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Quantitative Structure–Activity Relationships in 1-Aryl-2-(alkylamino)ethanol Antimalarials[1]

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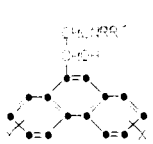
A quantitative structure–activity relationship has been formulated for 646 antimalarials acting against *P. berghei* in mice. The equation developed has 14 terms, 9 of which are indicator variables. The correlation coefficient for the QSAR is 0.898 and the standard deviation is 0.309. The antimalarials are all arylcarbinols of the type X-ArCHOHCH$_2$NR$_1$R$_2$. Sixty different aryl structures, including a variety of heterocycles, are contained in the study. The most important determinate of activity is found to be the electron-withdrawing ability of the substituents X; the hydrophobic character of X and R play less important roles. Suggestions for more potent analogues are made and the level of activity of about 100 additional analogues is also considered.

The use of quinine in the treatment of malaria constitutes one of the oldest successful examples of chemotherapy. Its replacement by synthetic drugs is a most interesting chapter in modern chemotherapy.[2]

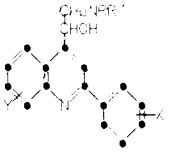
Prior to World War II, pamaquine, quinacrine, and chloroquine were developed in Germany. The war stimulated a huge increase in research for synthetic antimalarials which has been documented by Wiselogle and Coatney;[3] this work yielded, among others, amodiaquine, primaquine, and chlorguanide. The impetus of this research was also responsible for the somewhat later development of pyrimethamine and chloroproguanide.

During the later 1940s it began to become clear that various strains of malaria were more or less resistant to many of the known drugs. Drug resistance has been confirmed in South America, Southeast Asia, Central Africa, and New Guinea. All human malaria parasites have shown drug resistance. During the period of the Vietnam war, renewed interest in drug development came about as a result of developing resistance to known drugs, resistance of mosquitoes to residual insecticides, and the inability to use insecticides under some conditions. The Walter Reed Army Institute has taken the leading role in the current effort to find more effective antimalarial drugs.

The extensive history of malaria chemotherapy has been well reviewed by Thompson and Werbel[2a] and Pinder.[2b] Our concern in this report is with compounds of types I–III



I



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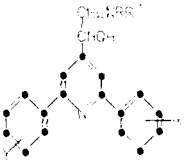
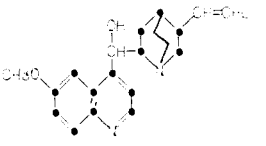


III

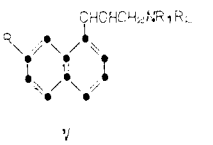
and a number of closely related congeners (see Table II).

We considered analogues of type I in a preliminary analysis[4] of the structure–activity relationship of phenanthrene carbinols. These compounds can be regarded as analogues of quinine, IV. Early efforts were made by



IV

Rabe,[5,6] Kaufmann,[7] Karrer,[8] and Ruzicka[9,10] to make quinoline analogues of quinine by replacing the quinuclidine unit with simpler structures. None of these early efforts were successful in a chemotherapeutic sense. King[11] and his co-workers produced the first quite active synthetic derivatives of type V.



V

Up to this time, chemists had not been able to break away from the conservative idea that there was something magical about the quinoline ring which was essential for antimalarial activity. May and Mosettig[12] broke out of this restricting view by showing that analogues of I were active against malaria. It was soon shown that even the simple aromatic rings such as naphthalene, benzene, and pyridine could be turned into arylcarbinols with antimalarial activity. The limits have never been reached on the kind of aromatic ring which will serve as the base for an aminocarbinol-type antimalarial.

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Table I. Phenanthrenes Acting Against Malaria (*P. berghei*)

no.	ring substit	NRR'[a]	log 1/C obsd	log 1/C calcd[b]	|Δ log 1/C|
set I					
1	2,4-Cl_2; 6-CF_3	2-Pip	4.43	4.36	0.07
2	2,3-Br_2; 6-CF_3	$N(Bu)_2$	4.36	4.26	0.10
3	3-CF_3; 5,7-Cl_2	2-Pip	4.35	4.21	0.14
4	1,3,6-Br_3	$N(Bu)_2$	4.35	4.08	0.27
5	1,3-Cl_2; 6-CF_3	$N(Bu)_2$	4.29	4.05	0.24
6	2,5,7-Cl_3	2-Pip	4.29	4.01	0.28
7	3-CF_3; 6-Cl	2-Pip	4.25	3.91	0.34
8	2,4-Br_2; 6-CF_3	$N(Bu)_2$	4.24	4.41	0.17
9	1,3-Br_2; 6-CF_3	2-Pip	4.22	4.20	0.02
10	2,3-Cl_2; 6-CF_3	2-Pip	4.21	4.24	0.03
set II[c]					
1	2,4-$(CF_3)_2$; 6,7-Cl_2	$N(Pr)_2$	5.18	4.83	0.35
2	1,2,3,4-Cl_4; 6-CF_3	2-Pip	4.82	5.18	0.36
3	2,4-$(CF_3)_2$; 7-Cl	2-Pip	4.82	4.34	0.48
4	2,4-$(CF_3)_2$; 6-Cl	2-Pip	4.74	4.47	0.27
5	2,4-$(CF_3)_2$; 6,7-Cl_2	2-Pip	4.47	4.88	0.41
6	2,4,6-Cl_3	2-Pip	4.46	4.26	0.20
7	1,2-Cl_2; 6-CF_3	2-Pip	4.46	4.24	0.22
8	2-CF_3	2-Pip	4.39	3.24	1.15
9	1,3,6-Cl_3	$N(Pr)_2$	4.30	4.00	0.30
10	3-CF_3, 6,7-Cl_2	$N(Pr)_2$	4.30	4.32	0.02

[a] Pip = 2-piperdinyl. [b] Calculated using eq 4. [c] In our previous publication,[13] compound 116 in Table I was listed as 2,4-$(Me)_2$ and was badly predicted; this error resulted because compound 190 in Table I in the paper by Nodiff et al. [E. A. Nodiff, A. J. Saggiomo, K. Tanabe, E. H. Chen, M. Shimbo, M. P. Tyagi, A. Kozuka, H. Otomasu, B. L. Verma, and D. Goff, *J. Med. Chem.*, **18**, 1011 (1975)] is incorrectly labeled, while it is correctly shown in Table X to be 2,4-$(CF_3)_2$.

In our first analysis of Walter Reed data of Vietnam war vintage of analogues of I tested against *P. berghei* in mice, we formulated eq 1 and 2. In these expressions, π_{X+Y} is

$$\log 1/C = 0.33\pi_{X+Y} + 0.85\sigma_{X+Y} + 2.52 \quad (1)$$

$$n = 102;\ r = 0.894;\ s = 0.278$$

$$\log 1/C = 0.31\pi_{X+Y} + 0.78\sigma_{X+Y} + 0.13\Sigma\pi - 0.015\Sigma\pi^2 + 2.35 \quad (2)$$

$$n = 102;\ r = 0.908;\ s = 0.263$$

the sum of the π constants for substituents in the 1–8 positions of the phenanthrene ring, while $\Sigma\pi$ is this sum plus π for R and R′. These equations correlate the molar concentration of drug necessary to cure 50% of mice of malaria. In all, 107 congeners were studied, but five were dropped because they were very poorly fit. The most interesting feature of eq 1 is that it correlates 80% of the variance in log $1/C$ without considering R and R′. Considering the hydrophobic character of R and R′ in eq 2 results in a small (about 2%) but significant improvement over eq 1. This could have been brought out more clearly if more analogues with either very small or very large R groups had been tested. Equation 2 gave an ideal $\Sigma\pi_0$ of 4.4.

After the publication of eq 1 and 2, new data on phenanthrenes and structures of types VI–X became available. Fitting these new data to the same forms as eq 1 and 2 yields eq 3 and 4.[13] Although the sharpness of

$$\log 1/C = 0.29\pi_{X+Y} + 0.97\sigma_{X+Y} + 2.53 \quad (3)$$

$$n = 212;\ r = 0.849;\ s = 0.328$$

$$\log 1/C = 0.29\pi_{X+Y} + 0.90\sigma_{X+Y} + 0.11\Sigma\pi - 0.013\Sigma\pi^2 + 2.41 \quad (4)$$

$$n = 212;\ r = 0.860;\ s = 0.319$$

the new correlations is not as good as eq 1 and 2, the predictive ability illustrated in Table I is good. The 10 most active members of each set are listed in Table I along with the observed and calculated (eq 4) activities. Seven of the 10 of the second 109 congeners are more active than any of those in set I, yet 9 out of 10 are reasonably well predicted by eq 4. The coefficients of eq 4 are close to those of eq 2 and π_0 (4.1) is also in good agreement. Very little information that was not known at the time eq 2 was derived was gained for the SAR in the testing of over 100 new congeners.

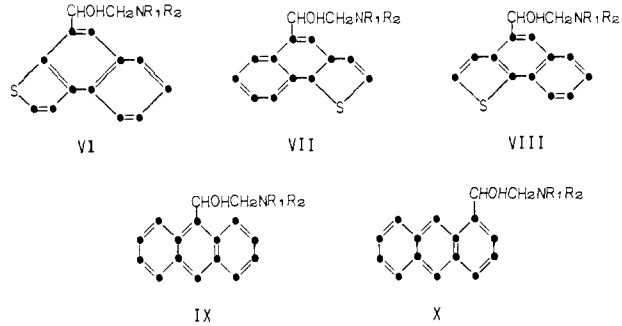
A slight change in the use of σ in eq 3 and 4 was made. In eq 3 and 4, σ_m was used for substituents in positions 2, 4, 6, and 8, and σ_p was used for positions 1, 3, 5, and 7. We erred in the derivation of eq 1 and 2 in using σ_p for groups in the 6 and 8 position. This makes only a slight difference in the results.

Equations 2 and 4 clearly show the predictive value of QSAR and the importance of avoiding redundancy in drug design. A variety of other examples also support the predictive value of QSAR.[14]

Moreover, as Unger[15a] and others[4] have pointed out, the redundancy in the first set of 102 congeners is great. Unger clustered the 102 congeners on the basis of π_{X+Y} and σ_{X+Y}; then, using interactive APL, he made 50 random draws of 10 compounds each from the clusters. Fifty correlation equations were derived, one for each set of 10 congeners, and their coefficients averaged to give eq 5. Note that

$$\log 1/C = 0.29(\pm0.05)\pi_{X+Y} + 0.90(\pm0.1)\sigma_{X+Y} + 2.6(\pm0.2) \quad (5)$$

$$n = 10;\ r = 0.90 \pm 0.06$$



the coefficients and quality of correlation in eq 5 are very close to those of eq 1.

Unger illustrated the value of cluster analysis[15a] in drug design by repeating the above process; however, instead of selecting one congener from each cluster, all 10 were selected from the same large cluster which contained 43 members. Averaging the 50 derived correlation equations as before yields eq 6. Even the coefficients in this equation

$$\log 1/C = 0.20(\pm 0.3)\pi_{X+Y} + 0.80(\pm 0.6)\sigma_{X+Y} + 2.7(\pm 0.8) \quad (6)$$

$$n = 10;\ r = 0.60 \pm 0.1$$

are close to those of eq 1; however, the standard deviations on r and the coefficients are quite large and the correlation coefficient (r) is very low; hence, any given equation out of the 50 might give quite misleading information. Unger's study clearly illustrates the value of the proper selection of substituents in drug design.

Since we were most interested in showing predictive values of QSAR, we did not attempt to use indicator variables[16,17] in deriving eq 3 and 4 to improve the correlation. Our aim in this report has been to encompass the widest variety of arylcarbinols into a QSAR to summarize and better define the work on this important class of antimalarials. The data in Table II (see paragraph concerning supplementary material) have been used to formulate eq 7–10.

