 201].

In physical chemistry Free Wilson type approaches have been used since long time to derive Hammett σ constants from rate and equilibrium constants [7], to derive π values [10, 202, 203] and hydrophobic fragmental constants [203–206] from partition coefficients and for some other additive molecular properties. In addition, the Free Wilson model has been used to analyze the cyclodextrin complexation of compounds [207], electronic absorption spectra [208], the fastness properties of dyes [209–212], fluorescence intensity [213], molecule geometry [214], NMR spectral data [215], partition coefficients [216], partitioning of ion pairs [217], permeability through synthetic membranes [218] and R_m values [157].

3 The Relationship between Free Wilson and Hansch Analyses

3.1 The Equivalence of the Activity Contributions

Although the Free Wilson model and linear Hansch analysis look quite different, they are fundamentally related. Both approaches start from the additivity concept of group contributions to biological activity. While Free and Wilson were only interested to attribute incremental values to all different groups and substituents, the Hansch model interprets such activity contributions in physicochemical terms.

If all physicochemical parameters Φ_j in a linear Hansch equation (Equation (22)) are additive constitutive properties, like π, MR, σ or E_s, and as long as there are only linear terms in Equation (22), Free Wilson type activity contributions for each substituent can be calculated from a Hansch equation by Equation (23) [48].

$$\log 1/C = k_1\Phi_1 + k_2\Phi_2 + \ldots + k_n\Phi_n + c = \sum k_j\Phi_j + c \quad (22)$$

$$a_i = \sum_j k_j\Phi_{ij}. \quad (23)$$

The close theoretical relationship between Hansch analysis and Free Wilson analysis was first recognized and theoretically proven by Singer and Purcell [219] who also stated that this relationship does not apply to parabolic Hansch equations. Although this statement has been questioned by Cammarata [49, 177], it was confirmed theoretically and by practical examples in later investigations [48, 220].

For the data of Table 1 several Hansch equations were derived [48, 49, 66, 221], e.g. Equations (24)–(26).

$$\log 1/C = 1.15(\pm 0.19)\pi - 1.47(\pm 0.38)\sigma^+ + 7.82 \quad (24)$$
$$(n = 22;\quad r = 0.944;\quad s = 0.197)$$

$$\log 1/C = 0.83(\pm 0.27)\pi_{meta} + 1.33(\pm 0.20)\pi_{para} - 0.92(\pm 0.50)\sigma^+_{meta} - 1.89(\pm 0.57)\sigma^+_{para} + 7.80 \quad (25)$$
$$(n = 22;\quad r = 0.966;\quad s = 0.164)$$

$$\log 1/C = 1.26(\pm 0.19)\pi - 1.46(\pm 0.34)\sigma^+ + 0.21(\pm 0.17)E_s^{meta} + 7.62 \quad (26)$$
$$(n = 22;\quad r = 0.959;\quad s = 0.173)$$

Free Wilson type activity contributions can be derived from each equation by using the corresponding π, σ and E_s values (after eliminating the constant term). The close numerical equivalence of Free Wilson group contributions and those derived from the different Hansch equations can be seen at a glance (Table 4). The only prerequisite for such a comparison is the use of the Fujita Ban model instead of the classical model (in order to normalize all group contributions to $a_H = 0$) and to normalize all physicochemical parameters Φ_j to $\Phi_H = 0$ [48].

In data sets suited for Free Wilson analysis the upper limit of correlation that can be achieved by a linear Hansch analysis is given by the correlation coefficient of the Free Wilson analysis [48]. If this correlation coefficient is high, there may be a good chance to derive a linear Hansch equation. If it is low, nonlinear models should be tested.

Hansch equations have been derived from Free Wilson group contributions (e.g. [12, 50, 57, 103]). This approach as well as the direct comparison of Free Wilson group contributions with those derived from Hansch equations can be used to improve the fit of Hansch equations by a better selection of the physicochemical parameters [48].

3.2 Indicator Variables and the Mixed Approach

Indicator variables are used in Hansch equations to account for the effects of certain structural features on the

Table 4. Antiadrenergic Activities of N,N-Dimethyl-α-bromo-phenethylamines (Table 1). Physicochemical Parameters, Activity Contributions from Fujita Ban Analysis (Table 2, Equation (18)) and Hansch Analysis (Equations (24)–(26)) and Statistical Parameters [48].

Substituent	Physicochemical parameters π	σ^+	E_s^{meta}	Activity contributions a_i, calculated from Fujita Ban analysis	Hansch analysis Equation (24)	Equation (25)	Equation (26)
Meta-H	0	0	1.24	0	0	0	0
Meta-F	0.13	0.35	0.78	−0.30	−0.37	−0.21	−0.44
Meta-Cl	0.76	0.40	0.27	0.21	0.29	0.26	0.17
Meta-Br	0.94	0.41	0.08	0.43	0.48	0.40	0.34
Meta-I	1.15	0.36	−0.16	0.58	0.79	0.62	0.63
Meta-CH_3	0.51	−0.07	0	0.45	0.69	0.49	0.48
Para-H	0	0	–	0	0	0	0
Para-F	0.15	−0.07	–	0.34	0.28	0.33	0.29
Para-Cl	0.70	0.11	–	0.77	0.64	0.72	0.72
Para-Br	1.02	0.15	–	1.02	0.95	1.07	1.07
Para-I	1.26	0.14	–	1.43	1.24	1.41	1.38
Para-CH_3	0.52	−0.31	–	1.26	1.05	1.28	1.11
	μ/c			7.82	7.82	7.80	7.88[a]
	Number of cpds.		n	22	22	22	22
	Correlation coeff.		r	0.969	0.944	0.966	0.959
	Standard deviation		s	0.194	0.197	0.164	0.173

[a] Calculated from $\mu = c + 0.21\ E_s^{meta\text{-}H}$.

biological activity that cannot be explained in terms of physicochemical parameters [222–224]. Such indicator variables are frequently used in regression analyses [44, 45] and their use in quantitative structure activity relationships has been rationalized by Hansch as "the extrathermodynamic approach assisted by the Free Wilson method" [224]. Consequently both models, Free Wilson analysis (in the form of the Fujita Ban model) and Hansch analysis have been combined to a mixed approach (Equation (27)) [57],

$$\log 1/C = \sum a_i + \sum k_j \Phi_j + c \qquad (27)$$

where Φ_j are physicochemical parameters of substituents for which an extrathermodynamic relationship can be derived, while a_i are Free Wilson type parameters (indicator variables or dummy variables) for certain structural features (usually at other positions in the molecule) that cannot be parameterized in physicochemical terms.

From the extensive work of Hansch and his group on the structure activity relationships of enzyme inhibitors many successful applications of this combined approach resulted. Today the use of indicator variables in Hansch analyses is the most powerful tool of classical QSAR.

Typical uses of Free Wilson type indicator variables in Hansch equations are reviewed in Table 5 (including nonlinear equations, compare chapter 3.3).

