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Structure-Activity Correlations for Organophosphorus Ester Anticholinesterases. I. QSAR Applied to Inhibition Rates[a)]

QSAR for cholinesterase inhibition by organophosphorus esters

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(ABBREVIATIONS AND SYMBOLS)

QSAR	=	quantitative structure-activity relationship
OP	=	organophosphorus
AChE	=	acetylcholinesterase
BuChE	=	butyrylcholinesterase
MO	=	molecular orbital
ChE	=	cholinesterase
σ and σ_I	:	see page 4 for first use
E'_s	:	ditto
π	:	ditto
D	:	ditto
DR	:	see page 7 for first use

Abstract

Quantitative structure-activity relationships have been derived for acetyl- and butyrylcholinesterase inhibition by various organophosphorus esters. Bimolecular inhibition rate constants correlate well with hydrophobic and steric parameters, and with the presence or absence of charged groups on the inhibitor.

1 Introduction

Interest in organophosphorus (OP) ester anticholinesterases prompted a computational study aimed at predicting rate constants for acetyl- and butyrylcholinesterase (AChE and BuChE) inhibition by various OP esters.

Two approaches appeared reasonable: (1) a multiple-linear regression analysis to develop quantitative structure-activity relationships (QSAR) between enzyme inhibition rate constants and OP ester hydrophobic, inductive, and steric substituent constants; and (2) molecular orbital (MO) calculations on OP esters seeking correlations connecting parameters such as atomic charges and orbital energies with alkaline hydrolysis rate constants. The use of QSAR to predict biological activities of new molecules is a well-established discipline [1], and applying MO calculations to OP esters is an active topic [2-5]. This article involves the first or QSAR approach, and a companion article [6] involves the second or MO approach.

The active site in AChE or BuChE consists of esteratic and anionic regions, with inhibition proceeding through reversible binding of the OP ester to the enzyme (via coulombic interaction with the anion subsite or via hydrophobic forces), followed by phosphonylation of a serine hydroxyl in the esteratic region [7-10]. ChE inhibition, at low inhibitor concentration, follows second-order kinetics [11-13]:

$$-d[ChE]/dt = k_2[ChE][OP] \qquad (1)$$

with rate constants paralleling approximately the inherent toxicities of various OP compounds [7,8,14,15]. A number of QSAR studies have been conducted on ChE-OP reactions [16-20], indicating that the ChE inhibition rate constants do correlate well with appropriate steric,

hydrophobic and inductive substituent constants. However, the exact correlations depend on the type and source of ChE and on the type of OP ester. In a study containing perhaps the most extensive set of ChE inhibition data ever reported, Kabachnik and coworkers [20] demonstrated qualitatively the importance of hydrophobic interactions in AChE and BuChE inhibition by 66 structurally related OP esters. Because these workers ignored the potential influence of steric or inductive effects, we reexamined their data to obtain QSAR based on steric and inductive as well as hydrophobic effects.

2 Methods

The OP esters investigated by Kabachnik and coworkers [20] fall into six series (Table 1); for each of the 66 compounds, they determined k_2 for horse serum BuChE inhibition, and for 52 of the compounds they also reported k_2 for bovine erythrocyte AChE inhibition. To develop QSAR for these compounds, we compiled the following substituent constants for the R and R′ groups in Table 1: σ_I (inductive), E'_s (steric), π (hydrophobic) and D (ionic). σ_I was chosen over the Taft σ^* since there is concern [21-24] that the latter does not adequately separate inductive and steric effects. Most of the values were obtained from refs. 21 and 22; where values were unreported, we estimated σ_I by Equation 2 or 3 for linear or branched hydrocarbon chains, respectively [21]:

$$-\sigma_I = 0.137(\text{No. carbon atoms})/(\text{No. hydrogen atoms}) \quad (2)$$

$$-\sigma_I = -\sigma_I(CH_3) + 0.00941(\text{No. carbons at branch i})/(\text{No. branch points, i}) \quad (3)$$

E'_s values were obtained from MacPhee and coworkers [25]; where values

for long chain linear alkyl groups were unavailable, we assumed, as suggested by these workers, a limiting value of $-E'_s = 0.31$. Values for π were obtained from the extensive compilation of Kramer [26] for acyclic alkyl alcohols; where values for specific groups were unavailable, we estimated π, in accordance with ref. 27, by Equation 4:

$$\pi[R(CH_2)_n] = \pi_R + 0.50(n) \quad (4)$$

A dummy parameter, D, set at +1 for the charged compounds of Series III and VI, and set at 0 for the other uncharged compounds, was employed because the methyl sulfonium cationic moiety was expected to influence ChE inhibition rates, via coulombic interactions with the enzyme anionic site(s).