Method

Our approach to the development of an overall QSAR for the arylcarbinol antimalarials of Table II (supplementary material) has been to first study subsets having a common aryl unit and then merge these into a final QSAR (eq 10). The parent partition coefficients for these structures are given in Table III. We have placed the definition of the symbols used for the aryl moieties of Table II (supplementary material) in Table IV. We have also indicated the numbering system used for the various rings; in some instances this is not standard but has been used to parallel that of phenanthrene as much as possible. The phenanthrene congeners constitute the largest and best-behaved set and we have elected to use them as the archetypical congener; this has been of help to us in parameterizing and organizing the other congeners.

We have derived a "best" equation for each of the three major subsets and then shown its stepwise development. We have given the best equation (lowest standard deviation) in each class in the stepwise development tables; that is, we have listed the best one-variable, two-variable equation, etc., regardless of the terms which occur therein.

Phenanthrene Analyses. We have reevaluated all of our previous log $1/C$ values for phenanthrene.[4,13] Wherever possible in this report, the mol/kg concentration was determined by a linear interpolation between the concentration required to cure two mice and that required for three mice; that is, log $1/C$ in Table II refers to the molar concentration (mol/kg) of drug necessary to cure 2.5 out of the 5 test mice. We believe that this gives a more consistent result than plotting all data and attempting to draw the best line for estimating the 2.5 end point. In those instances where a high enough concentration to cure 3 mice was not tested, a linear extrapolation was made from the highest cure (1 or 2) to the 2.5 level. If only a 4 or 5 cure concentration (mg/kg) was given, extrapolation was made from the 4-cure concentration. When doses for several equivalent cures were found, these were averaged. Values were calculated and then averaged when data on two isomers (erythro and threo) were given. As in our first report,[4] for those drugs which did not achieve any cures, a linear extrapolation to the concentration needed to give an increase in lifespan of 30 days was made. The choice in the number of days was arbitrary; however, it seems to be a fortunate one, since the use of an indicator variable in the QSAR can serve to combine two types of data. Sixty-day survival is taken as cure in the Rane mouse test.

Careful reexamination of our previous log $1/C$ values has led us to conclude that seven of these (**99–101**, **104–107**) in Table I of ref 4 must really be considered as inactive. These have not been included in Table II, but are placed in Table XIII.

To account for electronic effects, σ was chosen with respect to the side-chain attachment; that is, for the phenanthrene ring, σ_p was used for positions 1, 3, 5, 7, and 10 and σ_m was used for the 2, 4, 6, and 8 positions. Attempts in earlier studies to factor electronic effects by position using $\mathcal{F}$ and $\mathcal{R}$ did not give significantly better results and of course required many more parameters.

In our first studies we were limited by the lack of log P values to the use of π constants for hydrophobic effects; to remedy this situation, we have prepared some typical arylcarbinols shown in Table III. Only one log P was measured for the quinoline and pyridine homologues in Table III from which the others were calculated using phenanthrene data (see footnotes). The log P values were determined between 1-octanol and 0.1 N HCl. We are assuming that it is the protonated form of the drug which is transported under physiological conditions. This is not a vital assumption because the difference between protonated and unprotonated species would be reasonably constant. All compounds in Table III are unsubstituted on the aryl ring. In order to test additivity principles, we measured log P values on five substituted phenanthrenes obtained from the Walter Reed files (ring substituents are given first, followed by side chain; examples 1–5).

(1) 3,6-Cl_2; $CHOHCH_2N(Pr)_2$

$$\log P_{\text{parent molecule (Table I)}}(1.69) + 2\pi_{Cl}(1.42) = 3.11$$

observed log P = 3.31

(2) 2,3-Cl_2, 6-CF_3; $CHOHCH_2N(Pr)_2$

$$\log P_{\text{parent molecule}}(1.69) + 2\pi_{Cl}(1.42) + \pi_{CF_3}(0.88) = 3.99$$

observed log P = 3.79

(3) 3,7-Br_2; $CHOHCH_2N(Pr)_2$

$$\log P_{\text{parent molecule}}(1.69) + 2\pi_{Br}(1.72) = 3.41$$

observed log P = 3.63

(4) 10-Br; $CHOHCH_2N(Bu)_2$

$$\log P_{\text{parent molecule}}(2.57) + \pi_{Br}(0.86) = 3.43$$

observed log P = 3.23

(5) 2,4-$(CF_3)_2$, 6,7-Cl_2; $CHOHCH_2N(Pr)_2$

$$\log P_{\text{parent molecule}}(1.69) + 2\pi_{Cl}(1.42) + 2\pi_{CF_3}(1.76) = 4.87$$

observed log P = 4.77

In two of the examples (2 and 5) one would expect and one finds slightly lower log P values because two substituents are adjacent to each other; however, the other examples are not in as good agreement as one sometimes finds. In any case, we believe that the accuracy of the physicochemical parameters is considerably better than that of the biological data.

To calculate log P values for substituted phenanthrene carbinols, log P values of Table III plus π constants[18] from

the benzene system were used. The benzylic OH was esterified in a number of congeners; this moiety is specified in Table II by being set off by a colon. Preliminary calculations showed that the best results for these esters were obtained by using log P for the unesterified congener. It is possible that the ester groups are quickly hydrolyzed.

Branched alkyl groups occur in the side chain in several examples. We have used −0.2 for the branching factor for each alkyl group in calculating log P for these.

We have had to use fragment constants in a few instances[19] to calculate log P. The symbol f refers to log P for a fragment, while F refers to a bond factor or an interaction between two electronegative groups separated by one (F_{P_1}) or two (F_{P_2}) carbon atoms. The details on the calculation of F_{P_1} and F_{P_2} are to be published later.[20]

2-Phenylquinolines. The largest number of the quinoline derivatives (**218–433**) are 2-phenylquinolines. In parameterizing substituents in this system, we have used σ_p for positions 3, 6, 8, 2′, and 4′ (the prime positions are on the 2-phenyl moiety). For positions 2, 5, 7, 3′, and 5′, σ_m has been used. It was surprising to find that if $\sum\sigma$ was factored into two terms, one for the 2-phenyl ring and one for the quinoline ring, no improvement in correlation was found. The coefficients of the two terms were essentially identical.

The hydrophobic properties of the two rings differ significantly. A better correlation was obtained by setting π constants to zero for substituents on the 2-phenyl moiety; hence, $\sum\pi$ for quinolines refers only to groups on the quinoline ring.

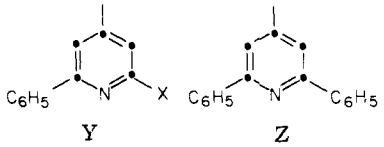
2-X-Quinolines. A number of quinolines with substituents other than phenyl in the 2 position were studied and their log P values calculated. For cases where X = CF_3 (0.88), $C(Me)_3$ (1.98), adamantyl (3.30), OC_6H_5 (2.08), NHC_6H_5 (1.37), COC_6H_5 (1.05), or thienyl (1.61), the π values in parentheses were used as follows:

$$\log P_{\text{2-X-quinoline-4-CHOHCH}_2\text{NRR}'} = \log P_{\text{2-phenylquinoline-4-CHOHCH}_2\text{NRR}'} - \pi_{C_6H_5}(1.96) + \pi_X$$

The π value was not added to $\sum\pi$ for the X substituents themselves. Indicator variables were tested to account for special steric and/or nonspecific interaction of these substituents. The σ_m for each of these substituents was added to $\sum\sigma$. In a number of instances, substituents are present on OC_6H_5 and NHC_6H_5; we have simply added σ for these substituents to $\sigma_{OC_6H_5}$ or $\sigma_{NHC_6H_5}$ and then added this sum to $\sum\sigma$. Although it is realized that this is not a strictly correct way to handle the electronic effect of 2 substituents, in general, it appears to be a reasonable approximation. Since we have explored the use of indicator variables with 2-CF_3, 2-OC_6H_5, and 2-NHC_6H_5, electronic and hydrophobic information which we cannot properly and directly parameterize were carried in these terms. In the end, these indicator variables did not turn out to be significant.

Pyridines. Most of the pyridines were 2,6-diphenyl derivatives whose log P values were calculated using data of Table III. A number of variations were calculated as follows:

$$\log P_y = \log P_z - \pi_{C_6H_5} + \pi_x$$

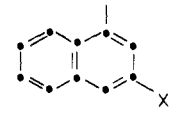


Y Z

where π_x = $CH{=}CHC_6H_5$ (2.68), COC_6H_5 (1.05), CF_3 (0.88), $C(Me)_3$ (1.96), adamantyl (3.30).

Miscellaneous (492–646). For the thiaphenanthrenes (e.g., **506–519**) the figure of 0.32 (difference between log $P_{C_6H_5}$ and log $P_{\text{thiophene}}$) was subtracted from the appropriate phenanthrene log P. Since log P for anthracene is 0.01 less than that of phenanthrene, this conversion factor was used for anthracene congeners (e.g., **520–528**).

Log P for naphthalene analogues of the type



were calculated as follows:

$$\log P_{\text{3-X-naphthalene-1-CHOHCH}_2\text{NR}_2} = \log P_{\text{phenanthrene-9-CHOHCH}_2\text{NR}_2} - \log P_{\text{phenanthrene}} + \log P_{\text{naphthalene}} + \pi_X \text{ (e.g., 529–542)}$$

For each of the following nuclei (see Table IV for definition), σ was selected as follows for the ring positions:

Q2, Q4, Q5, Q7

σ_m: 2, 4, 5, 7, 3′, 5′

σ_p: 3, 6, 8, 2′, 4′

Q3, Q6, Q8

σ_m: 3, 6, 8, 3′, 5′

σ_p: 2, 4, 5, 7, 2′, 4′

P1, P3

σ_m: 2, 4, 6, 8, 9

σ_p: 1, 3, 5, 7, 10

P, P4

σ_m: 2, 4, 6, 8

σ_p: 1, 3, 5, 7, 10

A1, A9

σ_m: 1, 3, 6, 8

σ_p: 2, 4, 5, 7, 10

N1

σ_m: 3, 6, 8, 3′, 5′

σ_p: 2, 4, 5, 7, 2′, 4′

T1, T5, T7, T17

σ_m: 2, 4, 6, 8

σ_p: 1, 3, 5, 7, 10

PY

σ_m: 3′, 5′, 3″, 5″

σ_p: 2′, 4′, 2″, 4″

Synthesis of New Phenanthrene Carbinols. In addition to eight known phenanthrene carbinols [compounds 1–7, Table III, and $CH_2N(C_8H_{17})_2$], four new derivatives were prepared. Compounds 1–3 were prepared

		mp, °C	% yield	solvent for recrystn
(1)	$CH_2NHC_2H_5$	152.5–153.5	27	acetone + hexane
(2)	$CH_2NHC_3H_7$	134–136	32	acetone + hexane
(3)	$CH_2NHC_4H_9$	189–190	45	ethyl acetate + methanol
(4)	2-piperidinyl	288–290	22	ethyl acetate + methanol