Table 5. The Use of Indicator Variables in Hansch Analyses

Biological Activity and References
Adenosine receptor binding [225]
Antiadrenergic activity [81]
Antiallergic activity [82, 226]
Antibacterial activity [223]
Antifungal activity [227]
Antiinflammatory activity [98]
Antimalarial activity [228]
Antitumor activity [229–234]
Carbonic anhydrase inhibition [235, 236]
Cholinesterase inhibition [222]
Chymotrypsin inhibiton [237–241]
Complement inhibition [224, 242, 243]
Dihydrofolate reductase inhibition [236, 237, 243–248]
Guanine deaminase inhibition [243, 249]
Inhibition of various enzymes [243]
Papain ligand interactions [250]
Thyromimetic activity [48, 57, 251]
Toxicity [29]
Trypsin inhibition [252]

3.3 Nonlinear Models

At approximately the same time as Free and Wilson formulated their model, Bocek and Kopecky [175, 176] tested an additive model, a multiplicative model and a combined model to describe the toxicity of disubstituted benzenes. They found that Equation (28), where b and e are empirical terms like in Free Wilson analysis, was the best model to fit the data.

$$\log[LD_{50}]_{HH} - \log[LD_{50}]_{XY} = b_X + b_Y + e_X \cdot e_Y. \qquad (28)$$

In their comparison of Hansch and Free Wilson analysis Singer and Purcell [219] stated that the Bocek Kopecky model corresponds to nonlinear Hansch analysis, which is true indeed [48]. However, the application of Equation (28) is inhibited by the usually much too large number of parameters. While certain interaction terms play a role in some Free Wilson analyses (e.g. [12]), only a few Bocek Kopecky type equations have been published [48, 118, 132, 165, 175, 176, 178].

Due to the relationship between Hansch and Free Wilson analysis the mixed approach (Equation (27), chapter 3.2) can be extended to a nonlinear model [57, 253], where either the parabolic Hansch model [8–10, 254] or the bilinear model [255–258] are combined with Free Wilson type parameters or with other indicator variables (Equations (29) and (30); $\Phi = \pi$, MR or other additive property).

$$\log 1/C = k\Phi^2 + \sum k_j \Phi_j + \sum a_i + c \qquad (29)$$

$$\log 1/C = -b \cdot \log(\beta \cdot 10^{\Phi} + 1) + \sum k_j \Phi_j + \sum a_i + c \qquad (30)$$

Examples for the successful application of this approach are listed together with the applications of linear models in Table 5 (chapter 3.2). It should be noted that Equations (27), (29) and (30) are nothing else than a mathematical notation for the use of different types of indicator variables in Hansch analyses.

4 Models Related to Free Wilson Analysis

There is a wide range of models which are more or less related to Free Wilson analysis. For a series of dihydrofolate reductase inhibitors Hansch et al. [132] tested indicator variables and interaction terms without strictly following the rules of Free Wilson analysis. In other cases insignificant variables have been removed from Free Wilson analyses by stepwise regression procedures [e.g. 29, 145, 187, 259]. The name "reduced Free Wilson model" is used by Mager [29, 187] to characterize this approach. It may be seen as a transition from normal Free Wilson analysis, where the number of variables is predetermined by the structure, to the pattern recognition approach [31, 75, 260–264], where a large number of parameters, encoding different structural features, is tested for their ability to separate groups with different (biological) properties.

In medicinal chemistry the reduced Free Wilson model and related approaches have been used for the quantitative description of antiadrenergic activity [77], antibacterial activity [57, 60, 86], anticonvulsant activity [259], antifungal activity [259], antiinflammatory activity [259], benzodiazepine receptor binding [124], learning and behaviour [145] and toxicity [29, 185–187].

Some other approaches are based on Free Wilson analysis and on the concept of a hyperstructure. In the DARC-PELCO approach [265–269] the hyperstructure is made up from the parent skeleton and from all fragments of linear and branched substituents at this frame, ordered in concentric spheres. The greatest disadvantage of the DARC-PELCO approach comes from the large number of variables needed [22]. The results of DARC-PELCO analyses have been compared with results from Hansch and Free Wilson analyses; no real advantages of the DARC-PELCO method can be seen [55, 84, 85, 270, 271].

Other approaches based on a more or less hypothetical hyperstructure and on a strategy related to Free Wilson analysis are the minimal steric difference (MSD) [272] and the minimal topological difference (MTD) approach

[272–274], the SIBIS (steric maps) method [275, 276] and the topological pharmacophore methods [20, 277–281], LOGANA [278, 279, 281] and LOCON [278, 280, 281].