To correlate data for these substituent parameters with k_2 values for the Kabachnik OP esters, we used a stepwise linear regression analysis (the Prophet "Fit Multiple" program) for statistical analysis. This method allowed calculation of (a) correlation matrix for substituent constants; (b) multiple and single correlations of rate constants and substituent constant values; (c) correlation coefficient, standard deviation of regression and significance level (Student's T test); and (d) residuals (observed minus fitted rate constants) and distribution frequency of the residuals. The program automatically provided the most statistically significant multiple correlation and omitted variables that did not improve the precision of the correlation.

3 Results

3.1 QSAR for BuChE

3.1.1 Series II, III, V and VI Compounds

We grouped these compounds together since they have a common

structure, $CH_3P(O)(OR)SCH_2CH_2Y$, where Y = SR′ or $\overset{\oplus}{S}(CH_3)R'$, and R and R′ are alkyl groups. Since hydrophobic, inductive and steric substituent effects may vary with location on a parent molecule, we examined effects at sites R and R′ separately. Substituent constants for Series II, III, V and VI compounds and their BuChE inhibition rates are given in Tables 2 and 3; the best correlation is Equation 5 (see Table 6). A squared correlation matrix of variables obtained for this series of compounds showed a fairly high degree of collinearity among certain parameters, e.g., π_R vs σ_R or E'_{s_R}; σ_R vs E'_{s_R}; $\pi_{R'}$ vs $\sigma_{R'}$ or $E'_{s_{R'}}$; $\sigma_{R'}$ vs $E'_{s_{R'}}$. Thus, the substituents were not sufficiently independent with respect to "pure" steric, hydrophobic and electronic effects to delineate their importance in determining log k_2. The substituent collinearity data suggested that electronic effects are included in π and E'_s, which may explain why σ_R and $\sigma_{R'}$ were not significant parameters in Equation 5. Residuals were quite small in magnitude, and also symmetrically distributed around zero. This is consistent, of course, with the extremely high r and relatively small s for Equation 5.

For the combined Series II, III, V and VI, evaluating significance levels of individual parameters (as in single-parameter equations) and of the same parameters paired with the parameter D (in two-parameter correlations) suggested that including D did not alter the relative importance of the other parameters; π_R, σ_R, E'_{s_R}, $\pi_{R'}$, $\sigma_{R'}$ and $E'_{s_{R'}}$ remained the most important secondary parameters. This was confirmed by individual correlation Equations 6 and 7 (see Table 6) derived for Series II and V (D = 0) and Series III and VI (D = 1), respectively. These equations suggest that the locations of R and R′ have little influence on the hydrophobic and steric effects.

This was confirmed by Equation 8 (for all four series combined) in which only the summation parameters ($\pi = \pi_R + \pi_{R'}$, etc.) were included. We conclude that including the parameter D to account for the higher activity of cationic sulfonium compounds, and merging data for all four series, are valid, and that the reactivity is primarily a function of total hydrophobic and steric effects by R and R´.

3.1.2 Series I and IV Compounds

We grouped these compounds together because they have a common structure, $CH_3P(O)(OR)SR'$, where $R' = (CH_2)_nR''$ or $n\text{-}C_4H_9$, and R is alkyl and R" is an alkyl or phenyl group. As above, hydrophobic, electronic and steric substituent constants were considered separately for R and R´ (see Tables 4 and 5). The best correlation for BuChE inhibition by Series I and IV compounds is Equation 9 in Table 6. We tried to improve on it by including a binary parameter (DR = 0 or 1) to account for possible differences between Series I and IV. Including DR proved unrewarding, however, indicating that the two series can be justifiably combined for regression analysis. The relatively high significance of π_R and $\pi_{R'}$ suggests that total molecular hydrophobicity is of great importance, with specific locations of R and R´ being only of possible secondary importance. Equation 10 involving summed electronic and hydrophobic parameters is consistent with this interpretation.