Table II. Parameters Used in the Derivation of Equations 7-10

no.	substituents	symbol	log 1/C calcd[a]	log 1/C obsd	log 1/C calcd[b]	|Δ log 1/C|	ref[c]
1	2,4-$(CF_3)_2$, 6,7-Cl_2; $N(Pr)_2$	P	4.58	5.18	4.32	0.86	1
2	2,4-$(CF_3)_2$, 7-Cl; 2-Pip	P	4.29	4.82	4.12	0.70	1
3	1,2,3,4-Cl_4, 6-CF_3; 2-Pip	P	4.58	4.75	4.22	0.53	1
4	3,6-$(CF_3)_2$; CH_2NHBu	P	4.38	4.73	4.25	0.48	1
5	3,6-$(CF_3)_2$; $CH_2NH(t\text{-Bu})$	P	4.39	4.73	4.25	0.48	1
6	2,4-$(CF_3)_2$, 6-Cl; 2-Pip	P	4.40	4.72	4.20	0.52	1
7	1,3-Cl_2, 6-CF_3; CH_2NHBu	P	4.39	4.62	4.30	0.32	34
8	3,6-$(CF_3)_2$; $CH_2NH(c\text{-}C_6H_{11})$	P	4.14	4.53	4.08	0.44	1
9	1,3-Cl_2, 6-CF_3; NHBu	P	4.09	4.48	3.98	0.50	34
10	2,4-$(CF_3)_2$, 6,7-Cl_2; 2-Pip	P	4.59	4.48	4.32	0.16	1
11	3,6-$(CF_3)_2$; NH(Pr)	P	4.06	4.48	3.90	0.58	1
12	1,3-Cl_2, 6-CF_3; $CH_2N(Bu)_2$	P	4.36	4.47	4.29	0.18	1
13	2,4,6-$(CF_3)_3$; 2-Pip	P	4.48	4.47	4.27	0.20	1
14	2,4,6-Cl_3; 2-Pip	P	4.25	4.46	4.07	0.39	1
15	1,2-Cl_2, 6-CF_3; 2-Pip	P	4.10	4.45	3.91	0.53	1
16	2,4-Cl_2, 6-CF_3; 2-Pip	P	4.32	4.43	4.13	0.29	1
17	3,4-Cl_2, 6-CF_3; 2-Pip	P	4.10	4.40	3.91	0.48	1
18	2-CF_3; 2-Pip	P	3.43	4.39	3.39	1.00	1
19	3,6-$(CF_3)_2$; NHEt	P	4.04	4.39	3.88	0.51	1
20	3,6-$(CF_3)_2$; NH(4-Hept)	P	4.05	4.33	3.93	0.40	1
21	2,4-$(CF_3)_2$; $N(Pr)_2$	P	3.97	4.31	3.85	0.46	34
22	2,3-Br_2, 6-CF_3; $N(Bu)_2$	P	4.13	4.31	3.98	0.33	1
23	3-CF_3, 5,7-Cl_2; 2-Pip	P	4.18	4.30	4.04	0.26	1
24	3-CF_3, 6,7-Cl_2; $N(Pr)_2$	P	4.20	4.30	3.98	0.32	1
25	1,3-Cl_2, 6-CF_3; $N(Bu)_2$	P	4.07	4.29	3.98	0.31	1
26	2,5,7-Cl_3; 2-Pip	P	4.01	4.29	3.91	0.38	1
27	2,4-Br_2, 6-CF_3; $N(Bu)_2$	P	4.37	4.28	4.21	0.07	1
28	2,6-Br_2; $N(Pr)_2$	P	3.90	4.27	3.79	0.47	1
29	3,4-Cl_2, 6-CF_3; $N(Pent)_2$	P	4.02	4.26	3.89	0.37	1
30	3-CF_3, 6-Cl; 2-Pip	P	3.98	4.25	3.84	0.41	1
31	3,6-$(CF_3)_2$; NHMe	P	4.01	4.23	3.84	0.39	1
32	3,6-$(CF_3)_2$; $CH_2N(Pr)_2$	P	4.39	4.23	4.25	0.02	1
33	2,4-Br_2; $N(Bu)_2$	P	3.90	4.22	3.82	0.40	1
34	2,4,6-Cl_3; $N(Bu)_2$	P	4.23	4.21	4.08	0.13	1
35	3,5,7-Cl_3; $N(Bu)_2$	P	3.89	4.21	3.84	0.37	1
36	1,3-Br_2, 6-CF_3; 2-Pip	P	4.14	4.20	4.03	0.17	1
37	3,6-$(CF_3)_2$; NH(3-Pent)	P	4.07	4.20	3.93	0.27	1
38	2,3-Cl_2, 6-CF_3; 2-Pip	P	4.10	4.19	3.91	0.27	1
39	1,3,6-Br_3; $N(Bu)_2$	P	4.07	4.19	4.00	0.19	1
40	1,3,6-Cl_3; $N(Pr)_2$	P	4.01	4.19	3.91	0.28	1
41	2-CF_3, 7-Cl; 2-Pip	P	3.77	4.19	3.69	0.50	1
42	2,4-$(CF_3)_2$; 2-Pip	P	3.97	4.19	3.84	0.34	1
43	2,3,5,7-Cl_4; $N(Bu)_2$	P	4.17	4.18	4.02	0.16	1
44	2,3,5,6-Cl_4; $N(Bu)_2$	P	4.18	4.18	3.96	0.22	1
45	2,3,6,7-Cl_4; $N(Bu)_2$	P	4.18	4.18	3.96	0.22	1
46	2,6-Br_2; $N(Bu)_2$	P	3.90	4.17	3.82	0.35	1
47	2,6-Br_2; 2-Pip	P	3.90	4.13	3.79	0.34	1
48	2,4,7-Cl_3; $N(Bu)_2$	P	4.12	4.12	4.00	0.12	1
49	2,6-Cl_2; 2-Pip	P	3.80	4.12	3.70	0.42	1
50	3,6-$(CF_3)_2$; $CH_2N(Et)_2$	P	4.37	4.12	4.22	0.10	1
51	1,3,6-Cl_3; 2-Pip	P	4.01	4.12	3.91	0.21	1
52	3-CF_3, 7-Cl; 2-Pip	P	3.86	4.12	3.76	0.36	1
53	3,6-$(CF_3)_2$; CH_2-2-Pip	P	4.07	4.11	3.93	0.18	1
54	3,6-$(CF_3)_2$; 2-(H_8-quinoline)	P	3.80	4.11	3.75	0.36	1
55	3,6-$(CF_3)_2$; NHBu	P	4.07	4.11	3.92	0.19	1
56	3,6-$(CF_3)_2$; $N(Bu)_2$	P	4.07	4.10	3.93	0.17	1
57	1,3-Cl_2, 6-CF_3; 2-Pip	P	4.09	4.10	3.97	0.12	1
58	3-Cl, 6-CF_3; 2-Pip	P	3.77	4.09	3.69	0.40	1
59	2-Cl, 6-CF_3; 2-Pip	P	3.89	4.07	3.77	0.30	1
60	2-Br, 6-CF_3; $N(Bu)_2$	P	3.94	4.07	3.84	0.23	1
61	2,6-Cl_2; $N(Pr)_2$	P	3.81	4.06	3.71	0.35	1
62	2,6-Cl_2; $N(Et)_2$	P	3.77	4.06	3.66	0.40	1
63	1,3,5,7-Cl_4; $N(Bu)_2$	P	4.15	4.05	4.08	0.03	1
64	2-Cl, 5-CF_3; 2-Pip	P	3.98	4.05	3.84	0.21	1
65	3,4-Cl_2, 6-CF_3; $N(Pr)_2$	P	4.10	4.03	3.92	0.11	1
66	3,6-$(CF_3)_2$; $CH_2N(Bu)_2$	P	4.37	4.03	4.25	0.22	1
67	3-CF_3, 6,7-Cl_2; 2-Pip	P	4.20	4.02	3.98	0.04	1
68	2,6-Cl_2; $N(Pent)_2$	P	3.80	4.01	3.74	0.27	1
69	3,6-$(CF_3)_2$; 2-Pip	P	4.06	3.99	3.91	0.08	1
70	3,4-Cl_2, 6-CF_3; $N(Bu)_2$	P	4.08	3.98	3.92	0.06	1
71	2,3,6-Br_3; $N(Bu)_2$	P	4.10	3.97	3.95	0.02	1
72	2-Br, 6-CF_3; 2-Pip	P	3.93	3.96	3.82	0.14	1
73	3,6-Br_2; $N(Pr)_2$	P	3.77	3.95	3.70	0.25	1
74	2,7-Br_2, 10-OMe; $N(Bu)_2$	P	3.55	3.94	3.57	0.37	1
75	2,4-$(CF_3)_2$; $N(Me)_2$	P	3.92	3.94	3.79	0.15	1

Table II (*Continued*)