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References

[1] Bruice, T. C., Kharasch, N. and Winzler, R. J., *Arch. Biochem. Biophys. 62,* 305–317 (1956).
[2] Fried, J. and Borman, A., *Vitamines and Hormones.* Advances in Research and Applications, Volume 16, Edited by R. S. Harris, G. F. Marrian and K. V. Thimann, Academic Press, New York 1958, N.Y., pp. 303–374.
[3] Zahradnik, R. and Chvapil, M., *Experientia 16,* 511–512 (1960).
[4] Zahradnik, R., *Experientia 18,* 534–536 (1962).
[5] Zahradnik, R., *Arch. Int. Pharmacodyn. Ther. 135,* 311–329 (1962).
[6] Chvapil, M., Zahradnik, R. and Cmuchalova, B., *Arch. Int. Pharmacodyn. Ther. 135,* 330–343 (1962).
[7] Chapman, N. B. and Shorter, J., *Advances in Linear Free Energy Relationships.* Plenum Press, London 1972, England.
[8] Hansch, C. and Fujita, T., *J. Amer. Chem. Soc. 86,* 1616–1626 (1964).
[9] Hansch, C., *Acc. Chem. Res. 8,* 232–239 (1969).
[10] Hansch, C., *Drug Design,* Volume 1, Edited by E. J. Ariens, Academic Press, New York 1971, N.Y., pp. 271–342.
[11] Free, S. M. Jr. and Wilson, J. W., *J. Med. Chem. 7,* 395–399 (1964).
[12] Fujita, T. and Ban, T., *J. Med. Chem. 14,* 148–152 (1971).
[13] Austel, V., *QSAR and Strategies in the Design of Bioactive Compounds,* Edited by J. K. Seydel, VCH Weinheim 1985, Fed. Rep. Ger., pp. 247–250.
[14] Cativiela, C., Elguero, J., Mathieu, D., Melendez, E. and Phan Tan Luu, R., *Eur. J. Med. Chem. – Chim. Ther. 18,* 359–363 (1983).
[15] Martin, Y. C., *Quantitative Drug Design. A Critical Introduction,* Marcel Dekker, New York 1978, N.Y.
[16] Craig, P. N., *Biological Correlations – The Hansch Approach,* Edited by R. F. Gould, Advan. Chem. Ser. 114, 115–129 (1972).
[17] Purcell, W. P., Bass, G. E. and Clayton, J. M., *Strategy of Drug Design: A Guide to Biological Activity,* Wiley, New York 1973, N.Y.
[18] Gaebler, E., Franke, R. and Oehme, P., *Pharmazie 31,* 1–14 (1976).
[19] Franke, R., *Optimierungsmethoden in der Wirkstoff-Forschung.* Quantitative Struktur-Wirkungs-Analyse, Akademie-Verlag, Berlin 1980, Germ. Dem. Rep.
[20] Franke, R., *Theoretical Drug Design Methods,* Elsevier, Amsterdam 1984, The Netherlands.
[21] Grieco, C., Silipo, C. and Vittoria, A., *Farmaco, Ed. Sci. 31,* 607–626 (1976).
[22] Seydel, J. K. and Schaper, K. J., *Chemische Struktur und biologische Aktivität von Wirkstoffen. Methoden der Quantitativen Struktur-Wirkung-Analyse,* Verlag Chemie, Weinheim 1979, Fed. Rep. Ger.
[23] Cammarata, A. and Rogers, K. S., *Advances in Linear Free Energy Relationships,* Edited by N. B. Chapman and J. Shorter, Plenum Press, London 1972, England, pp. 401–444.
[24] Chu, K. C., *Burger's Medicinal Chemistry,* Volume 1, Edited by M. E. Wolff, Wiley, New York 1980, N.Y., pp. 393–418.
[25] Craig, P. N., *Chem. Inf. Syst.,* Edited by J. E. Ash and E. Hyde, Ellis Horwood Ltd., Chichester 1975, England, pp. 259–268.
[26] Glasser, A. C., *Meth. Find. Exptl. Clin. Pharmacol. 6,* 563–569 (1984).
[27] Hansch, C., *Drug Development Research 1,* 267–309 (1981).
[28] Lewi, P. J., *Drug Design,* Volume 7, Edited by E. J. Ariens, Academic Press, New York 1976, N.Y., pp. 209–278.
[29] Mager, P. P., *Med. Res. Rev. 3,* 435–498 (1983).
[30] Osman, R., Weinstein, H. and Green, J. P., *Computer-Assisted Drug Design,* Edited by E. C. Olsen and R. C. Christoffersen, ACS Symposium Series 112, Washington 1979, D.C., pp. 21–77.
[31] Stuper, A. J., Brugger, W. E. and Jurs, P. C., *Computer Assisted Studies of Chemical Structure and Biological Function,* Wiley, New York 1979, N.Y.
[32] Bruns, H., *Chem.-Ztg. 96,* 417–423 (1972).
[33] Esaki, T., *Kagaku To Yakugaku No Kyoshitsu 48,* 55–62 (1975); ref. C.A. 84, 98956y.
[34] Franke, R. and Oehme, P., *Pharmazie 28,* 489–508 (1973).
[35] Mager, H., *Sci. Pharm. 45,* 71–75 (1977).
[36] Sabljic, A. and Trinajstic, N., *Kem. Ind. 28,* 467–477 (1979); ref. C.A. 92, 103849n.
[37] Schultz, O. E., *Pharm. Ztg. 120,* 1449–1455 (1975).
[38] Schultz, O. E., *Pharm. Ztg. 121,* 73–79 (1976).
[39] Schwartz, I., *Stud. Cercet. Chim. 21,* 721–746 (1973); ref. C.A. 79, 73404a.
[40] Zhang, Z. and Wang, S., *Yiyao Gongye 1983,* 30–37; ref. C.A. 100, 114331x.
[41] Graham, J. D. P. and Karrar, M. A., *J. Med. Chem. 6,* 103–107 (1963).
[42] Kubinyi, H. and Kehrhahn, O.-H., *J. Med. Chem. 19,* 1040–1049 (1976).
[43] Snedecor, G. W. and Cochran, W. G., *Statistical Methods,* The Iowa State University Press, Ames 1973, Iowa.
[44] Daniel, C. and Wood, F. S., *Fitting Equations to Data,* John Wiley & Sons, New York 1980, N.Y.
[45] Draper, N. R. and Smith, H., *Applied Regression Analysis,* John Wiley & Sons, New York 1981, N.Y.
[46] Schaad, L. J., Werner, R. H., Dillon, L., Field, L. and Tate, C. E., *J. Med. Chem. 18,* 344–351 (1975).
[47] Schaad, L. J. and Hess, B. A. Jr., *J. Med. Chem. 20,* 619–625 (1977).
[48] Kubinyi, H. and Kehrhahn, O.-H., *J. Med. Chem. 19,* 578–586 (1976).
[49] Cammarata, A., *J. Med. Chem. 15,* 573–577 (1972).
[50] Cammarata, A. and Yau, S. J., *J. Med. Chem. 13,* 93–97 (1970).
[51] Ban, T. and Fujita, T., *J. Med. Chem. 12,* 353–356 (1969).
[52] Purcell, W. P. and Clayton, J. M., *J. Med. Chem. 11,* 199–203 (1968).
[53] Bindal, M. C., Singh, P. and Gupta, S. P., *Arzneim.-Forsch. 32,* 719–721 (1982).
[54] Hudson, D. R., Bass, G. E. and Purcell, W. P., *J. Med. Chem. 13,* 1184–1189 (1970).
[55] Kubinyi, H., unpublished results.
[56] Buckler, R. T., *J. Med. Chem. 15,* 578–583 (1972).
[57] Kubinyi, H., *J. Med. Chem. 19,* 587–600 (1976).
[58] Katz, R., Osborne, S. F. and Ionescu, F., *J. Med. Chem. 20,* 1413–1419 (1977).
[59] Lehmann, P. A., Rodrigues de Miranda, J. F. and Ariens, E. J., *Progress in Drug Research,* Volume 20, Edited by E. Jucker, Birkhaeuser, Basel 1976, Switzerland, pp. 101–142.
[60] Kubinyi, H., *Arzneim.-Forsch. 27,* 750–758 (1977).
[61] Meiske, W., Gaebler, E. and Franke, R., *Pharmazie 31,* 740–742 (1976).
[62] Esaki, T., *Anal. Chim. Acta 133,* 657–665 (1981).

