Notes

Hansch and Free–Wilson Analyses of Inhibitory Potencies of Some 1-Decyl-3-carbamoylpiperidines against Butyrylcholinesterase and Comparison of the Two Methods[1]

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For some time now it has been our objective to conduct a comparative study of the mathematical model of Free and Wilson[3] and the linear free-energy-related model of Hansch.[4] For such a study one needs a series of congeners which can be treated by both methods and reliable activity data for each molecule in the series. Although limited in size, an ideal system meeting these requirements is the series of 1-decyl-3-carbamoylpiperidines which were evaluated for their inhibitory potencies against butyrylcholinesterase (acylcholine acylhydrolase, EC 3.1.1.8).[5,6] In 1965 we reported the results of the application of the Free-Wilson model using I_{50} values (molarity of compound effecting 50% inhibition) to 12 homologs of this series.[7] In this paper we are presenting the results of Hansch and Free–Wilson analyses of six of these derivatives and a comparison of the two methods.

Calculations.—The following variations of the generalized Hansch equation[4] (eq 1) were used in this study (eq 2–10). In eq 2–10 pI_{50} is the negative logarithm of

$$\log (1/C_x) = -a\pi^2 + b\pi + \rho\sigma + c \quad (1)$$

$$pI_{50} = -a\pi^2 + b\pi + \rho\mu + c \quad (2)$$

$$pI_{50} = -a\pi^2 + b\pi + \rho m + c \quad (3)$$

$$pI_{50} = -a\pi^2 + b\pi + \rho\sigma^* + c \quad (4)$$

$$pI_{50} = b\pi + \rho\mu + c \quad (5)$$

$$pI_{50} = b\pi + \rho\sigma^* + c \quad (6)$$

$$pI_{50} = -a\pi^2 + \rho\mu + c \quad (7)$$

$$pI_{50} = b\pi + \rho m + c \quad (8)$$

$$pI_{50} = -a\pi^2 + b\pi + c \quad (9)$$

$$pI_{50} = b\pi + c \quad (10)$$

I_{50}, a, b, ρ, and c are the constants generated by the regression analysis, π is the free-energy-related substituent constant defined as the logarithm of the partition coefficient of the derivative minus the logarithm of the partition coefficient of the parent compound, μ is the electric dipole moment of the identically substituted nicotinamides,[8] m is the amide group dipole moment,[9] and σ^* is the Taft substituent constant which is dependent only upon the net polar effect of the substituent[10] and is analogous to the Hammett substituent constant.[11] The π values used in the regression analyses were derived from a phenoxyacetic acid system and were obtained from the literature.[12]

The Free–Wilson regression analysis of these same compounds followed previously described methods.[7,13] Unlike most series treated by this method, there is very little variety in the substituent groups since they constitute a homologous series. All calculations were carried out with an IBM 1620[II] computer. The Hansch regression analysis employed a program written by one of the authors (J. M. C.). The correlation coefficients, r, and F ratios were calculated according to standard methods.[14]

Results and Discussion

Table I gives the constants generated from the regression analyses of eq 2–10, the squares of the correlation coefficients, and the F ratios for the Hansch analysis of the butyrylcholinesterase inhibitory potencies of six 1-decyl-3-carbamoylpiperidine hydrobromides. The correlations of all six equations are quite good. Since the level of significance of the F ratio for each regression analysis is greater than 99%,[14] the F ratios *per se* are given as a means of comparison of the relative significance of the various equations. Since eq 13 has the greatest F ratio, it was used in all Hansch calculations.

From the Free–Wilson analysis of these compounds, Table II gives a relative ranking of the activity contributions of the substituent groups and the parent moiety. The significance of this regression was quite good; the square of the correlation coefficient is 0.999 with the level of significance of the F ratio greater than 99%.[14] From these data, it appears that increasing chain length of the alkane substituents parallels an increase in inhibitory activity. It may also be observed that, as might be expected from receptor

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(2) The work reported in this paper constitutes a segment of the thesis to be submitted by John M. Clayton to the Graduate School—Medical Sciences of the University of Tennessee in partial fulfillment for the degree of Doctor of Philosophy.

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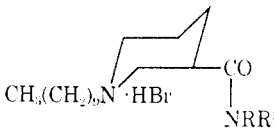
TABLE I