no.	substituents	symbol	log 1/C calcd[a]	log 1/C obsd	log 1/C calcd[b]	|Δ log 1/C|	ref[c]
76	3,4-Cl_2, 6-CF_3; $N(Hept)_2$	P	3.75	3.92	3.71	0.21	1
77	3,6-$(CF_3)_2$; $N(Pr)_2$	P	4.06	3.92	3.91	0.01	1
78	2,3-Cl_2, 6-Br; 2-Pip	P	4.07	3.91	3.89	0.02	1
79	2,5,7-Cl_3; $N(Bu)_2$	P	4.00	3.91	3.92	0.01	1
80	1,3,6-Cl_3; $N(Et)_2$	P	4.00	3.90	3.88	0.02	1
81	3,6-$(CF_3)_2$; $CH_2NH(i\text{-}Pr)$	P	4.38	3.89	4.24	0.35	1
82	3,6-$(CF_3)_2$; 3-Pip	P	4.06	3.89	3.91	0.02	1
83	3,6-Cl_2; CH_2-2-Pip	P	3.70	3.89	3.64	0.25	1
84	3,6-$(CF_3)_2$; $N(Hept)_2$	P	3.81	3.89	3.79	0.10	34
85	3,6-$(CF_3)_2$; $CH_2N(Pent)_2$	P	4.30	3.89	4.22	0.33	1
86	2,4-Cl_2, 6-SMe; $N(Bu)_2$	P	4.04	3.88	3.93	0.05	2
87	3-CF_3, 6-Cl; $N(Bu)_2$	P	3.99	3.88	3.87	0.01	1
88	3-CF_3, 6-Br; 2-Pip	P	4.03	3.86	3.88	0.02	1
89	3,6,7-Cl_3; 2-Pip	P	3.91	3.86	3.77	0.09	1
90	2,6-$(CF_3)_2$; 2-Pip	P	3.97	3.85	3.84	0.00	1
91	2-SMe, 5,6-Cl_2; $N(Bu)_2$	P	3.82	3.84	3.71	0.13	2
92	2,6-Cl_2; $N(Bu)_2$	P	3.83	3.81	3.74	0.07	1
93	1,3-Cl_2, 6-Br; 2-Pip	P	4.06	3.81	3.95	0.14	1
94	3,6-$(CF_3)_2$; $NH(i\text{-}Pr)$	P	4.05	3.80	3.89	0.09	1
95	3,6-Cl_2; $N(Bu)_2$	P	3.71	3.79	3.66	0.13	1
96	1,3,7-Cl_3; 2-Pip	P	3.90	3.79	3.83	0.04	1
97	2-CF_3; $N(Bu)_2$	P	3.48	3.79	3.45	0.34	1
98	3,6-$(CF_3)_2$; NH(Hex)	P	4.06	3.78	3.93	0.15	1
99	6-Br; $N(Hept)_2$:$OPO(OPh)_2$	P	3.31	3.75	3.38	0.37	34
100	2-SMe, 6,7-Cl_2; $N(Bu)_2$	P	3.82	3.74	3.71	0.03	2
101	2,4-Cl_2, 6-CF_3; $N(Bu)_2$	P	4.30	3.74	4.14	0.40	1
102	2-SO_2Me, 6,7-Cl_2; $N(Bu)_2$	P	3.78	3.74	3.50	0.24	1
103	1,3-Cl_2; 2-Pip	P	3.57	3.73	3.54	0.19	1
104	5-CF_3; 2-Pip	P	3.52	3.73	3.46	0.27	1
105	3,6-Br_2; $N(Pent)_2$	P	3.73	3.72	3.71	0.01	1
106	1,3,6-Cl_3; $N(Bu)_2$	P	4.00	3.72	3.92	0.20	1
107	3,6-$(CF_3)_2$; $C_2H_4N(Hept)_2$	P	3.63	3.72	3.66	0.06	34
108	3,6-$(CF_3)_2$; $NH(c\text{-}C_6H_{11})$	P	3.84	3.72	3.76	0.04	1
109	3-I, 6-CF_3; $N(Bu)_2$	P	3.80	3.72	3.77	0.05	1
110	2,7-Cl_2, 10-OMe; $N(Bu)_2$	P	3.48	3.71	3.50	0.21	1
111	3-Br, 6-CF_3; 2-Pip	P	3.80	3.70	3.73	0.03	1
112	2,3,6-Cl_3; 2-Pip	P	4.03	3.69	3.85	0.16	1
113	2-Cl, 6-CF_3; $N(Bu)_2$	P	3.90	3.69	3.80	0.11	1
114	2-Cl, 6-CF_3; $N(Hept)_2$	P	3.67	3.68	3.68	0.00	1
115	4-CF_3, 7-Cl; 2-Pip	P	3.77	3.66	3.69	0.03	1
116	3-Cl, 6-CF_3; $N(Bu)_2$	P	3.79	3.65	3.72	0.07	1
117	3,6-Br_2; $N(Bu)_2$	P	3.77	3.63	3.72	0.09	1
118	4-CF_3; 2-Pip	P	3.43	3.62	3.39	0.23	1
119	3-Cl, 6-CF_3; $N(Hept)_2$	P	3.55	3.61	3.60	0.01	1
120	3,6-Br_2; $NH(t\text{-}Bu)$	P	3.77	3.61	3.70	0.09	1
121	2,3-Br_2, 6-CF_3; 2-Pip	P	4.17	3.58	3.98	0.40	1
122	2-SO_2Me, 5,6-Cl_2; $N(Bu)_2$	P	3.78	3.57	3.50	0.07	2
123	6-CF_3; $N(Hept)_2$	P	3.34	3.56	3.40	0.16	1
124	3-I, 6-CF_3; $N(Hept)_2$	P	3.51	3.55	3.60	0.05	1
125	6-Br; $N(Hept)_2$	P	3.31	3.55	3.38	0.17	1
126	1,2-Cl_2 6-CF_3; $N(Bu)_2$	P	4.08	3.55	3.92	0.37	1
127	3,6-$(CF_3)_2$; $NH(CH_2)_3CH(OEt)_2$	P	4.07	3.55	3.93	0.38	1
128	4,6-$(CF_3)_2$; 2-Pip	P	3.97	3.54	3.84	0.30	1
129	1,3-Cl_2, 6-CF_3; $N(Hept)_2$	P	3.74	3.53	3.77	0.24	1
130	6-Br; $N(Hept)_2$:O-succinate	P	3.31	3.52	3.38	0.14	34
131	4-Br, 6-CF_3; $N(Bu)_2$	P	3.94	3.52	3.84	0.32	1
132	5,7-Cl_2; 2-Pip	P	3.57	3.52	3.54	0.02	1
133	3,6-Br_2; $N(Hex)_2$	P	3.65	3.51	3.67	0.16	1
134	2-Br; $N(Bu)_2$	P	3.44	3.50	3.42	0.08	1
135	3,6-Cl_2; 2-Pip	P	3.69	3.50	3.62	0.12	1
136	6-Br; 2-Pip	P	3.39	3.49	3.36	0.13	1
137	3,6-Cl_2; 2-pyrolidine-NMe	P	3.47	3.46	3.46	0.00	34
138	3,6-Br_2; $N(Hept)_2$	P	3.52	3.45	3.58	0.13	1
139	6-Br; 2-Pip-NMe	P	3.42	3.44	3.40	0.04	1
140	6-Br; $N(Hept)_2$-NO	P	3.44	3.43	3.44	0.01	1
141	3-CF_3; 2-Pip	P	3.52	3.43	3.46	0.03	1
142	1-Br, 6-CF_3; $N(Hept)_2$	P	3.55	3.43	3.61	0.18	1
143	6,10-Br_2; $N(Hept)_2$	P	3.52	3.42	3.58	0.16	34
144	6-CF_3; 2-Pip	P	3.43	3.37	3.39	0.02	1
145	3,6-Cl_2; $NH(c\text{-}C_6H_{11})$	P	3.48	3.36	3.49	0.13	1
146	2,7-Br_2, 10-OMe; $N(Hept)_2$	P	3.30	3.35	3.43	0.08	1
147	6-OCF_3; 2-Pip	P	3.42	3.34	3.40	0.06	1
148	1,2,6,7-Cl_4; $N(Bu)_2$	P	4.18	3.34	3.96	0.62	1
149	2,7-Cl_2, 10-OMe; $N(Hept)_2$	P	3.27	3.34	3.39	0.05	1
150	1,6-Br_2; $N(Hept)_2$	P	3.51	3.33	3.58	0.25	34

Table II (*Continued*)

no.	substituents		symbol	log 1/C calcd[a]	log 1/C obsd	log 1/C calcd[b]	|Δ log 1/C|	ref[c]
151	10-Br; $N(Hept)_2$		P	3.17	3.33	3.29	0.04	1
152	3-SO_2Me, 6-CF_3; 2-Pip		P	3.58	3.32	3.35	0.03	1
153	3,6-Br_2; 2-Pip		P	3.76	3.31	3.70	0.39	1
154	2,6-$(SMe)_2$; $N(Bu)_2$		P	3.43	3.30	3.45	0.15	2
155	2-Br; 2-Pip		P	3.39	3.25	3.36	0.11	1
156	2-Cl, 7-CF_3; 2-Pip		P	3.98	3.25	3.84	0.59	1
157	1,3-$(Me)_2$, 6-CF_3; 2-Pip		P	3.38	3.25	3.45	0.20	1
158	7,8-$(CH)_4$; $N(Hept)_2$		P	3.07	3.25	3.24	0.01	34
159	6-CF_3; $N(Bu)_2$		P	3.48	3.23	3.45	0.22	1
160	6,10-Br_2; $N(Bu)_2$		P	3.77	3.23	3.72	0.49	1
161	7-CF_3; 2-Pip		P	3.52	3.22	3.46	0.24	1
162	6-Br; 2-Pip-NBu		P	3.44	3.22	3.44	0.22	1
163	3,6-$(t\text{-}Bu)_2$; $N(Bu)_2$		P	3.22	3.19	3.51	0.32	1
164	3-CF_3, 6-Me; 2-Pip		P	3.58	3.16	3.55	0.39	1
165	3-Me, 6-CF_3; 2-Pip		P	3.41	3.16	3.43	0.27	1
166	2,3-(OCH_2O), 6-Cl; 2-Pip		P	3.09	3.14	3.07	0.07	1
167	3-CF_3; $N(Hept)_2$		P	3.43	3.12	3.47	0.35	1
168	3,6-Cl_2; $N(Hept)_2$		P	3.50	3.12	3.55	0.43	1
169	2-Cl; $N(Hept)_2$		P	3.28	3.09	3.35	0.26	1
170	5-Cl; $N(Hept)_2$		P	3.17	3.09	3.27	0.18	1
171	6-F; $N(Hept)_2$		P	3.22	3.08	3.26	0.18	1
172	2-Cl; $N(Bu)_2$		P	3.39	3.01	3.38	0.37	1
173	—; $CH_2N(Hept)_2$		P	3.20	3.00	3.35	0.35	1
174	3-Cl, 6-OMe; $N(Hept)_2$		P	3.26	2.98	3.34	0.36	1
175	6-Br; NEt(2-MeO-5-NH_2-Bzl)		P	3.08	2.97	3.11	0.14	1
176	7-Cl; $N(Hept)_2$		P	3.17	2.97	3.27	0.30	1
177	—; $N(Hept)_2$		P	2.92	2.87	3.05	0.18	1
178	6-Me; 2-Pip		P	2.94	2.83	3.02	0.19	1
179	10-Me; $N(Bu)_2$		P	2.92	2.79	3.03	0.24	1
180	2-Br, 6-SO_2Me; $N(Bu)_2$	(2)	P	2.93	3.43	2.57	0.86	34
181	3,6-Cl_2; quinuclidine	(1)	P	2.84	2.98	2.68	0.30	34
182	3-CF_3, 6-Cl; $N(Hept)_2$	(2)	P	3.12	2.90	2.95	0.05	34
183	1,6-Br_2; $N(Bu)_2$	(2)	P	3.13	2.90	2.93	0.03	34
184	4-Cl; $N(Hept)_2$	(2)	P	2.64	2.82	2.55	0.26	34
185	3-CF_3; $N(Bu)_2$	(2)	P	2.93	2.80	2.72	0.08	34
186	6-Cl; $N(Bu)_2$	(2)	P	2.75	2.77	2.58	0.19	34
187	5-Cl; $N(Bu)_2$	(2)	P	2.64	2.77	2.50	0.27	34
188	1-Cl; $N(Bu)_2$	(2)	P	2.64	2.65	2.50	0.15	34
189	2-Cl; N-Pip	(2)	P	2.51	2.56	2.39	0.17	34
190	3,6-$(CF_3)_2$; $CH_2N(Hept)_2$	(E)	P	3.40	3.20	3.26	0.06	16
191	2,7,10-Br_3; $N(Hept)_2$	(E)	P	3.06	3.16	2.97	0.19	35
192	2,7,10-Br_3; $N(Bu)_2$	(E)	P	3.43	3.09	3.20	0.11	34
193	2-Br, 6-SMe; $N(Bu)_2$	(E)	P	3.03	3.04	2.84	0.20	34
194	2,5- or 7-Cl_2; $N(Hept)_2$	(E)	P	2.64	2.79	2.75	0.03	34
195	10-OC_6H_5; $N(Bu)_2$	(E)	P	2.11	2.71	2.62	0.09	35
196	1-OH; $CH_2N(Oct)_2$	(E)	P	2.53	2.65	2.20	0.45	34
197	6-Cl; $N(Hept)_2$	(E)	P	2.64	2.59	2.55	0.03	34
198	6-F; $N(Bu)_2$	(E)	P	2.35	2.58	2.43	0.14	34
199	1-Cl; $N(Hept)_2$	(E)	P	2.53	2.56	2.47	0.08	34
200	—; $N(Oct)_2$	(E)	P	2.86	2.54	2.20	0.34	34
201	—; 2-Pip	(E)	P	2.73	2.53	2.11	0.41	34
202	1-OH; $CH_2N(Hex)_2$	(E)	P	2.21	2.52	2.27	0.25	34
203	10-Cl; $N(Bu)_2$	(E)	P	2.34	2.52	2.50	0.02	35
204	10-Br; $N(Bu)_2$	(E)	P	2.24	2.51	2.54	0.03	34
205	7-Cl; $N(Bu)_2$	(E)	P	2.64	2.51	2.50	0.01	34
206	10-OMe; $N(Hept)_2$	(E)	P	2.67	2.51	2.10	0.41	35
207	3-Cl, 6-OMe; $N(Bu)_2$	(E)	P	2.61	2.49	2.57	0.08	34
208	6-Br; NH-2-norbornyl	(E)	P	2.19	2.49	2.47	0.02	37
209	—; $CH_2N(Bu)_2$	(E)	P	2.38	2.45	2.56	0.11	16
210	6-Br; 2-(1,2,3,4-4*H*-quinoline)	(E)	P	2.58	2.44	2.47	0.03	37
211	3-Cl; $N(Hept)_2$	(E)	P	2.64	2.44	2.47	0.03	34
212	3-F; $N(Bu)_2$	(E)	P	2.58	2.43	2.27	0.15	34
213	-; $N(Hex)_2$	(E)	P	2.64	2.40	2.28	0.12	34
214	3-F; $N(Hept)_2$	(E)	P	2.75	2.32	2.31	0.01	34
215	8-Cl, $N(Bu)_2$	(E)	P	2.06	2.32	2.58	0.26	34
216	6-Br; $N(CH_2)_5$	(E)	P	2.58	2.29	2.47	0.18	37
217	—; NH(*t*-Bu)	(E)	P	2.22	2.09	2.12	0.03	34
218	6,8,3',4'-Cl_4; $CH_2N(Bu)_2$		Q2P	3.90	4.67	4.21	0.46	16
219	6-Cl, 8-CF_3,4'-Cl; $N(Bu)_2$		Q2P	3.97	4.61	4.08	0.53	34
220	6,8-Cl_2, 4'-I; $N(Bu)_2$		Q2P	4.03	4.50	4.06	0.44	9
221	8-CF_3, 4'-Cl; 2-Pip		Q2P	3.88	4.45	3.90	0.55	9
222	6-Me, 7-Cl; 4'-Cl; $N(Bu)_2$		Q2P	3.74	4.22	3.69	0.53	9
223	3-F, 6,8,4'-Cl_3; $N(Bu)_2$		Q2P	3.85	4.22	3.93	0.29	10
224	6,4'-I_2; $N(Bu)_2$		Q2P	3.84	4.22	3.85	0.37	11
225	6,8-Cl_2, 3',4'-Cl_2; $N(Bu)_2$		Q2P	3.95	4.21	3.92	0.29	10