[63] Roesner, T., Franke, R. and Kuehne, R., *Pharmazie 33*, 226–228 (1978).
[64] Roesner, T., Kuehne, R. and Franke, R., Abh. Akad. Wiss. DDR, Abt. Math., Naturwiss., Tech. 1978, 317–320; ref. C.A. 91, 14619z.
[65] Craig, P. N., Hansch, C. H., McFarland, J. W., Martin, Y. C., Purcell, W. P. and Zahradnik, R., *J. Med. Chem. 14*, 447 (1971).
[66] Unger, S. H. and Hansch, C., *J. Med. Chem. 16*, 745–749 (1973).
[67] Waisser, K., Macháček, M. and Čeladńik, M., *QSAR in Design of Bioactive Compounds*, Edited by M. Kuchar, Prous, Barcelona 1984, Spain, pp. 425–432.
[68] Deljac, V., Maysinger, D., Maksimovic, M., Radovic, L. and Binenfeld, Z., *Naucno-Teh. Pregl. 32*, 35–39 (1982); ref. C.A. 98, 12483w.
[69] Maksimovic, M., Maysinger, D., Deljac, V. and Binenfeld, Z., *Acta Pharm. Jugosl. 31*, 159–160 (1981); ref. C.A. 96, 99047n.
[70] Kelder, J., de Boer, T., de Graaf, J. S. and Wieringa, J. H., *QSAR and Strategies in the Design of Bioactive Compounds*, Edited by J. K. Seydel, VCH Weinheim 1985, Fed. Rep. Ger., pp. 162–169.
[71] Maysinger, D., Birus, M. and Movrin, M., *Acta Pharm. Jugosl. 30*, 9–13 (1980); ref. C.A. 93, 142658q.
[72] Urbankova, I., *Cesk. Farm. 33*, 331–335 (1984); ref. C.A. 102, 40063d.
[73] Mager, P. P. and Seese, A., *Pharmazie 36*, 427–429 (1981).
[74] Mager, P. P. and Seese, A., *Pharmazie in unserer Zeit 10*, 97–108 (1981).
[75] Wijnne, H., *Biological Activity and Chemical Structure*, Proc. IUPAC IUPHAR Symp., Edited by J. A. Keverling Buisman, Elsevier, Amsterdam 1977, The Netherlands, pp. 211–229.
[76] Pellerano, C., Savini, L., Berkoff, C. E., Thomas, J. and Actor, P., *Farmaco, Ed. Sci. 30*, 965–973 (1975).
[77] Gombar, V., *Arzneim.-Forsch. 36*, 1014–1018 (1986).
[78] Lukovits, I., *Mol. Pharmacol. 22*, 725–731 (1982).
[79] Lukovits, I., *QSAR in Design of Bioactive Compounds*, Edited by M. Kuchar, Prous, Barcelona 1984, Spain, pp. 359–364.
[80] Lukovits, I., *Acta Pharm. Jugosl. 36*, 219–224 (1986).
[81] Borea, P. A., Bonora, A., Bertolasi, V. and Gilli, G., *Arzneim.-Forsch. 30*, 1613–1617 (1980).
[82] Borea, P. A., *Arzneim.-Forsch. 32*, 325–330 (1982).
[83] Borea, P. A., *Boll. Soc. Ital. Biol. Sper. 57*, 633–637 (1981); ref. C.A. 95, 125878k.
[84] Duperray, B., Chastrette, M., Cohen Makabeh, M. and Pacheco, H., *Eur. J. Med. Chem. – Chim. Ther. 11*, 323–336 (1976).
[85] Hall, L. H. and Kier, L. B., *Eur. J. Med. Chem. – Chim. Ther. 13*, 89–92 (1978).
[86] Martin, Y. C., Jones, P. H., Perun, T. J., Grundy, W. E., Bell, S., Bower, R. R. and Shipkowitz, N. L., *J. Med. Chem. 15*, 635–638 (1972).
[87] Maysinger, D., Birus, M. and Movrin, M., *Pharm. Acta Helv. 56*, 151–154 (1981).
[88] Miyashita, Y., Takahashi, Y., Yotsui, Y., Abe, H. and Sasaki, S., *CODATA Bull. 41*, 37–41 (1981); ref. C.A. 95, 180655k.
[89] Noel-Artis, A.-M., Berge, G., Fulcrand, P. and Castel, J., *Eur. J. Med. Chem. – Chim. Ther. 20*, 25–32 (1985).
[90] Sun, H., Xu, L. and Shen, M., *Huadong Huagong Xueyuan Xuebao 1982*, 309–311; ref. C.A. 98, 86082m.
[91] Toth-Martinez, B. L., Dinya, Z. and Hernadi, F., *Adv. Pharmacol. Res. Pract.*, Proc. Congr. Hung. Pharmacol. Soc., 3rd, Volume 3, Issue Chem. Struct.-Biol. Act. Relat., Quant. Approaches, Edited by F. Darvas, Pergamon, Oxford 1980, England, pp. 339–349.
[92] Tinland, B., *Farmaco, Ed. Sci. 30*, 935–936 (1975).
[93] Borea, P. A., Gilli, G. and Bertolasi, V., *Farmaco, Ed. Sci. 34*, 1073–1082 (1979).
[94] Lapszewicz, J., Lange, J., Rump, S. and Walczyna, K., *Acta Pharm. Suec. 14*, Suppl. 48 (1977).
[95] Galdino, S. L., Pitta, I. R. and Luu-Duc, C., *Farmaco, Ed. Sci. 41*, 59–68 (1986).
[96] Kulkarni, V. M., *Curr. Sci. 46*, 801–803 (1977).
[97] Tinland, B., Decoret, C. and Badin, J., *Pharmacol. Res. Commun. 4*, 195–199 (1972).
[98] Gombar, V., Kapoor, V. K. and Singh, H., *Arzneim.-Forsch. 33*, 1226–1230 (1983).
[99] Badin, J. and Tinland, B., *Res. Commun. Chem. Pathol. Pharmacol. 6*, 1099–1100 (1973).
[100] Mizuta, E., Suzuki, N., Miyake, Y., Nishikawa, M. and Fujita, T., *Chem. Pharm. Bull. 23*, 5–12 (1975).
[101] Tinland, B. and Badin, J., *Farmaco*, Ed. Sci. 29, 886–888 (1974).
[102] Gombar, V., Kapoor, V. K. and Singh, H., *Arzneim.-Forsch. 32*, 7–9 (1982).
[103] Craig, P. N., *J. Med. Chem. 15*, 144–149 (1972).
[104] Craig, P. N. and Hansch, C. H., *J. Med. Chem. 16*, 661–667 (1973).
[105] Halgas, J., Sutoris, V., Foltinova, P. and Sekerka, V., *Chem. Zvesti 37*, 799–808 (1983); ref. C.A. 100, 103234s.
[106] Halgas, J., Sutoris, V., Sekerka, V., Foltinova, P. and Solcaniova, E., *Chem. Zvesti 37*, 663–676 (1983); ref. C.A. 100, 156529y.
[107] Sun, H., Chen, Z., Xu, G. and Xu, L., *Yaoxue Xuebao 17*, 107–111 (1982); ref. C.A. 96, 192936m.
[108] Butula, L. and Maysinger, D., *Pharm. Acta. Helv. 56*, 273–275 (1981).
[109] Pop, R. D., Schwartz, I., Coman, M., Muresan, A. and Simiti, I., *Rev. Roum. Biochim. 16*, 135–139 (1979); ref. C.A. 92, 174204j.
[110] Berkoff, C. E., Craig, P. N., Gordon, B. P. and Pellerano, C., *Arzneim.-Forsch. 23*, 830–839 (1973).
[111] Chiriac, A., Dragomir, O., Motoc, F. and Motoc, I., Univ. Timisoara, [Prepr.], Ser. Chim. 1979, 3 pp.; ref. C.A. 93, 197549k.
[112] De, A. U. and Ghose, A. K., *Indian J. Chem. 16B*, 513–515 (1978).
[113] De, A. U. and Pal, D., *J. Indian Chem. Soc. 53*, 1049–1052 (1976).
[114] Maysinger, D., Birus, M. and Movrin, M., *Acta Pharm. Jugosl. 29*, 15–18 (1979); ref. C.A. 91, 32658r.
[115] Rekker, R. F., *Dev. Pharmacol. 3* (Struct.-Act. Relat. Anti-Tumour Agents) 23–46 (1983).
[116] Simiti, I., Schwartz, I. and Coman, M., *Rev. Roum. Biochim. 11*, 139–143 (1974); ref. C.A. 82, 132793p.
[117] Tinland, B., *Farmaco*, Ed. Sci. 31, 888–890 (1976).
[118] Elguero, J. and Fruchier, A., *Afinidad 39*, 548–550 (1982); ref. C.A. 98, 154901e.
[119] Franke, R., Labes, D., Tonew, M., Zschiesche, W. and Heinisch, L., *Acta Biol. Med. Ger. 34*, 491–499 (1975).
[120] Michel, H. J., Franke, R. and Willitzer, H., *Abh. Akad. Wiss. DDR*, Abt. Math., Naturwiss., Tech. 1978, 89–96; ref. C.A. 91, 82981m.
[121] Thomas, J., Berkoff, C. E., Flagg, W. B., Gallo, J. J., Haff, R. F., Pinto, C. A., Pellerano, C. and Savini, L., *J. Med. Chem. 18*, 245–250 (1975).
[122] Tinland, B., *Res. Commun. Chem. Pathol. Pharmacol. 8*, 571–574 (1974).
[123] Schoenfeld, W. and Repke, K. R. H., *Quant. Struct. Act. Relat. 7* (1988), in press.
[124] Borea, P. A., *Arzneim.-Forsch. 33*, 1086–1088 (1983).
[125] Borea, P. A. and Ferretti, V., Biochem. *Pharmacol. 35*, 2836–2839 (1986).
[126] Schauzu, H. G. and Mager, P. P., *Pharmazie 38*, 490 (1983).
[127] Schaper, K. J., *Eur. J. Med. Chem. – Chim. Ther. 15*, 449–452 (1980).
[128] Purcell, W. P., *Biochim. Biophys. Acta 105*, 201–204 (1965).
[129] Beasley, J. G. and Purcell, W. P., *Biochim. Biophys. Acta 178*, 175–176 (1969).
[130] Clayton, J. M. and Purcell, W. P., *J. Med. Chem. 12*, 1087–1088 (1969).
[131] Purcell, W. P. and Clayton, J. M., *Mol. Orbital Stud. Chem. Pharmacol.*, Symp., Edited by L. B. Kier, Springer, New York 1970, N.Y., pp. 145–155.