HANSCH ANALYSIS OF BUTYRYLCHOLINESTERASE INHIBITORY POTENCY USING pI_{50} AS THE BIOCHEMICAL RESPONSE



R =	H	H	H	CH_3	C_2H_5	C_3H_7
R' =	H	CH_3	C_2H_5	CH_3	C_2H_5	C_3H_7

Equation[a,b]	Square of correlation coefficient, r^2	F ratio[c]	
$pI_{50} = -0.058\pi^2 + 0.923\pi - 0.456\mu + 5.589$ ($\pi_0 = 7.96$)	0.998	926.50	(11)
$pI_{50} = -0.060\pi^2 + 0.933\pi - 0.396m + 5.683$ ($\pi_0 = 7.78$)	0.998	1194.50	(12)
$pI_{50} = -0.119\pi^2 + 1.205\pi + 0.687\sigma^* + 3.533$ ($\pi_0 = 5.06$)	0.998	8084.10	(13)
$pI_{50} = 0.699\pi - 0.268\mu + 5.061$	0.994	274.30	(14)
$pI_{50} = 0.397\pi - 0.394\sigma^* + 4.566$	0.974	57.11	(15)
$pI_{50} = 0.132\pi^2 + 0.338\mu + 3.302$	0.943	24.71	(16)
$pI_{50} = 0.667\pi - 0.227m + 5.094$	0.994	269.08	(17)
$pI_{50} = 0.011\pi^2 + 0.535\pi + 4.203$	0.984	102.99	(18)
$pI_{50} = 0.570\pi + 4.187$	0.985	268.43	(19)

[a] See ref 5, 8-10, and 12. [b] pI_{50} is the negative logarithm of the molarity of compound effecting 50% inhibition. [c] Level of significance of the F ratio exceeds 99% for each equation.[14]

theories, the parent moiety quantitatively contributes the major portion of the inhibitory activity. The substituent groups either enhance or decrease this activity of the parent moiety depending upon the relationship between the group properties and the requirements for activity.

TABLE II

PARENT AND SUBSTITUENT ACTIVITY CONTRIBUTIONS GENERATED BY THE FREE–WILSON REGRESSION ANALYSIS

Group[a]	Act. contribution, pI_{50}[b]
H	−0.82
Me	−0.61
Et	−0.29
Pr	0.05
Parent moiety	5.89

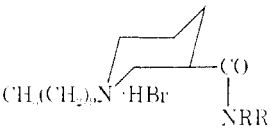
[a] The groups, substituted at positions R and R', and the parent moiety refer to the homologs in Table I. [b] pI_{50} is the negative logarithm of the molarity of compound effecting 50% inhibition.

One congener, 1-decyl-3-(N-ethyl-N-methylcarbamoyl)piperidine hydrobromide, was not included in either regression and, therefore, its calculated pI_{50} value can be treated as "predicted." Both predicted values, 5.00 by the Hansch method and 4.99 by the Free–Wilson analysis, are within the experimental error of the observed pI_{50}, 5.01 ± 0.03 (Table III).

Table III gives the observed and calculated pI_{50} values for both types of analyses and, therefore, provides data for comparing the two methods. Both correlations are very good. The calculated pI_{50} values from the Hansch analysis (eq 13, Table I) are all

TABLE III

OBSERVED AND CALCULATED BUTYRYLCHOLINESTERASE INHIBITORY POTENCIES OF SOME 1-DECYL-3-CARBAMOYLPIPERIDINE HYDROBROMIDES



		pI_{50}[a]		
			Calcd	
R	R'	Obsd	Free-Wilson[c]	Hansch[d]
H	H	4.21 ± 0.02[b]	4.25	4.21
H	Me	4.46 ± 0.03[b]	4.46	4.46
H	Et	4.86 ± 0.01[b]	4.78	4.86
Me	Me	4.66 ± 0.04[b]	4.66	4.66
Me	Et	5.01 ± 0.03[e]	4.99	5.00
Et	Et	5.28 ± 0.02[b]	5.32	5.29
Pr	Pr	5.98 ± 0.03[a]	5.98	5.98

[a] pI_{50} is the negative logarithm of the molarity of compound effecting 50% inhibition. [b] Taken from ref 5. [c] Taken from ref 6. This is the compound for which the inhibitory potency was predicted accurately 3 years before it was synthesized. The observed value, 5.01, was not included in either the Free–Wilson or Hansch regression analysis. [d] J. C. Beasley, unpublished results. [e] Calculated by summation of the substituent and parent activity contributions obtained from Table II. [f] Equation 13, Table I, was used.

within the experimental error of the observed values. The calculated pI_{50} values from the Free–Wilson analysis, however, are within the experimental error of the observed values for only three of the six compounds, and one of these compounds, the dipropyl derivative, is forced to fit since it represents a single observation. One must conclude that both models fit these data quite well although the Hansch method gives somewhat better quantitative results for this series.

Since the hydrophobic parameter, π, seems to be the most significant term in the Hansch analysis, the maximum or ideal π value, π_0, was calculated.[15] For the equation used in the Hansch analysis (eq 13, Table I), π_0 is 5.06. One might conclude, therefore, that the N,N-dipentyl derivative or other derivatives with combinations of substituents with similar π values would be worthy of synthesis and evaluation. For eq 11 and 12, π_0's are 7.96 and 7.76, respectively. Values of π between 5 and 8 would be expected to be optimum.

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3-Azaspiro[5.5]undecanes

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A broad program for the investigation of the chemical and pharmacological properties of heterocyclic compounds containing spiro carbon linkages at the ring

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