Table II (*Continued*)

no.	substituents	symbol	log 1/C calcd[a]	log 1/C obsd	log 1/C calcd[b]	|Δ log 1/C|	ref[c]
226	7-CF_3, 4'-Cl; $N(Bu)_2$	Q2P	3.70	4.14	3.77	0.37	34
227	6,8-$(Me)_2$, 4'-Cl; 2-Pip	Q2P	3.68	4.04	3.69	0.34	12
228	6,8-Cl_2, 4'-CF_3; $N(Bu)_2$	Q2P	3.91	4.04	4.02	0.02	9
229	6,8,4'-Cl_3; $N(Bu)_2$:OTHP	Q2P	3.79	4.03	3.87	0.15	34
230	6,8-Cl_2, 4'-Cl; $N(Bu)_2$	Q2P	3.79	4.03	3.87	0.15	34
231	6,8-Cl_2, 4'-F; $N(Bu)_2$	Q2P	3.52	3.98	3.64	0.34	9
232	6,8-Cl_2, 4'-Cl; 2-Pip	Q2P	3.93	3.97	3.96	0.01	9
233	8-CF_3, 4'-Me; 2-Pip	Q2P	3.64	3.94	3.66	0.28	9
234	6-OMe, 8-CF_3, 4'-Cl; $N(Bu)_2$	Q2P	3.61	3.93	3.68	0.25	34
235	6,8-Cl_2, 3'-CF_3; $N(Bu)_2$	Q2P	3.71	3.93	3.84	0.09	34
236	7-Cl, 4'-Cl; $N(Bu)_2$	Q2P	3.64	3.91	3.71	0.20	9
237	6,8-$(Me)_2$, 4'-Cl; $N(Bu)_2$	Q2P	3.55	3.90	3.62	0.28	34
238	6,8-Cl_2; 2-Pip	Q2P	3.60	3.90	3.67	0.23	34
239	8-CF_3, 4'-OMe; 2-Pip	Q2P	3.63	3.88	3.63	0.25	12
240	6-OMe, 7,4'-Cl_2; NHBu	Q2P	3.48	3.88	3.40	0.48	14
241	6-OMe, 7,4'-Cl_2; $N(Bu)_2$	Q2P	3.49	3.87	3.41	0.46	34
242	3,6,8,4'-Cl_4; $N(Bu)_2$	Q2P	3.98	3.87	4.10	0.23	10
243	7-Cl, 8-Me, 4'-Cl; $N(Hex)_2$	Q2P	3.58	3.85	3.58	0.27	34
244	6,8,4'-Cl_3; 4-Me-piperazine	Q2P	3.80	3.81	3.88	0.07	9
245	6-Cl, 4'-Cl; $N(Bu)_2$	Q2P	3.57	3.80	3.63	0.17	34
246	6,8-Me_2, 4'-Cl; $N(Hex)_2$	Q2P	3.41	3.75	3.52	0.22	34
247	6,8-Cl_2, 4'-Cl; N(Me)-*i*-Pr	Q2P	3.78	3.72	3.86	0.14	9
248	8-Me, 4'-F; 2-Pip	Q2P	3.22	3.72	3.28	0.44	34
249	3,2'-C_2H_4, 6,8,4'-Cl_2; N-Pip	Q2P	3.83	3.69	3.95	0.26	34
250	8-CF_3, 4'-Cl; $N(Bu)_2$	Q2P	3.76	3.69	3.83	0.14	9
251	7-CF_3, 3',4'-Cl_2; $N(Hex)_2$	Q2P	3.69	3.68	3.70	0.02	34
252	8-CF_3; 2-Pip	Q2P	3.53	3.68	3.59	0.09	34
253	8-Me, 4'-Cl; 2-Pip	Q2P	3.54	3.67	3.55	0.12	34
254	6,8-Cl_2, 2',4'-Cl_2; $N(Bu)_2$	Q2P	3.87	3.66	3.98	0.32	10
255	6,8,3',4'-Cl_4; $NHCH_2C_6H_5$	Q2P	3.80	3.66	3.78	0.12	15
256	6,7-Cl_2, 4'-OMe; $N(Bu)_2$	Q2P	3.68	3.63	3.59	0.04	14
257	7-F, 4'-Cl; $N(Bu)_2$	Q2P	3.53	3.62	3.58	0.04	34
258	6,8-Me_2, 4'-F; 2-Pip	Q2P	3.38	3.61	3.43	0.18	9
259	6,8-Cl_2, 3',4'-Cl_2; NH(c-Pr)	Q2P	3.82	3.60	3.79	0.19	9
260	3,2'-C_2H_4, 6,8,3'-Cl_3; N-Pip	Q2P	3.73	3.60	3.75	0.15	34
261	6,8,4'-Cl_3; NH-1-adamantyl	Q2P	3.58	3.59	3.69	0.10	34
262	7-CF_3, 4'-Cl; $N(Hex)_2$	Q2P	3.58	3.55	3.69	0.14	34
263	6,8,4'-Cl_3; NH(c-pent)	Q2P	3.62	3.53	3.71	0.18	34
264	7-Cl; 2-Pip-6-Me	Q2P	3.30	3.52	3.41	0.11	9
265	6,8,4'-Cl_3; N-Pip	Q2P	3.62	3.49	3.71	0.22	34
266	7-I, 4'-Cl; $N(Bu)_2$	Q2P	3.69	3.43	3.77	0.34	11
267	8-Me; 2-Pip	Q2P	3.18	3.38	3.23	0.14	12
268	6-OMe, 7-Cl, 4'-OMe; $N(Hex)_2$	Q2P	3.25	3.38	3.15	0.23	34
269	6,8-Cl_2, 4'-Cl; $N(Hex)_2$	Q2P	3.61	3.37	3.76	0.39	34
270	6-OMe, 3',4'-Cl_2; $N(Hex)_2$	Q2P	3.28	3.35	3.22	0.13	34
271	6,7-Cl_2, 4'-OMe; $N(Hex)_2$	Q2P	3.58	3.35	3.53	0.18	14
272	6,8-Cl_2; $N(Hex)_2$	Q2P	3.39	3.35	3.54	0.19	9
273	6-OMe, 3',4'-Cl_2; $N(Bu)_2$	Q2P	3.38	3.33	3.29	0.04	9
274	6-Cl, 3',4'-$(OMe)_2$; $N(Bu)_2$	Q2P	3.42	3.33	3.31	0.02	14
275	6-Cl, 3',4'-$(OMe)_2$; $N(Hex)_2$	Q2P	3.39	3.32	3.30	0.02	14
276	7-OMe, 3',4'-Cl_2; $N(Et)_2$	Q2P	3.53	3.32	3.45	0.13	34
277	6-OMe, 7-Cl, 4'-OMe; $N(Bu)_2$	Q2P	3.28	3.32	3.16	0.16	14
278	6,8-Cl_2, 3'-CF_3; $N(Hex)_2$	Q2P	3.51	3.32	3.71	0.39	9
279	8-Cl, 4'-Cl; $N(Hex)_2$	Q2P	3.46	3.32	3.56	0.24	9
280	7-Cl, 3',4'-$(OMe)_2$; $N(Hex)_2$	Q2P	3.47	3.32	3.38	0.06	9
281	7,8-$(CH{=}CH)_2$, 6-Cl, 3',4',5'-$(OMe)_3$; $N(Bu)_2$	Q2P	3.46	3.32	3.24	0.08	22
282	7,4'-Cl_2; $N(Hex)_2$	Q2P	3.54	3.28	3.64	0.36	34
283	3-OMe, 6,8-$(Me)_2$, 4'-Cl; $N(Bu)_2$	Q2P	3.40	3.26	3.46	0.20	10
284	7-Cl, 4'-Cl; NH-1-adamantyl	Q2P	3.45	3.24	3.53	0.29	34
285	7-OMe, 3',4'-Cl_2; $N(Bu)_2$	Q2P	3.59	3.21	3.51	0.30	14
286	7,8-$(CH{=}CH)_2$, 4'-Cl; 2-Pip	Q2P	3.50	3.20	3.49	0.29	34
287	8-Me, 4'-OMe; 2-Pip	Q2P	3.29	3.18	3.27	0.09	12
288	6,8-Cl_2; N-Pip	Q2P	3.31	3.17	3.44	0.27	9
289	6,8-Cl_2, 3'-I; $N(Bu)_2$	Q2P	3.65	3.16	3.79	0.63	11
290	6,4'-$(OMe)_2$, 8-Cl; $N(Hex)_2$	Q2P	3.18	3.15	3.21	0.06	34
291	6-OMe, 3',4'-Cl_2; $N(Et)_2$	Q2P	3.32	3.15	3.23	0.08	14
292	6-Cl, 3',4'-$(OMe)_2$; $N(Oct)_2$	Q2P	3.16	3.15	3.14	0.01	9
293	8-CF_3, 4'-Cl; $N(Hept)_2$	Q2P	3.50	3.13	3.66	0.53	9
294	6-Cl, 3',4'-$(OMe)_2$; $N(Et)_2$	Q2P	3.29	3.12	3.21	0.09	34
295	6-F, 4'-Cl; $N(Bu)_2$	Q2P	3.38	3.11	3.42	0.31	34
296	6-Cl, 3',4'-$(OMe)_2$; $N(Oct)_2$	Q2P	3.16	3.11	3.14	0.03	14
297	7-OMe, 3',4'-Cl_2; $N(Hex)_2$	Q2P	3.49	3.10	3.44	0.34	14
298	7,4'-Cl_2, 8-Me; $N(i\text{-}Pent)_2$	Q2P	3.72	3.09	3.67	0.58	34
299	7-Cl, 3',4'-OCH_2O; $N(Bu)_2$	Q2P	3.28	3.09	3.20	0.11	34
300	6-OMe, 7-Cl; 4'-Cl; $N(Hex)_2$	Q2P	3.39	3.07	3.34	0.27	14