[132] Hansch, C., Silipo, C. and Steller, E. E., *J. Pharm. Sci. 64,* 1186–1191 (1975).
[133] Naray-Szabo, G., *THEOCHEM 31,* 197–202 (1986); ref. C.A. 105, 90807g.
[134] Mizuta, E., Nishikawa, K., Omura, K. and Oka, Y., *Chem. Pharm. Bull. 24,* 2078–2088 (1976).
[135] Reiter, J., Toldy, L., Schaefer, I., Szondy, E., Borsy, J. and Lukovits, I., *Eur. J. Med. Chem. – Chim. Ther. 15,* 41–53 (1980).
[136] Schauzu, H. G. and Mager, P. P., *Pharmazie 38,* 562 (1983).
[137] Tang, Z.-M., Wu, J.-J., Mao, X.-Q., Chen, M.-Y. and Li, Y.-M., *Yao Hsueh Hsueh Pao 15,* 410–421 (1980); ref. C.A. 95, 906m.
[138] Justice, J. B. Jr., *J. Med. Chem. 21,* 465–468 (1978).
[139] Smithfield, W. R. and Purcell, W. P., *J. Pharm. Sci. 56,* 577–579 (1967).
[140] Pliska, V., *Experientia 34,* 1190–1192 (1978).
[141] Pliska, V., *Perspectives in Peptide Chemistry,* Ed. A. Eberle, R. Geiger and T. Wieland, Karger, Basel 1981, Switzerland, pp. 221–235.
[142] Pliska, V., *J. Steroid Biochem. 20,* 1512 (1984).
[143] Pliska, V. and Heiniger, J., in: *QSAR in Drug Design and Toxicology,* D. Hadzi and B. German-Blažič (Eds.), Elsevier, Amsterdam 1987, pp. 263–267.
[144] Greven, H. M. and de Wied, D., *Front. Hormone Res.,* Volume 4, Edited by T. B. van Wimersma Greidanus, Karger, Basel 1977, Switzerland, pp. 140–152.
[145] Kelder, J. and Greven, H. M., *Recl. Trav. Chim. Pays-Bas 98,* 168–172 (1979).
[146] Tinland, B., *Farmaco, Ed. Sci. 28,* 831–834 (1973).
[147] Singh, H., Gombar, V. and Jain, D. V. S., Proc. Indian Acad. Sci. [Ser.] Chem. Sci. 89, 77–86 (1980); ref. C.A. 93, 106805b.
[148] Tinland, B., *Farmaco, Ed. Sci. 30,* 423–424 (1975).
[149] Tinland, B., *Farmaco, Ed. Sci. 31,* 233–236 (1976).
[150] Fulcrand, P., Berge, G., Noel, A.-M., Chevallet, P., Castel, J. and Orzalesi, H., *Eur. J. Med. Chem. – Chim. Ther. 13,* 177–182 (1978).
[151] Orzalesi, H., Castel, J., Fulcrand, P., Berge, G., Noel, A.-M. and Chevallet, P., *Compt. Rend. Acad. Sc. Paris Ser.* C 279, 709–712 (1974).
[152] Prikulis, A., Grinberga, B., Katlaps, I. and Grinshtein, V., *Latv. PSR Zinat. Akad. Vestis, Kim Ser. 1982,* 181–185; ref. C.A. 97, 51649d.
[153] Gombar, V., Proc. Indian Acad. Sci. [Ser.] Chem. Sci. 91, 255–260 (1982); ref. C.A. 97, 155963t.
[154] Ezhov, V. V., Potashnikov, P. F. and Sokol'skii, G. A., *Khim.-Farm. Zh. 14,* 52–56 (1980).
[155] Maysinger, D., Movrin, M. and Ljubic, M., *Acta Pharm. Jugosl. 32,* 177–184 (1982); ref. C.A. 98, 47102y.
[156] Meister, A., Tschaepe, M. and Schroetter, E., *Pharmazie 32,* 174–177 (1977).
[157] Fernandez Gomez, P. and Vila Jato, J. L., *Arch. Farmacol. Toxicol. 10,* 199–204 (1984); ref. C.A. 102, 197525d.
[158] Kvetina, J., Laznicek, M., Kvetinova, M. and Waisser, K., *Biopharm. Pharmacokinet.,* Eur. Congr., 2nd, Volume 2, Edited by J. M. Aiache and J. Hirtz, Lavoisier, Paris 1984, France, pp. 451–460.
[159] Laznicek, M., Waisser, K., Kvetina, J. and Beno, P., *Pharmacochem. Libr. 8* (QSAR Toxicol. Xenobiochem.), 249–256 (1985).
[160] Waisser, K., Laznicek, M. and Kvetina, J., *Cesk Farm. 34,* 359–361 (1985); ref. C.A. 104, 45347a.
[161] Labes, D. and Hagen, V., *Pharmazie 34,* 554–556 (1979).
[162] Zeelen, F. J., *Biological Activity and Chemical Structure,* Proc. IUPAC IUPHAR Symp., Edited by J. A. Keverling Buisman, Elsevier, Amsterdam 1977, The Netherlands, pp. 147–160.
[163] Gryglewski, R. J., Ryznerski, Z., Gorczyca, M. and Krupinska, J., *Adv. Prostaglandin Thromboxane Res.,* Volume 1, Edited by B. Samuelsson and R. Paoletti, Raven Press, New York 1976, N.Y., pp. 117–120.
[164] Darvas, F., Budai, Z., Petocz, L. and Kosoczky, I., *Res. Commun. Chem. Pathol. Pharmacol. 12,* 243–254 (1975).
[165] Mukhomorov, V. K., *Khim.-Farm. Zh. 16,* 1086–1089 (1982).
[166] Grassy, G., Terol, A., Belly, A., Robbe, Y., Chapat, J.-P., Granger, R., Fatome, M. and Andrieu, L., *Eur. J. Med. Chem. – Chim. Ther. 10,* 14–18 (1975).
[167] Hu, B., Zhong, D., Huang, R., Li, M., Li, S., Song, X., Tang, W., Zhang, C. and Song, Y. et al., *Zhongguo Yixue Kexueyuan Xuebao 7,* 6–14 (1985); ref. C.A. 103, 192400v.
[168] Kulkarni, V. M., *Indian J. Chem. 14B,* 190–193 (1976).
[169] Nisato, D., Wagnon, J., Callet, G., Mettefeu, D., Assens, J. L., Plouzane, C., Tonnerre, B. and Fauchere, J. L., in: *QSAR in Drug Design and Toxicology,* D. Hadzi and B. German-Blažič (Eds.), Elsevier, Amsterdam 1987, pp. 277–284.
[170] Jain, D. V. S. and Gombar, V., *Int. J. Quantum Chem. 20,* 419–427 (1981).
[171] Bigler, A. J., Boegesoe, K. P., Toft, A. and Hansen, V., *Eur. J. Med. Chem. – Chim. Ther. 12,* 289–295 (1977).
[172] Baumes, R., Tien Duc, H. C. N., Elguero, J. and Fruchier, A., *An Quim. Ser. C 79,* 128–131 (1983); ref. C.A. 101, 203886v.
[173] Boucherle, A., Cousse, H., Mouzin, G., Dussourd d'Hinterland, L. and Queffelec, J. F., *Boll. Chim. Farm. 115,* 89–99 (1976); ref. C.A. 85, 206b.
[174] Cousse, H., Mouzin, G. and Dussourd d'Hinterland, L., *Chim. Ther. 8,* 466–468 (1973).
[175] Bocek, K., Kopecky, J., Krivucova, M. and Vlachova, D., *Experientia 20,* 667–668 (1964).
[176] Kopecky, J., Bocek, K. and Vlachova, D., *Nature 207,* 981 (1965).
[177] Cammarata, A. and Bustard, T. M., *J. Med. Chem. 17,* 981–985 (1974).
[178] Antonov, N. S., Gevenyan, M. I. and Tseirova, L. T., *Khim.-Farm. Zh. 16,* 325–329 (1982).
[179] Balynina, E. S., Timofievskaya, L. A. and Zel'tser, M. R., *Gig. Tr. Prof. Zabol. 1982,* 35–39; ref. C.A. 96, 212001h.
[180] Darvas, F., Lopata, A., Budai, Z. and Petocz, L., *Pharmacochem. Libr. 8* (QSAR Toxicol. Xenobiochem.), 199–210 (1985).
[181] Dillingham, O. E., Mast, R. W., Bass, G. E. and Autian, J., *J. Pharm. Sci. 62,* 22–30 (1973).
[182] Ezhov, V. V., Dan'shin, B. I., Potashnikov, P. F. and Sokol'skii, G. A., *Zh. Vses. Khim. O-va. 23,* 224–225 (1978); ref. C.A. 89, 36467j.
[183] Hall, L. H., Kier, L. B. and Phipps, G., *Environm. Toxicol. Chem. 3,* 355–365 (1984).
[184] Krasovitskaya, M. L. and Ainbinder, N. E., *Deposited Doc.,* VINITI 2749-83, 8 pp. (1983); ref. C.A. 101, 85078h.
[185] Mager, P. P., Seese, A., Hikino, H., Ohta, T., Ogura, M., Ohizumi, Y., Konno, C. and Takemoto, T., *Pharmazie 36,* 717 (1981).
[186] Mager, P. P., Seese, A. and Takeya, K., *Pharmazie 36,* 381–382 (1981).
[187] Mager, P. P., Mager, H. and Barth, A., *Sci. Pharm. 47,* 265–297 (1979).
[188] Darvas, F., Lopata, A., Budai, Z. and Petocz, L., *QSAR and Strategies in the Design of Bioactive Compounds,* Edited by J. K. Seydel, VCH Weinheim 1985, Fed. Rep. Ger., pp. 324–327.
[189] Waisser, K., Leifertova, O. and Vanzura, J., *Cesk. Farm. 35,* 55–57 (1986); ref. C.A. 105, 3361r.
[190] Bordas, B., Kovacs, M., Tuske, M., Darvas, F. and Matolcsy, G., Abh. Akad. Wiss. DDR, Abt. Math., Naturwiss., Tech. 1979, 333–344; ref. C.A. 92, 141627w.
[191] Kirino, O., Takayama, C., Fujinami, A., Yanagi, K. and Minobe, M., *Nippon Noyaku Gakkaishi 9,* 351–353 (1984); ref. C.A. 102, 19470z.
[192] Lopata, A., Darvas, F., Valko, K., Mikite, G., Jakucs, E. and Kis-Tamas, A., *Pestic. Sci. 14,* 513–520 (1983).
[193] Gupta, S. P. and Singh, P., *Indian J. Chem. 16B,* 411–414 (1978).
[194] Purcell, W. P., Martin, M. and Carbo, R., *Afinidad 33,* 159–166 (1976); ref. C.A. 85, 42008u.