3.2 QSAR for AChE

We did not attempt correlations for AChE inhibition by the combined Series II, III, V and VI because k_2 data were available for only 12 of the

26 compounds in these series (Tables 2 and 3). However, AChE correlations were obtained for the combined Series I and IV compounds (Tables 4 and 5). As before, hydrophobic, electronic (or inductive) and steric substituent constants were considered separately for R and R′. Examination of the distribution of residuals relative to activity values predicted by the correlation model revealed that two outliers were markedly inconsistent with the model; hence, two compounds, IV.48 and IV.49, were deleted, resulting in an improved correlation, Equation 11 (Table 6). Again, the use of parameter DR to account for differences between Series I and IV proved not to be significant, indicating the validity of combining data for the two series. Parameter collinearity was indicated for some variables, notably $\pi_{R'}$ vs $\sigma_{R'}$.

Attempts to use total molecular hydrophobic, electronic and steric parameters ($\pi = \pi_R + \pi_{R'}$, σ, E'_s) resulted in much poorer correlations. This suggests that geometric distribution of these properties is important in determining activity. Equation 11 shows that electronic effects are important in both R and R′, while steric effects are somewhat more important at R′ than at R; significance levels for the parameters indicated that hydrophobic effects were much more important at R′ than at R.

3.3 QSAR for Combined Data

Since the results above indicated that basically similar molecular properties contribute to activity in all six series, we performed a combined QSAR analysis of all the data. Because interseries differences do exist that are not adequately accounted for by hydrophobic, electronic and steric substituent constants, parameters D and DR were retained. For Series I and IV compounds, with structures $CH_3P(O)(OR)SR'$, DR = 0, and for

Series II, III, V and VI compounds, with structures $CH_3P(O)(OR)SCH_2CH_2Y$, DR = 1. The parameter D, as noted above, has the value 0 or 1 according as Y is SR′ or $\overset{\oplus}{S}(CH_3)R'$.

3.3.1 QSAR for Combined BuChE Data

The best correlation for inhibition of BuChE by the entire set of 66 compounds is Equation 12 (Table 6). Covariance analysis indicated substantial collinearity between π_R and σ_R, DR and D, $\pi_{R'}$ and $\sigma_{R'}$, and E'_{s_R} and σ_R. An equally valid correlation, in which the steric parameter does not appear, is Equation 13. Consistent with earlier indications that locations of R and R′ are of only secondary importance is the fact that an equally good correlation can be obtained using total molecular parameters (Equation 14).

3.3.2 QSAR for Combined AChE Data

The best correlation for inhibition of AChE by the 52 compounds for which log k_2 data are available is Equation 15. The corresponding correlation based on total molecular parameters π, σ, E'_s, D and DR, namely, Equation 16, was not quite as good.

4 Discussion

As may be seen from Equation 5 (Table 6), the kinetics of inhibition of BuChE by Series II, III, V and VI compounds correlate very precisely with substituent constants π, E'_s and D. Thus, the high $r^2 = 0.987$ indicates that Equation 5 explains 98.7% of the variation in log k_2; further support for the precision of this correlation was seen in low residuals calculated between actual and fitted rate constants. It is not possible

to assess the relative importance of the individual substituent constants in Equation 5, partly because, as noted in Sect. 3.1.1, there is a high degree of collinearity among certain constants. However, since the coefficients of π_R and $\pi_{R'}$ are essentially equivalent, as are the coefficients of E'_{s_R} and $E'_{s_{R'}}$, we may conclude that R and R′ participate equally in binding interactions with BuChE. Since the dummy parameter D is 0 or 1, a coefficient of 2.57 for this parameter signifies that incorporating a methyl sulfonium group into a Series III or IV compound increases anti-BuChE activity in the ionic compound relative to the corresponding nonionic (Series II or V) compound by a factor of $10^{2.57} = 372$.

It is now useful to compare our correlations with those reported in the literature. The importance of hydrophobic binding in controlling BuChE-OP ester reactions, noted previously by Kabachnik and coworkers [20], has been confirmed in the present study that has provided a quantitative description of the correlations. The Kabachnik work also demonstrated that hydrophobic effects level off for very long alkyl groups, suggesting a hydrophobic region of limited size on the active surface of BuChE. This plateau is not apparent in the present analysis. Chiriac and coworkers [17] and Langel and Järv [18] also correlated BuChE-OP ester reactions, examining reactivities of $ROP(O)(C_6H_5)OCH_2CH_2SR'$ and $(C_2H_5O)_2P(O)SR$, respectively. In both cases BuChE inhibition rate constants correlated strongly with hydrophobic (π) constants, and showed some dependence on steric and/or inductive constants. On the other hand, Hansch and Deutsch [16] examined fly-head AChE reactions with $R(C_2H_5O)P(O)OC_6H_4NO_2$ and

found k_2 to correlate strongly with E_s and σ constants, but poorly with π values. Evidently, the active surface of fly-head AChE differs considerably from that of horse-serum BuChE.