Table II (*Continued*)

no.	substituents		symbol	log 1/C calcd[a]	log 1/C obsd	log 1/C calcd[b]	|Δ log 1/C|	ref[c]
301	7,8-(CH=CH)$_2$, 3,2',4'-(Me)$_3$, 6-Cl; N(Bu)$_2$		Q2P	3.20	3.05	3.30	0.25	22
302	7,8-(CH=CH)$_2$; 2-Pip		Q2P	3.13	3.05	3.17	0.12	34
303	6,7-OCH$_2$O; 4'-Cl; N(Bu)$_2$		Q2P	3.24	2.99	3.13	0.14	34
304	6-OMe, 7-Cl, 4'-OMe; N(Et)$_2$		Q2P	3.15	2.92	3.06	0.14	14
305	6-OMe; N(Bu)$_2$		Q2P	2.83	2.89	2.90	0.01	34
306	6,8-Cl$_2$,4'-OH; N(Bu)$_2$		Q2P	3.35	2.66	3.44	0.78	34
307	5,8-(OMe)$_2$, 4'-Cl; NH-1-adamantyl		Q2P	3.06	2.48	3.11	0.63	34
308	2,8-(CF$_3$)$_2$; 2-Pip		Q2F	3.61	4.41	3.72	0.68	21
309	2,7-(CF$_3$)$_2$; 2-Pip		Q2F	3.55	4.05	3.66	0.39	21
310	2,8-(CF$_3$)$_2$, 6-OMe; 2-Pip		Q2F	3.46	3.98	3.57	0.41	21
311	2,6-(CF$_3$)$_2$; 2-Pip		Q2F	3.61	3.65	3.72	0.07	21
312	2,8-(CF$_3$)$_2$; NHBu		Q2F	3.52	3.65	3.67	0.02	19
313	2,8-(CF$_3$)$_2$; N(Bu)$_2$		Q2F	3.59	3.60	3.73	0.13	19
314	2,8-(CF$_3$)$_2$; CH$_2$NH(*t*-Bu)		Q2F	3.55	3.47	4.02	0.55	19
315	2-CF$_3$, 7,8-(CH)$_4$; 2-Pip		Q2F	3.28	3.44	3.35	0.09	23
316	2-CF$_3$, 6-Cl, 7,8-(CH=CH)$_2$; 2-Pip		Q2F	3.58	3.43	3.65	0.22	23
317	2,8-(CF$_3$)$_2$; CH$_2$-2-Pip		Q2F	3.54	3.36	3.69	0.33	19
318	2,8-(CF$_3$)$_2$; C(Me)$_2$NHBu		Q2F	3.60	3.27	3.74	0.47	19
319	2,6-(CF$_3$)$_2$; CH$_2$N(Bu)$_2$		Q2F	3.62	3.31	4.07	0.76	34
320	2-CF$_3$, 6-OMe; 2-Pip		Q2F	2.89	2.97	3.00	0.03	20
321	2-CF$_3$, 8-Me; 2-Pip		Q2F	3.25	2.93	3.35	0.42	20
322	2-CF$_3$, 6,8-Me$_2$; 2-Pip		Q2F	3.43	2.93	3.54	0.61	20
323	2,8-(CF$_3$)$_2$; NHPr		Q2F	3.46	2.92	3.63	0.71	19
324	2,8-(CF$_3$)$_2$; N(Pr)$_2$		Q2F	3.49	2.88	3.65	0.77	19
325	2-CF$_3$, 6-Me; 2-Pip		Q2F	3.25	2.84	3.35	0.51	34
326	6,8-Cl$_2$, 4'-CF$_3$; N(Bu)$_2$		Q2COP	4.12	4.86	4.23	0.63	18
327	6,3',5'-Cl$_3$, 8-CF$_3$; N(Bu)$_2$		Q2COP	4.26	4.82	4.43	0.39	18
328	6,8-Cl$_2$, 3',5'-(CF$_3$)$_2$; N(Bu)$_2$		Q2COP	4.12	4.64	4.29	0.35	18
329	6-Cl, 8,3'-(CF$_3$)$_2$; N(Bu)$_2$		Q2COP	4.10	4.52	4.26	0.26	18
330	6,3',4'-Cl$_3$, 8-CF$_3$; N(Bu)$_2$		Q2COP	4.37	4.52	4.35	0.17	18
331	6,8,4'-Cl$_3$; N(Bu)$_2$		Q2COP	3.99	4.48	4.08	0.40	18
332	6,4'-Cl$_2$, 8-CF$_3$; N(Bu)$_2$		Q2COP	4.18	3.98	4.28	0.30	18
333	6,8-Cl$_2$; N(Bu)$_2$		Q2COP	3.66	3.03	3.79	0.76	18
334	6,8,4'-Cl$_3$; 2-Pip		Q2OP	4.07	4.16	4.11	0.05	17
335	6,8,3',4'-Cl$_4$; 2-Pip		Q2OP	4.26	4.10	4.17	0.07	17
336	6,4'-Cl$_2$; 2-Pip		Q2OP	3.82	3.23	3.83	0.60	17
337	6-Me, 4'-Cl; 2-Pip		Q2NP	3.44	2.87	3.45	0.58	17
338	2-*t*-Bu, 6-Cl, 7,8-(CH=CH)$_2$; N(Bu)$_2$		Q2TB	3.26	2.98	3.37	0.39	22
339	2-*t*-Bu, 6-Cl; N(Bu)$_2$		Q2TB	3.21	2.91	3.31	0.40	30
340	5'-Br; N(Bu)$_2$		Q2TH	3.09	3.06	3.18	0.12	34
341	5'-Br; N(CH$_2$)$_5$		Q2TH	2.91	2.89	3.01	0.12	34
342	2-adamant-1-yl, 8-CF$_3$; N(Bu)$_2$		Q2AD	3.40	3.59	3.52	0.07	30
343	2-adamant-1-yl, 6,8-Cl$_2$; N(Bu)$_2$		Q2AD	3.41	3.29	3.55	0.26	30
344	6,8,3',4'-Cl$_4$; N(Bu)$_2$		Q2P4H	3.93	3.60	3.91	0.31	25
345	4'-Cl; N(Bu)$_2$		Q3P3N	3.26	2.85	3.31	0.56	24
346	7-Cl; N(Et)$_2$		Q	2.83	3.03	3.04	0.01	34
347	3-Me, 6,8,2',4'-Cl$_4$; N(Bu)$_2$	(2)	Q2P	3.12	3.15	3.15	0.00	10
348	6,8,4'-Me$_3$; 2-Pip	(1)	Q2P	2.75	3.11	2.66	0.45	12
349	3-Me, 6,8,4'-Cl$_3$; N(Bu)$_2$	(2)	Q2P	3.06	3.06	3.06	0.00	10
350	6-Me, 4'-OMe; 2-Pip	(2)	Q2P	2.59	3.00	2.48	0.52	12
351	7-CF$_3$, 4'-Cl; N(Hex)$_2$	(2)	Q2P	2.70	2.85	2.76	0.09	34
352	6-OMe, 3',4'-Cl$_2$; N(C$_2$H$_4$OEt)$_2$	(2)	Q2P	2.68	2.83	2.49	0.34	14
353	7-Cl; N(Oct)$_2$	(1)	Q2P	2.36	2.82	2.45	0.37	9
354	7-Cl, 3',4'-(OMe)$_2$; N(Et)$_2$	(2)	Q2P	2.67	2.81	2.49	0.31	14
355	6,4'-Cl$_2$, 7-OMe; N(Hex)$_2$	(2)	Q2P	2.83	2.80	2.69	0.11	9
356	6,8,4'-Me$_3$; N(Et)$_2$	(2)	Q2P	2.59	2.80	2.55	0.25	9
357	6,4'-Cl$_2$, 7-OMe; N(Bu)$_2$	(2)	Q2P	2.93	2.76	2.76	0.00	32
358	7-Cl; 2-Pip	(1)	Q2P	2.70	2.72	2.66	0.06	34
359	6,8,4'-Me$_3$; N(Bu)$_2$	(2)	Q2P	2.63	2.72	2.59	0.13	32
360	2-Ph-quinine	(2)	Q2P	2.00	2.72	1.97	0.75	22
361	6-Cl; 2-Pip-NMe	(2)	Q2P	2.66	2.70	2.61	0.09	34
362	8-Cl; 2-Pip	(2)	Q2P	2.62	2.69	2.58	0.11	34
363	6,8-Cl$_2$; 4-Ph-piperazine	(1)	Q2P	2.59	2.66	2.63	0.03	13
364	7,4'-Cl$_2$; 4-Me-piperazine	(2)	Q2P	2.76	2.66	2.74	0.08	13
365	6,8-Cl$_2$; NH(c-pent)	(1)	Q2P	2.61	2.54	2.64	0.10	34
366	—; N(Bu)$_2$	(2)	Q2P	2.28	2.54	2.26	0.28	9
367	7-F, 4'-F; N(Bu)$_2$	(1)	Q2P	2.53	2.52	2.53	0.01	13
368	6-Me; 2-Pip	(1)	Q2P	2.49	2.47	2.44	0.03	12
369	2-CF$_3$, 6-Cl; 2-Pip	(1)	Q2F	2.70	2.53	2.70	0.17	20
370	6,8-Me$_2$; 4'-Cl; 2-Pip	(2)	Q2OP	3.12	2.72	3.05	0.33	17
371	4'-Cl; 2-Pip	(2)	Q2OP	2.84	2.68	2.75	0.07	17
372	6,8-Me$_2$, 4'-Cl; 2-Pip	(2)	Q2NP	2.89	2.74	2.81	0.07	17
373	6,4'-Cl$_2$; 2-Pip	(2)	Q2NP	2.88	2.72	2.79	0.07	17
374	4'-Cl; 2-Pip	(1)	Q2NP	2.57	2.52	2.48	0.04	17
375	4'-Cl; N(Bu)$_2$	(E)	Q2P	2.63	2.73	2.57	0.16	34

Table II (*Continued*)