[195] Schoenfelder, D. and Franke, R., Abh. Akad. Wiss. DDR, Abt. Math., Naturwiss., Tech. 1978, 303–309; ref. C.A. 91, 19651p.
[196] Gibbons, L. K., Koldenhoven, E. F., Nethery, A. A., Montgomery, R. E. and Purcell, W. P., *J. Agric. Food Chem. 24*, 203–206 (1976).
[197] Maysinger, D. and Movrin, M., *Arzneim.-Forsch. 30*, 1839–1840 (1980).
[198] Bordas, B., Darvas, F., Tuske, M. and Lopata, A., *Adv. Pharmacol. Res. Pract.*, Proc. Congr. Hung. Pharmacol. Soc., 3rd, Volume 3, Issue Chem. Struct.-Biol. Act. Relat., Quant. Approaches, Edited by F. Darvas, Pergamon, Oxford 1980, England, pp. 331–338.
[199] Dinya, Z., Timar, T., Hosztafi, S., Fodor, A., Deak, P., Somogyi, A. and Berenyi, M., *QSAR and Strategies in the Design of Bioactive Compounds*, Edited by J. K. Seydel, VCH Weinheim 1985, Fed. Rep. Ger., pp. 403–409.
[200] Kirino, O. and Casida, J. E., *J. Agric. Food Chem. 33*, 1208–1213 (1985).
[201] Serebryakov, E. P., Epstein, N. A., Yasinskaya, N. P. and Kaplun, A. B., *Phytochemistry 23*, 1855–1863 (1984).
[202] Leo, A., Hansch, C. and Elkins, D., *Chem. Rev. 71*, 525–616 (1971).
[203] Hansch, C. and Leo, A., *Substituent Constants for Correlation Analysis in Chemistry and Biology*, Wiley-Interscience, New York 1979, N.Y.
[204] Rekker, R. F., *The Hydrophobic Fragmental Constant*. Its Derivation and Application. A Means of Characterizing Membrane Systems, Elsevier, Amsterdam 1977, The Netherlands.
[205] Rekker, R. F. and de Kort, H. M., *Eur. J. Med. Chem. – Chim. Ther. 14*, 479–488 (1979).
[206] Leo, A., Jow, P. Y. C., Silipo, C. and Hansch, C., *J. Med. Chem. 18*, 865–868 (1975).
[207] Lopata, A., *Magy. Kem. Lapja 41*, 41–46 (1986); ref. C.A. 105, 197039k.
[208] Cativiela, C., Laureiro, J. I. G. and Elguero, J., *Gaz. Chim. Ital. 116*, 119–125 (1986).
[209] Carpignano, R., Savarino, P., Barni, E., di Modica, G. and Papa, S. S., *J. Soc. Dyers Colour. 101*, 270–276 (1985); ref. C.A. 104, 7192p.
[210] Carpignano, R., Savarino, P., di Modica, G. and Scavia, G., *Tinctoria 81*, 97–110 (1984); ref. C.A. 101, 172983t.
[211] Carpignano, R., Barni, E., di Modica, G., Grecu, R. and Bottaccio, G., *Dyes Pigm. 4*, 195–211 (1983); ref. C.A. 99, 55053u.
[212] Grecu, R., Pieroni, M. and Carpignano, R., *Dyes Pigm. 2*, 305–318 (1981); ref. C.A. 95, 221286m.
[213] Yamamoto, K., Sunada, H., Yonezawa, N. and Otsuka, A., *Bunseki Kagaku 28*, 205–208 (1979); ref. C.A. 91, 29856y.
[214] Schmit, J. P. and Rousseau, G. G., *J. Steroid Biochem. 9*, 921–927 (1978).
[215] Cativiela, C., Garcia, J. I. and Elguero, J., *An. Quim. Ser. C 83*, 278–282 (1987).
[216] Inoue, S., Ogino, A., Kise, M., Kitano, M., Tsuchiya, S. and Fujita, T., *Chem. Pharm. Bull. 22*, 2064–2068 (1974).
[217] Lee, H. K., Chien, Y. W., Lin, T. K. and Lambert, H. J., *J. Pharm. Sci. 67*, 847–849 (1978).
[218] Gasco, M. R., Trotta, M., Carlotti, M. E. and Carpignano, R., *Int. J. Pharm. 18*, 235–245 (1984).
[219] Singer, J. A. and Purcell, W. P., *J. Med. Chem. 10*, 1000–1002 (1967).
[220] Schaad, L. J., Hess, B. A. Jr., Purcell, W. P., Cammarata, A., Franke, R. and Kubinyi, H., *J. Med. Chem. 24*, 900–901 (1981).
[221] Hansch, C. and Lien, E. J., *Biochem. Pharmacol. 17*, 709–720 (1968).
[222] Hansch, C., *J. Org. Chem. 35*, 620–621 (1970).
[223] Martin, Y. C. and Lynn, K. R., *J. Med. Chem. 14*, 1162–1166 (1971).
[224] Hansch, C. and Yoshimoto, M., *J. Med. Chem. 17*, 1160–1167 (1974).
[225] Hamilton, H. W., Ortwine, D. F., Worth, D. F., Badger, E. W., Bristol, J. A., Bruns, R. F., Haleen, S. J. and Steffen, R. P., *J. Med. Chem. 28*, 1071–1079 (1985).
[226] Ford, R. E., Knowles, P., Lunt, E., Marshall, S. M., Penrose, A. J., Ramsden, C. A., Summers, A. J. H., Walker, J. L. and Wright, D. E., *J. Med. Chem. 29*, 538–549 (1986).
[227] Dittmar, W., Druckrey, E. and Urbach, H., *J. Med. Chem. 17*, 753–756 (1974).
[228] Kim, K. H., Hansch, C., Fukunaga, J. Y., Steller, E. E., Jow, P. Y. C., Craig, P. and Page, J., *J. Med. Chem. 22*, 366–391 (1979).
[229] Panthananickal, A., Hansch, C., Leo, A. and Quinn, F. R., *J. Med. Chem. 21*, 16–26 (1978).
[230] Hansch, C., Leo, A., Schmidt, C., Jow, P. Y. C. and Montgomery, J. A., *J. Med. Chem. 23*, 1095–1101 (1980).
[231] Fink, S. I., Leo, A., Yamakawa, M., Hansch, C. and Quinn, F. R., *Farmaco, Ed. Sci. 35*, 965–979 (1980).
[232] Khwaja, T. A., Pentecost, S., Selassie, C. D., Guo, Z. and Hansch, C., *J. Med. Chem. 25*, 153–156 (1982).
[233] Denny, W. A., Cain, B. F., Atwell, G. J., Hansch, C., Panthananickal, A. and Leo, A., *J. Med. Chem. 25*, 276–315 (1982).
[234] Selassie, C. D., Hansch, C., Khwaja, T. A., Dias, C. B. and Pentecost, S., *J. Med. Chem. 27*, 347–357 (1984).
[235] Hansch, C., McClarin, J., Klein, T. and Langridge, R., *Mol. Pharmacol. 27*, 493–498 (1985).
[236] Hansch, C. and Klein, T. E., *Acc. Chem. Res. 19*, 392–400 (1986).
[237] Yoshimoto, M. and Hansch, C., *J. Med. Chem. 19*, 71–98 (1976).
[238] Yoshimoto, M. and Hansch, C., *J. Org. Chem. 41*, 2269–2273 (1976).
[239] Hansch, C., Grieco, C., Silipo, C. and Vittoria, A., *J. Med. Chem. 20*, 1420–1435 (1977).
[240] Grieco, C., Hansch, C., Silipo, C., Smith, R. N., Vittoria, A. and Yamada, K., *Arch. Biochem. Biophys. 194*, 542–551 (1979).
[241] Silipo, C., Hansch, C., Grieco, C. and Vittoria, A., *Arch. Biochem. Biophys. 194*, 552–557 (1979).
[242] Yoshimoto, M., Hansch, C. and Jow, P. Y. C., *Chem. Pharm. Bull. 23*, 437–444 (1975).
[243] Silipo, C. and Hansch, C., *J. Med. Chem. 19*, 62–71 (1976).
[244] Silipo, C. and Hansch, C., *J. Amer. Chem. Soc. 97*, 6849–6861 (1975).
[245] Fukunaga, J. Y., Hansch, C. and Steller, E. E., *J. Med. Chem. 19*, 605–611 (1976).
[246] Hansch, C., Hathaway, B. A., Guo, Z., Selassie, C. D., Dietrich, S. W., Blaney, J. M., Langridge, R., Volz, K. W. and Kaufman, B. T., *J. Med. Chem. 27*, 129–143 (1984).
[247] Hathaway, B. A., Guo, Z., Hansch, C., Delcamp, T. J., Susten, S. S. and Freisheim, J. H., *J. Med. Chem. 27*, 144–149 (1984).
[248] Blaney, J. M., Hansch, C., Silipo, C. and Vittoria, A., *Chem. Rev. 84*, 333–407 (1984).
[249] Silipo, C. and Hansch, C., *Mol. Pharmacol. 10*, 954–962 (1974).
[250] Hansch, C. and Calef, D. F., *J. Org. Chem. 41*, 1240–1243 (1976).
[251] Dietrich, S. W., Bolger, M. B., Kollman, P. A. and Jorgensen, E. C., *J. Med. Chem. 20*, 863–880 (1977).
[252] Recanatini, M., Klein, T., Yang, C.-Z., McClarin, J., Langridge, R. and Hansch, C., *Mol. Pharmacol. 29*, 436–446 (1986).
[253] Kubinyi, H., *Progress in Drug Research*, Volume 23, Edited by E. Jucker, Birkhaeuser, Basel 1979, Switzerland, pp. 97–198.
[254] Hansch, C. and Clayton, J. M., *J. Pharm. Sci. 62*, 1–21 (1973).
[255] Kubinyi, H., *Arzneim.-Forsch. 26*, 1991–1997 (1976).
[256] Kubinyi, H., *J. Med. Chem. 20*, 625–629 (1977).
[257] Kubinyi, H., *Farmaco, Ed. Sci. 34*, 248–276 (1979).
[258] Kubinyi, H., *QSAR in Design of Bioactive Compounds*, Edited by M. Kuchar, Prous, Barcelona 1984, Spain, pp. 321–346.