Series I and IV compounds are similar to Series II, III, V and VI compounds in that their activity toward BuChE depends upon hydrophobicity in both R and R´. However, one notable difference is that the former compounds are less dependent on steric effects, and more dependent on electronic effects, than are the latter compounds. This is not surprising since the insulating effect of the $-SCH_2CH_2-$ group is absent in Series I and IV compounds, so that the electronic effect, $\sigma_{R'}$, of the substituent R´ is proximal to the reaction center. The significance of electronic effects is even more apparent in the activity of Series I and IV compounds toward AChE where the σ_R and $\sigma_{R'}$ terms have large regression coeffficients (Equation 11, Table 6). Moreover, inhibition of AChE by these compounds appears to be more sensitive to substituent location inasmuch as the dominant π and E'_s terms are those which involve R´.

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Table 1. Structural Representations for OP Inhibitors, $CH_3P(O)(OR)SR'$ [20]

Series	R	R′
I.1 to I.24	C_2H_5	Alkyl (C_1 to C_{10})
II.25 to II.30	C_2H_5	CH_2CH_2S-Alkyl (C_1 to C_{10})
III.31 to III.36	C_2H_5	$CH_2CH_2\overset{\oplus}{S}(CH_3)$-Alkyl ($C_1$ to C_{10})
IV.37 to IV.52	Alkyl (C_1 to C_{10})	n-C_4H_9
V.53 to V. 59	Alkyl (C_1 to C_8)	$CH_2CH_2SC_2H_5$
VI.60 to VI.66	Alkyl (C_1 to C_8)	$CH_2CH_2\overset{\oplus}{S}(CH_3)C_2H_5$

Table 2. Inhibition Rates and Substituent Parameters for Series II and III Compounds, $CH_3P(O)(OR)SCH_2CH_2Y$[a)]

Compd. No.	log k_2 [M^{-1} min^{-1}] AChE	BuChE	R´	$\pi_{R'}$	$\sigma_{R'}$	$E'_{s_{R'}}$
Y = SR´; D = 0:						
II.25	4.60	3.51	CH_3	0.56	-0.046	0.0
26	4.78	3.83	C_2H_5	1.0	-0.055	-0.08
27	4.95	4.88	n-C_4H_9	2.0	-0.058	-0.31
28	5.60	5.11	n-C_6H_{13}	3.0	-0.061	-0.31
29	5.52	5.48	n-C_8H_{17}	4.0	-0.0645	-0.31
30	5.30	5.60	n-$C_{10}H_{21}$	5.0	-0.0652	-0.31
Y = $\overset{\oplus}{S}(CH_3)R'$; D = 1:						
III.31	7.74	6.00	CH_3	0.56	-0.046	0.0
32	8.40	6.57	C_2H_5	1.0	-0.055	-0.08
33	8.34	7.04	n-C_4H_9	2.0	-0.058	-0.31
34	9.04	7.95	n-C_6H_{13}	3.0	-0.061	-0.31
35	8.66	8.00	n-C_8H_{17}	4.0	-0.0645	-0.31
36	8.67	8.26	n-$C_{10}H_{21}$	5.0	-0.0652	-0.31

a) $R = C_2H_5$; $\pi_R = 1.0$; $\sigma_R = -0.055$; $E'_{s_R} = -0.08$

Table 3. Inhibition Rates and Substituent Parameters for Series V and VI Compounds, $CH_3P(O)(OR)SCH_2CH_2Y$