no.	substituents		symbol	log 1/C calcd[a]	log 1/C obsd	log 1/C calcd[b]	|Δ log 1/C|	ref[c]
376	6-Cl, 7-OMe; 4′-OMe; $N(Bu)_2$	(E)	Q2P	2.72	2.71	2.51	0.20	9
377	6-Cl, 7,4′-$(OMe)_2$; $N(Hex)_2$	(E)	Q2P	2.69	2.64	2.50	0.14	9
378	—; $N(Pent)_2$	(E)	Q2P	2.33	2.57	2.30	0.27	9
379	4′-OMe; 2-Pip	(E)	Q2P	2.42	2.53	2.31	0.22	34
380	5,8-$(OMe)_2$, 4′-Cl; $N(Bu)_2$	(E)	Q2P	2.54	2.52	2.47	0.05	34
381	6,8-Cl_2; 4-Me-piperazine	(E)	Q2P	2.62	2.48	2.64	0.16	34
382	7-F, 4′-F; N-Pip	(E)	Q2P	2.32	2.45	2.33	0.12	9
383	6-OMe; $N(Et)_2$	(E)	Q2P	1.94	2.44	1.96	0.48	34
384	6,8-$(Me)_2$, 4′-Cl; CH(Me)$N(Bu)_2$	(E)	Q2P	2.84	2.42	2.82	0.40	34
385	6,4′-Me_2; 2-Pip	(E)	Q2P	2.61	2.42	2.51	0.09	34
386	6,8,2′,6′-Cl_4; $N(Bu)_2$	(E)	Q2P	2.99	2.41	3.04	0.63	34
387	4′-Me; 2-Pip	(E)	Q2P	2.46	2.38	2.35	0.03	34
388	—; 2-Pip	(E)	Q2P	2.32	2.37	2.27	0.10	34
389	6,8-Cl_2; NH-1-adamantyl	(E)	Q2P	2.61	2.36	2.64	0.28	13
390	6-F, 4′-Me; 2-Pip	(E)	Q2P	2.65	2.34	2.55	0.21	32
391	7,4′-F_2; 2-Pip	(E)	Q2P	2.58	2.32	2.54	0.22	13
392	7,4′-F_2; 4-Me-piperazine	(E)	Q2P	2.33	2.27	2.34	0.07	34
393	—; 2-pyrrolidine	(E)	Q2P	1.95	2.26	1.98	0.28	34
394	3′,5′-Me_2; 2-Pip	(E)	Q2P	2.35	2.24	2.27	0.03	34
395	6,8-Cl_2; *N*-morpholino	(E)	Q2P	2.35	2.23	2.43	0.20	34
396	2,8-$(CF_3)_2$; CH_2NHPr	(E)	Q2F	2.83	2.82	2.88	0.06	19
397	2,8-$(CF_3)_2$; NH(*t*-Bu)	(E)	Q2F	2.80	2.64	2.86	0.22	19
398	2,8-$(CF_3)_2$; $C(Me)_2NHEt$	(E)	Q2F	2.81	2.54	2.87	0.33	19
399	2-CF_3, 8-F; 2-Pip	(E)	Q2F	2.43	2.36	2.44	0.08	32
400	2-CF_3, 6-F; 2-Pip	(E)	Q2F	2.43	2.33	2.44	0.11	32
401	7,8-$(CH=CH)_2$, 3-Me, 6-Cl; $N(Bu)_2$	(E)	Q	2.55	2.38	2.56	0.18	22
402	8-CF_3; 2-Pip	(E)	Q	2.54	2.75	2.58	0.17	32
403	2-(1-Me-c-pent), 6,8-Cl_2; $N(Bu)_2$	(E)	Q	2.75	2.66	2.78	0.12	34
404	—; $N(Oct)_2$	(E)	Q	2.28	2.44	2.27	0.17	34
405	7-CF_3; $N(Bu)_2$	(E)	Q	2.51	2.51	2.55	0.04	32
406	2-$CONH_2$, 8-CF_3; 2-Pip	(E)	Q	2.37	2.42	2.50	0.08	34
407	2-NHC_4H_9; 2-Pip	(E)	Q	2.03	2.41	1.99	0.42	34
408	quinine: *O*-succinate	(E)	Q	1.83	2.28	1.84	0.44	34
409	2-OEt; $N(Bu)_2$	(E)	Q	2.12	2.24	2.15	0.08	34
410	2-Cl; $N(Et)_2$	(E)	Q	1.95	2.14	2.05	0.09	17
411	7-Cl; 2-Pip	(E)	Q	2.40	2.14	2.43	0.29	34
412	quinine	(E)	Q	1.83	2.06	1.84	0.22	22
413	dihydroquinine	(E)	Q	1.85	2.04	1.85	0.19	34
414	7,8-$(CH=CH)_2$, 3-Me; $N(Bu)_2$	(E)	Q	2.28	2.15	2.27	0.12	22
415	8-Cl; 2-Pip	(E)	Q	2.32	2.01	2.35	0.34	34
416	quinine: $OCOC_6H_5$	(E)	Q	1.83	1.98	1.84	0.14	34
417	6-OEt; quinuclidine-5-Et	(E)	Q	2.00	1.97	2.00	0.03	34
418	6,8-Cl_2, 3′-CF_3; $N(Bu)_2$	(E)	Q2OP	3.17	2.76	3.20	0.44	7
419	6-Me, 4′-Me; 2-Pip	(E)	Q2OP	2.75	2.35	2.66	0.31	34
420	2-*t*-Bu, 7,8-$(CH=CH)_2$; $N(Bu)_2$	(E)	Q2TB	2.34	2.65	2.32	0.33	34
421	2-*t*-Bu, 6-Me; $N(Bu)_2$	(E)	Q2TB	2.39	2.53	2.39	0.14	34
422	2-*t*-Bu, 6-Cl; 2-Pip	(E)	Q2TB	2.59	2.48	2.55	0.07	34
423	2-*t*-Bu, 6-Me, 7,8-$(CH=CH)_2$; $N(Bu)_2$	(E)	Q2TB	2.44	2.32	2.44	0.12	22
424	2-*t*-Bu; 2-Pip	(E)	Q2TB	2.28	2.08	2.24	0.16	34
425	5′-Br; $N(Et)_2$	(E)	Q2TH	2.26	2.38	2.28	0.10	34
426	5′-Br; $NMeCH_2C_6H_5$	(E)	Q2TH	2.21	2.26	2.21	0.05	34
427	6-Cl; $CH(CH_2OH)N(Et)_2$	(E)	Q2TH	2.19	2.12	2.27	0.15	34
428	2-adamant-1-yl, 6-Cl; $N(Bu)_2$	(E)	Q2AD	2.52	3.05	2.53	0.52	34
429	6,8-Cl_2; $N(Bu)_2$	(E)	Q2CH2P	2.76	2.60	2.77	0.17	34
430	8-Cl; $N(Bu)_2$	(E)	Q2CH2P	2.51	2.30	2.50	0.20	18
431	6,8-Cl_2; $N(Bu)_2$	(E)	Q2CF2P	2.80	2.61	2.81	0.20	34
432	8-Cl; $N(Bu)_2$	(E)	Q2CF2P	2.56	2.46	2.56	0.10	18
433	6,8-Cl_2; 2-Pip	(E)	Q2P4H	2.92	2.71	2.88	0.17	34
434	4′,4″-$(CF_3)_2$; $CH_2N(Bu)_2$		PY	3.97	4.57	4.21	0.36	16
435	4′,4″-$(CF_3)_2$; NH(2-Pent)		PY	4.40	4.44	4.11	0.33	26
436	4′,4″-$(CF_3)_2$; NH(4-Hept)		PY	4.33	4.35	4.05	0.30	26
437	4′,4″-$(CF_3)_2$; $N(Bu)_2$:O-succinate		PY	4.01	4.23	3.92	0.30	34
438	4′,4″-$(CF_3)_2$; 2-Pip		PY	4.02	4.19	3.96	0.23	33
439	4′,4″-$(CF_3)_2$; NH(c-C_6H_{11})		PY	4.01	4.17	3.76	0.41	26
440	4′,4″-$(CF_3)_2$; NH-Pent		PY	4.02	4.17	3.93	0.23	26
441	4′,4″-$(CF_3)_2$; NHBu		PY	4.03	4.16	3.95	0.21	26
442	4′,4″-$(CF_3)_2$; NH(2-Bu)		PY	4.40	4.15	4.12	0.02	26
443	4′,4″-$(CF_3)_2$; $N(4\text{-Hept})_2$		PY	3.94	4.15	3.83	0.32	26
444	4′,4″-Cl_2; NH(4-Hept)		PY	3.77	4.13	3.72	0.41	27
445	4′,4″-$(CF_3)_2$; $N(Bu)_2$		PY	4.01	4.09	3.92	0.16	26
446	4′,4″-Cl_2; NH(2-Bu)		PY	3.79	4.09	3.77	0.32	27
447	4′,4″-$(CF_3)_2$; NHPr		PY	4.02	4.03	3.96	0.07	26
448	4′,4″-$(CF_3)_2$; $N(Pent)_2$		PY	3.91	3.97	3.85	0.12	26
449	4′,4″-$(CF_3)_2$; NH(Hex)		PY	3.99	3.96	3.91	0.05	26
450	4′-CF_3, 4″-Br; NHBu		PY	3.73	3.94	3.78	0.16	26

Table II (*Continued*)

no.	substituents		symbol	log 1/C calcd[a]	log 1/C obsd	log 1/C calcd[b]	|Δ log 1/C|	ref[c]
451	3',3''-$(CF_3)_2$; NHBu		PY	3.82	3.94	3.83	0.11	26
452	4',4''-$(CF_3)_2$; NH(c-C_4H_7)		PY	4.01	3.85	3.80	0.05	26
453	4',4''-Cl_2; $N(Bu)_2$		PY	3.44	3.84	3.59	0.25	27
454	4',4''-Cl_2; 2-Pip		PY	3.42	3.83	3.61	0.22	33
455	4',4''-$(CF_3)_2$; NH(Oct)		PY	3.86	3.76	3.82	0.06	26
456	4',4''-$(CF_3)_2$; NHEt		PY	3.99	3.72	3.96	0.24	26
457	4',4''-Cl_2; $N(Bu)_2$:O-succinate		PY	3.44	3.71	3.59	0.12	27
458	4',4''-$(CF_3)_2$; NH(Hept)		PY	3.94	3.67	3.87	0.20	26
459	4'-CF_3, 4''-Br; $N(Bu)_2$		PY	3.72	3.62	3.75	0.13	26
460	4',4''-Cl_2; N(Me)Bu		PY	3.42	3.59	3.61	0.02	27
461	4',4''-Cl_2; N(Me)(2-Bu)		PY	3.78	3.59	3.77	0.18	27
462	4',4''-Cl_2; $N(Bu)_2NO$		PY	3.25	3.57	3.58	0.01	27
463	4',4''-Cl_2; NHBu		PY	3.43	3.56	3.60	0.04	27
464	4',4''-Cl_2; 2-Pip		PY	3.42	3.45	3.61	0.16	34
465	4'-Cl,4''-Br; $N(Bu)_2$		PY	3.44	3.36	3.58	0.22	27
466	4',4''-Br_2; $N(Bu)_2$		PY	3.43	3.31	3.57	0.26	27
467	4',4''-Cl_2; $N(Pr)_2$		PY	3.42	3.30	3.61	0.31	27
468	4',4''-Cl_2; N(Me)(*i*-Bu)		PY	3.42	3.29	3.77	0.48	27
469	4',4''-F_2; $N(Bu)_2$		PY	3.78	3.23	3.41	0.18	27
470	4',4''-Cl_2; NH-1-adamantyl		PY	3.08	3.23	3.39	0.16	26
471	4',4''-Cl_2; quinuclidine		PY	3.41	3.21	3.43	0.22	34
472	4',4''-Cl_2; $N(Et)_2$		PY	3.44	3.19	3.60	0.41	27
473	4',4''-Cl_2; $N(Me)_2$		PY	3.36	3.18	3.60	0.42	27
474	4',4''-Cl_2; $N(Hex)_2$		PY	3.32	3.18	3.43	0.25	27
475	4'-CF_3, 3'',4''-Cl_2; $N(Bu)_2$		PY	3.21	3.16	3.78	0.62	26
476	4',4''-Br_2; $N(Et)_2$		PY	3.44	3.13	3.61	0.48	27
477	4',4''-Cl_2; $N(Pent)_2$		PY	3.39	3.13	3.52	0.39	27
478	3',4',3'',4''-Cl_4; $N(Et)_2$		PY	3.36	3.04	3.74	0.70	27
479	3'',4',4''-Cl_3; $N(Bu)_2$		PY	2.98	3.00	3.62	0.63	27
480	4''-Cl; $N(Bu)_2$		PY	3.16	2.91	3.47	0.56	27
481	4'-CF_3, 4''-Cl; $N(Bu)_2$	(2)	PY	3.21	3.43	2.96	0.47	26
482	3'-CF_3, 3'',4''-Cl_2; $N(Bu)_2$	(2)	PY	3.05	2.90	2.93	0.03	26
483	4'-Cl, 4''-OMe; $N(Bu)_2$	(2)	PY	2.67	2.84	2.52	0.32	27
484	3',4',3'',4''-Cl_4; $N(Bu)_2NO$	(1)	PY	2.67	2.72	2.96	0.24	27
485	3',4'-Cl_2, 4''-OMe; $N(Bu)_2$	(1)	PY	2.44	2.68	2.58	0.10	27
486	3',4',3'',4''-Cl_4; $N(Bu)_2$	(1)	PY	2.67	2.63	2.84	0.21	26
487	4',4''-Cl_2; $N(Hept)_2$	(E)	PY	2.55	2.67	2.50	0.16	27
488	4',4''-F_2; $N(Hex)_2$	(E)	PY	2.77	2.58	2.55	0.03	27
489	4',4''-F_2; $N(Hept)_2$	(E)	PY	2.62	2.55	2.46	0.09	34
490	—; $N(Bu)_2$	(E)	PY	2.65	2.51	2.55	0.04	34
491	4',4''-$(OMe)_2$; $N(Bu)_2$	(E)	PY	2.14	2.17	2.24	0.07	34
492	4',4''-$(CF_3)_2$; $N(Bu)_2$		PY2VP		4.26	3.88	0.38	29
493	4',4''-$(CF_3)_2$; NHBu		PY2VP		3.89	3.92	0.03	29
494	4',4''-$(CF_3)_2$; NH(4-Hept)		PY22VP		4.24	3.87	0.37	29
495	4',4''-Cl_2; $N(Bu)_2$		PY22VP		4.18	3.51	0.67	29
496	4',4''-$(CF_3)_2$; $N(Bu)_2$		PY22VP		3.82	3.81	0.01	29
497	4',4''-$(CF_3)_2$; $N(Bu)_2$		PY2COP		3.91	4.15	0.24	29
498	2-CF_3, 4''-Cl; $N(Bu)_2$		Y2VP		4.37	3.72	0.65	29
499	2-CF_3, 4''-CF_3; NH(4-Hept)		Y		4.47	4.07	0.40	28
500	2-CF_3, 4''-CF_3; 2-Pip		Y		4.32	3.86	0.46	33
501	2-CF_3, 4''-CF_3; $N(Bu)_2$		Y		4.13	3.90	0.23	28
502	2-CF_3, 4''-CF_3; NHBu		Y		4.08	3.87	0.21	28
503	2-CF_3, 2''-CF_3; NHBu		Y		3.78	3.87	0.09	28
504	2-CF_3, 4''-CF_3; NH(3-Pent)		Y		3.28	4.05	0.77	28
505	2-CF_3, 4''-CF_3; N(*i*-Pent)$_2$		Y		3.04	4.07	1.03	28
506	3-CF_3, 6-Cl; $N(Bu)_2$		T7		3.84	3.86	0.02	3
507	1,3,6-Cl_3; $N(Bu)_2$		T7		3.53	3.92	0.39	3
508	1,3-Cl_2, 6-Me; $N(Hept)_2$		T7		3.48	3.50	0.02	3
509	3-Br, 6-Cl; $N(Bu)_2$		T7		3.43	3.68	0.25	3
510	3-CF_3, 6-Cl; $N(Hept)_2$		T7		3.38	3.77	0.39	3
511	1,3-Cl_2, 6-Me; $N(Bu)_2$		T7		3.30	3.64	0.34	3
512	1,3-Cl_2; $N(Hept)_2$		T7		3.00	3.50	0.50	3
513	1,3-Cl_2; $N(Bu)_2$		T7		3.20	3.57	0.37	4
514	6-Cl; $N(Bu)_2$		T17		3.36	3.34	0.02	5
515	3-CF_3; $N(Hept)_2$		T5		3.36	3.49	0.13	6
516	1,3-Cl_2; $N(Bu)_2$		T5		3.28	3.57	0.29	6
517	3-CF_3; $N(Bu)_2$		T5		2.98	3.50	0.52	6
518	6-CF_3; $N(Bu)_2$		T3		3.50	3.44	0.06	6
519	6-Br; $N(Bu)_2$		T3		3.37	3.41	0.04	6
520	4,8-Cl_2; $N(Hept)_2$		A1		3.56	3.55	0.01	1
521	4,8-Cl_2; $N(Bu)_2$		A1		3.39	3.66	0.27	1
522	—; $N(Hept)_2$		A1		2.99	3.05	0.06	1
523	4,5-Cl_2; $N(Hept)_2$		A9		3.92	3.47	0.45	1
524	10-Cl; $N(Hept)_2$		A9		3.70	3.27	0.43	1
525	10-Cl; $N(Bu)_2$		A9		3.51	3.30	0.21	1