[259] Darvas, F., Roehricht, J., Budai, Z. and Bordas, B., *Adv. Pharmacol. Res. Pract.*, Proc. Congr. Hung. Pharmacol. Soc., 3rd, Volume 3, Issue Chem. Struct.-Biol. Act. Relat., Quant. Approaches, Edited by F. Darvas, Pergamon, Oxford 1980, England, pp. 25–38.
[260] Kowalski, B. R. and Bender, C. F., *J. Amer. Chem. Soc. 94*, 5632–5639 (1972).
[261] Cammarata, A. and Menon, G. K., *J. Med. Chem. 19*, 739–748 (1976).
[262] Menon, G. K. and Cammarata, A., *J. Pharm. Sci. 66*, 304–314 (1977).
[263] Kirschner, G. L. and Kowalski, B. R., *Drug Design*, Volume 8, Edited by E. J. Ariens, Academic Press, New York 1979, N.Y., pp. 73–131.
[264] Jurs, P. C., Chou, J. T. and Yuan, M., *Computer-Assisted Drug Design*, Edited by E. C. Olsen and R. C. Christoffersen, ACS Symposium Series 112, Washington 1979, D.C., pp. 103–129.
[265] Dubois, J.-E., Laurent, D. and Aranda, A., *J. Chim. Phys. 70*, 1608–1615 (1973).
[266] Dubois, J.-E., Laurent, D. and Aranda, A., *J. Chim. Phys. 70*, 1616–1624 (1973).
[267] Aranda, A., *Compt. Rend. Acad. Sc. Paris Ser. C 276*, 1301–1304 (1973).
[268] Dubois, J.-E., Laurent, D., Bost, P., Chambaud, S. and Mercier, C., *Eur. J. Med. Chem. – Chim. Ther. 11*, 225–236 (1976).
[269] Dubois, J.-E., Mercier, C. and Panaye, A., *Acta Pharm. Jugosl. 36*, 135–169 (1986).
[270] Duperray, B., Chastrette, M., Cohen Makabeh, M. and Pacheco, H., *Eur. J. Med. Chem. – Chim. Ther. 11*, 433–437 (1976).
[271] Mercier, C. and Dubois, J.-E., *Eur. J. Med. Chem. – Chim. Ther. 14*, 415–423 (1979).
[272] Balaban, A. T., Chiriac, A., Motoc, I. and Simon, Z., *Steric Fit in QSAR*, Lecture Notes in Chemistry, Vol. 15, Springer, Berlin 1980, Fed. Rep. Ger.
[273] Simon, Z., Holban, S. and Motoc, I., *Rev. Roum. Biochim. 16*, 141–145 (1979); ref. C.A. 92, 71845q.
[274] Simon, Z., Ciubotariu, D. and Balaban, A. T., *QSAR and Strategies in the Design of Bioactive Compounds*, Edited by J. K. Seydel, VCH Weinheim 1985, Fed. Rep. Ger., pp. 370–373.
[275] Motoc, I., *Quant. Struct.-Act. Relat. 3*, 43–47 (1984).
[276] Motoc, I., *Quant. Struct.-Act. Relat. 3*, 47–51 (1984).
[277] Huebel, S., Roesner, T. and Franke, R., *Pharmazie 35*, 424–433 (1980).
[278] Streich, W. J. and Franke, R., *Quant. Struct.-Act. Relat. 4*, 13–18 (1985).
[279] Franke, R. and Streich, W. J., *Quant. Struct.-Act. Relat. 4*, 51–63 (1985).
[280] Franke, R. and Streich, W. J., *Quant. Struct.-Act. Relat. 4*, 63–69 (1985).
[281] Franke, R., Huebel, S. and Streich, W. J., *Environ. Health Perspect. 61*, 239–255 (1985).
[282] Cativiela, C., Garcia, J. I., Elguero, J., Mathieu, D. and Phan Tan Luu, R., *Quant. Struct. Act. Relat. 6*, 173–178 (1987).