Compd. No.	log k_2 [M^{-1} min^{-1}] / BuChE	R	π_R	σ_R	E'_{s_R}
Y = SR′; D = 0:[a)]					
V.53	2.98	CH_3	0.56	-0.046	0.0
54	4.76	n-C_3H_7	1.5	-0.058	-0.31
55	5.20	n-C_4H_9	2.0	-0.058	-0.31
56	5.23	n-C_5H_{11}	2.5	-0.064	-0.31
57	5.57	n-C_6H_{13}	3.0	-0.061	-0.31
58	6.45	n-C_7H_{15}	3.5	-0.062	-0.31
59	6.04	n-C_8H_{17}	4.0	-0.0645	-0.31
Y = $\overset{\oplus}{S}(CH_3)R'$; D = 1:[a)]					
VI.60	5.89	CH_3	0.56	-0.046	0.0
61	7.58	n-C_3H_7	1.5	-0.058	-0.31
62	7.68	n-C_4H_9	2.0	-0.058	-0.31
63	7.88	n-C_5H_{11}	2.5	-0.064	-0.31
64	8.26	n-C_6H_{13}	3.0	-0.061	-0.31
65	8.40	n-C_7H_{15}	3.5	-0.062	-0.31
66	8.45	n-C_8H_{17}	4.0	-0.0645	-0.31

a) $R' = C_2H_5$; $\pi_{R'} = 1.0$; $\sigma_{R'} = -0.055$; $E'_{s_{R'}} = -0.08$

Table 4. Inhibition Rates and Substituent Parameters for Series I Compounds, $CH_3P(O)(OR)SR'$; $R' = (CH_2)_nR''$.[a)]

Compd. No.	log k_2 [M^{-1} min^{-1}] AChE	BuChE	R"	n	$\pi_{R'}$	$\sigma_{R'}$	$E'_{s_{R'}}$
I.1	2.34	1.81	CH_3	1	1.0	-0.055	-0.08
2	2.72	2.15	CH_3	2	1.5	-0.057	-0.31
3	3.08	2.91	CH_3	3	2.0	-0.058	-0.31
4	3.42	3.42	CH_3	4	2.5	-0.061	-0.31
5	4.20	4.58	CH_3	5	3.0	-0.061	-0.31
6	4.32	4.52	CH_3	6	3.5	-0.061	-0.31
7	4.56	4.61	CH_3	7	4.0	-0.0645	-0.31
8	4.49	4.53	CH_3	8	4.5	-0.0649	-0.31
9	4.20	4.58	CH_3	9	5.0	-0.0652	-0.31
10	4.30	4.32	$t-C_4H_9$	1	2.32	-0.065	-1.63
11	3.20	3.67	$t-C_4H_9$	2	2.87	-0.0683	-0.33
12	3.34	4.26	$t-C_4H_9$	3	3.37	-0.0694	-0.31
13	3.86	4.96	$t-C_4H_9$	4	3.87	-0.0705	-0.31
14	4.04	4.95	$t-C_4H_9$	5	4.37	-0.0715	-0.31
15	4.28	4.99	$t-C_4H_9$	6	4.87	-0.0724	-0.31
16	3.20	2.82	$i-C_3H_7$	1	1.93	-0.064	-0.93
17	3.11	3.36	$i-C_3H_7$	2	2.43	-0.061	-0.32
18	2.92	3.39	$i-C_3H_7$	3	2.93	-0.0672	-0.31
19	3.95	4.77	$i-C_3H_7$	4	3.43	-0.0689	-0.31
20	4.34	4.98	$i-C_3H_7$	6	4.43	-0.0702	-0.31
21	4.48	5.08	C_6H_5[b)]	1	1.76	-0.026	-0.39
22	4.08	4.15	C_6H_5[b)]	2	2.02	-0.038	-0.35
23	4.25	4.82	C_6H_5[b)]	3	2.54	-0.044	-0.34
24	4.53	5.04	C_6H_5[b)]	4	3.04	-0.05	-0.33

a) $R = C_2H_5$; $\pi_R = 1.0$; $\sigma_R = -0.055$; $E'_{s_R} = -0.08$; $D = 0$.

b) $\pi[C_6H_5(CH_2)_n] = \pi[C_6H_5(CH_2)_nOH] - \pi[CH_3OH]$.

Table 5. Inhibition Rates and Substituent Parameters for Series IV Compounds, $CH_3P(O)(OR)SR'$; $R' = n\text{-}C_4H_9$.[a)]