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Review

The Measurement of Partition Coefficients

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Dedicated to Prof. Dr. Corwin Hansch on the occasion of his 70th birthday

Abstract

Partition coefficient (P) is a widely-measured property, yet there is considerable variation among published log P values. This paper examines the factors that can affect the measurement of partition coefficient, and makes recommendations as to good practice. Accuracy of partition coefficient determination can be affected by temperature, lack of mutual phase saturation, pH, buffer type and concentration, phase miscibility, solute concentration, solute and solvent purity, solute stability, phase volume ratio, solute adsorption and failure to reach equilibrium conditions. It is recommended that partitioning be carried out at constant temperature using either a stirred flask technique or the filter probe.

Key-words: partition coefficient, saturation, temperature control, purity, stability, adsorption, equilibrium, phase volume ratio, phase miscibility, shake-flask, stir-flask, filter probe.

1 Introduction

The importance of partition coefficient (P) in controlling the biological activity of xenobiotics was first shown by Meyer [1] and Overton [2], in their pioneering work on the narcosis of tadpoles. There is no doubt, however, that credit for recognising the full significance of the property and its influence on biological response must be given to Corwin Hansch and his co-workers at Pomona College. From their first paper [3] quantifying the herbicidal properties of phenoxyacetic acids, through an extensive review of partition coefficient and its uses [4] to very recent work on drug-enzyme interactions [5], they have demonstrated the over-riding importance of partition coefficient in quantitative structure-activity relationships (QSARs), and have sought to interpret the partitioning process and the nature of partition coefficient as a property.

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