Compd. No.	log k_2 [M^{-1} min^{-1}] AChE	BuChE	R	π_R	σ_R	E'_{s_R}
IV.37	2.42	1.76	CH_3	0.56	-0.046	0.0
38	3.75	3.65	$n\text{-}C_3H_7$	1.5	-0.058	-0.31
39	4.15	4.08	$n\text{-}C_4H_9$	2.0	-0.058	-0.31
40	3.83	4.20	$n\text{-}C_5H_{11}$	2.5	-0.064	-0.31
41	3.62	4.69	$n\text{-}C_6H_{13}$	3.0	-0.061	-0.31
42	3.65	6.04	$n\text{-}C_7H_{15}$	3.5	-0.062	-0.31
43	3.61	5.56	$n\text{-}C_8H_{17}$	4.0	-0.0645	-0.31
44	3.79	5.85	$n\text{-}C_9H_{19}$	4.5	-0.0649	-0.31
45	3.46	4.79	$n\text{-}C_{10}H_{21}$	5.0	-0.0652	-0.31
46	3.51	2.65	$i\text{-}C_3H_7$	1.3	-0.064	-0.48
47	4.15	3.64	$i\text{-}C_3H_7CH_2$	1.93	-0.064	-0.93
48	4.79	4.53	$i\text{-}C_3H_7(CH_2)_2$	2.43	-0.061	-0.32
49	5.63	4.59	$i\text{-}C_3H_7(CH_2)_3$	2.93	-0.0672	-0.31
50	3.97	4.81	$i\text{-}C_3H_7(CH_2)_4$	3.43	-0.0689	-0.31
51	3.93	4.48	$i\text{-}C_3H_7(CH_2)_5$	3.93	-0.0702	-0.31
52	3.77	2.98	$t\text{-}C_4H_9CH_2$	2.32	-0.065	-1.63

a) $\pi_{R'} = 2.0$; $\sigma_{R'} = -0.058$; $E'_{s_{R'}} = -0.31$; $D = 0$.

Table 6. Correlation Equations for log k_2 in terms of Substituent Constants for OP Esters.

Eqn. No.	Series	No. Cpds.	En-zyme	Coefficients for Substituent Constants[a]												Regression Analysis[b]		
				π_R	$\pi_{R'}$	σ_R	$\sigma_{R'}$	E'_{s_R}	$E'_{s_{R'}}$	D	DR	π	σ	E'_s	C	r	r^2	s
5	II,III,V,VI	26	BuChE	0.50	0.32	--	--	-3.67	-2.89	2.57	--	--	--	--	2.47	0.994	.987	.204
8	II,III,V,VI	26	BuChE	--	--	--	--	--	--	2.56	--	0.31	--	-4.17	2.54	0.982	.964	.323
6	II,V	13	BuChE	0.59	0.27	--	--	-3.38	-3.64	--	--	--	--	--	2.36	0.992	.964	.233
7	III,VI	13	BuChE	0.40	0.36	--	--	-3.95	-2.15	--	--	--	--	--	5.16	0.987	.974	.173
9	I,IV	40	BuChE	0.71	1.02	--	57.7	--	-0.92	--	--	--	--	--	3.39	0.854	.728	.562
10	I,IV	40	BuChE	--	--	--	--	--	-0.86	--	--	0.91	50.8	--	5.86	0.840	.710	.571
12	I-VI	66	BuChE	0.75	0.71	--	39.5	0.57	--	2.56	1.26	--	--	--	3.50	0.945	.893	.559
13	I-VI	66	BuChE	0.70	0.73	--	40.7	--	--	2.56	1.30	--	--	--	3.50	0.942	.888	.568
14	I-VI	66	BuChE	--	--	--	--	--	--	2.45	1.32	0.76	32.1	--	4.70	0.937	.878	.587
11	I,IV[c]	38	AChE	--	0.65	-61.0	47.4	--	-0.87	--	--	--	--	--	1.01	0.885	.783	.285
15	I,II,III.IV	52	AChE	--	0.44	-64.2	38.0	--	-0.66	3.35	1.57	--	--	--	0.98	0.965	.932	.450
16	I,II,III,IV	52	AChE	--	--	--	--	--	--	3.35	1.45	0.21	--	--	2.92	0.943	.890	.554

a) The use of the coefficients is illustrated by the explicit representation of equation (4): $\log k_2 = 0.50\pi_R + 0.32\pi_{R'} - 3.67E'_{s_R} - 2.89E'_{s_{R'}} + 2.57D + 2.47$.

b) r is the correlation coefficient, r^2 is the fraction of variation in log k_2 accounted for by the correlation equation, and s is the standard deviation.

c) Two compounds deleted.

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16. Abstract

Quantitative structure-activity relationships have been derived for acetyl- and butyrylcholinesterase inhibition by various organophosphorus esters. Bimolecular inhibition rate constants correlate well with hydrophobic and steric parameters, and with the presence or absence of charged groups on the inhibitor.

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