Table II (*Continued*)

no.	substituents		symbol	log 1/C calcd[a]	log 1/C obsd	log 1/C calcd[b]	|Δ log 1/C|	ref[c]
526	—; $N(Non)_2$		A9		3.24	2.90	0.34	34
527	—; $N(Hept)_2$		A9		3.07	3.05	0.02	1
528	2,3-Cl_2; $N(Bu)_2$		A9		2.89	3.52	0.63	1
529	6-Cl, 3′,4′-Cl_3; $N(Bu)_2$		N2P		4.81	3.76	1.05	7
530	6-Cl, 4′-Cl; $N(Bu)_2$		N2P		4.24	3.70	0.54	7
531	7-OMe, 4′-Cl; $N(Hept)_2$		N2P		4.18	3.09	1.09	7
532	7-OMe, 4′-Cl; $N(Bu)_2$		N2P		3.90	3.21	0.69	7
533	4′-Cl; $N(Bu)_2$		N2P		3.87	3.37	0.50	7
534	4′-Cl; $N(Et)_2$		N2P		3.51	3.30	0.21	7
535	4′-Cl; $N(Hept)_2$		N2P		3.35	3.24	0.11	7
536	6-Cl, 4′-Cl; NHBu		N2P		3.29	3.71	0.42	7
537	6-Cl, 7-OMe, 4′-Cl; $N(Hept)_2$		N2P		3.31	3.20	0.10	7
538	6,3′,4′-Cl_3, 7-OMe; 2-Pip		N2P		3.14	3.48	0.34	7
539	6,3′,4′-Cl_3, 7-OMe; $N(Bu)_2$		N2P		3.06	3.46	0.40	7
540	6-Cl, 7-OMe, 4′-Cl; $N(Bu)_2$		N2P		2.96	3.41	0.45	7
541	6-Cl, 7-OMe, 4′-Cl; 2-Pip		N2P		3.00	3.40	0.40	7
542	5,7-Cl_2, 4′-Cl; $N(Bu)_2$		N4P		3.33	3.69	0.36	7
543	3′,4′-Cl_2; $N(Bu)_2$		P1		2.96	3.27	0.31	8
544	3′,7-Cl_2; $N(Hept)_2$		P1		2.96	3.43	0.47	8
545	—; $N(Hept)_2$		P4N		2.90	3.07	0.17	34
546	1,3-Cl_2; $N(Bu)_2$		P5N		2.94	3.50	0.56	34
547	1,3-Cl_2; $N(Bu)_2$		P6N		2.94	3.51	0.57	34
548	3,6-$(CF_3)_2$; $N(Bu)_2$		DPE		3.22	3.92	0.70	34
549	3,6-Cl_2; $N(Bu)_2$		FH2		3.97	3.65	0.32	31
550	3,6-Cl_2; $N(Bu)_2$		FCO		3.39	3.80	0.40	31
551	6,8,4′-Cl_3; $N(Bu)_2$		Q2P5		3.60	3.87	0.27	34
552	6,8,4′-Cl_3; $N(Bu)_2$		Q2P7		3.02	3.21	0.19	34
553	6,4′-Cl_2; $N(Bu)_2$		Q2P8		2.90	3.03	0.13	34
554	2-CF_3, 3′′-CF_3; NHBu	(2)	Y		3.69	3.01	0.67	28
555	3-CF_3; $N(Bu)_2$	(2)	T7		2.81	2.70	0.11	4
556	3-CF_3; $N(Hept)_2$	(1)	T7		2.69	2.69	0.00	4
557	3-Br; $N(Bu)_2$	(2)	T5		2.82	2.52	0.30	6
558	3-Cl; $N(Hept)_2$	(2)	A1		3.10	2.56	0.54	1
559	3-Cl; $N(Bu)_2$	(2)	A1		2.72	2.58	0.14	1
560	4,5-Cl_2; $N(Bu)_2$	(2)	A9		2.76	2.78	0.02	1
561	5,7,3′,5′-Cl_4; $N(Bu)_2$	(2)	N2OP		2.90	3.31	0.41	7
562	7-Br; $N(Hex)_2$	(2)	P1		2.77	2.54	0.23	34
563	3′,4′-Cl_2, 7-Cl; $N(Hept)_2$	(1)	P1		2.71	2.55	0.16	8
564	1,3-Cl_2; $N(Hept)_2$	(2)	P5N		2.86	2.77	0.09	34
565	4′′-Cl; $N(Bu)_2$	(E)	PY2AD		2.72	2.62	0.10	34
566	3-CF_3; $N(Pr)_2$	(E)	T7		2.82	2.64	0.18	3
567	3-CF_3; $N(Pent)_2$	(E)	T7		2.69	2.74	0.05	3
568	1,3,6-Cl_3; $N(Hept)_2$	(E)	T7		2.67	2.97	0.30	3
569	3-Br; $N(Bu)_2$	(E)	T7		2.57	2.52	0.05	4
570	3-CF_3, 6-Me; $N(Bu)_2$	(E)	T7		2.52	2.78	0.26	3
571	3-CF_3; NHBu	(E)	T7		2.51	2.66	0.15	3
572	3-CF_3; $N(Hex)_2$	(E)	T7		2.49	2.73	0.24	3
573	3-Br, 6-Me; $N(Bu)_2$	(E)	T7		2.44	2.60	0.16	3
574	—; $N(Bu)_2$	(E)	T7		2.22	2.18	0.04	4
575	6-Cl; $N(Hept)_2$	(E)	T17		2.64	2.59	0.05	5
576	—; $N(Hept)_2$	(E)	T17		2.58	2.27	0.31	5
577	—; $N(Bu)_2$	(E)	T17		2.10	2.15	0.05	5
578	1,3-Cl_2; $N(Hept)_2$	(E)	T5		2.89	2.70	0.19	6
579	3-Br; $N(Hept)_2$	(E)	T5		2.67	2.51	0.16	6
580	6-CF_3; $N(Hept)_2$	(E)	T3		2.77	2.63	0.14	6
581	6-Br; $N(Hept)_2$	(E)	T3		2.68	2.60	0.08	6
582	—; $N(Bu)_2$	(E)	T3		2.38	2.18	0.20	6
583	8-Cl; $N(Hept)_2$	(E)	A1		2.36	2.56	0.20	40
584	6,7-Cl_2; $N(Bu)_2$	(E)	A1		2.48	2.72	0.24	36
585	8-Cl; $N(Bu)_2$	(E)	A1		2.26	2.58	0.32	40
586	5-Cl; $N(Hept)_2$	(E)	A1		2.44	2.48	0.04	36
587	—; $N(Bu)_2$	(E)	A1		2.27	2.20	0.06	40
588	5-Cl; $N(Bu)_2$	(E)	A1		2.10	2.50	0.40	36
589	—; $N(Bu)_2$	(E)	A2		2.49	2.20	0.28	40
590	—; $N(Hept)_2$	(E)	A2		2.62	2.26	0.36	40
591	3-CF_3, 10-Cl; CH_2NHBu	(E)	A9		3.00	3.25	0.25	36
592	10-Br; $N(Bu)_2$	(E)	A9		2.88	2.54	0.34	39
593	10-Cl; CH_2NHBu	(E)	A9		2.49	2.81	0.32	36
594	—; $N(Bu)_2$	(E)	A9		2.35	2.20	0.14	40
595	6,3′,4′-Cl_3; $N(Hept)_2$	(E)	N2P		2.60	2.90	0.30	7
596	6,3′,4′-Cl_3, 7-OMe; $N(Hept)_2$	(E)	N2P		2.58	2.38	0.19	7
597	4-Br, 6,4′-Cl_2; $N(Bu)_2$	(E)	N2OP		2.62	3.30	0.68	7
598	5,7,4′-Cl_3; $N(Bu)_2$	(E)	N2OP		2.57	3.20	0.63	7
599	5,7-Cl_2, 3-CF_3; $N(Bu)_2$	(E)	N2OP		2.52	3.32	0.80	7
600	5,7,3′,4′-Cl_4; $N(Bu)_2$	(E)	N2OP		2.49	3.23	0.74	7

Table II (*Continued*)

no.	substituents		symbol	log 1/C calcd[a]	log 1/C obsd	log 1/C calcd[b]	|Δ log 1/C|	ref[c]
601	5,7,4′-Cl_3; $N(Bu)_2$	(E)	N2COP		2.66	3.28	0.62	7
602	4-Br; $N(Oct)_2$	(E)	N		2.24	2.50	0.26	34
603	4-Br; $N(Pent)_2$	(E)	N		2.16	2.53	0.37	34
604	—; $N(Hept)_2$	(E)	P1		2.58	2.26	0.32	34
605	3′,4′-Cl_2; $N(Hept)_2$	(E)	P1		2.55	2.37	0.18	8
606	3′-Cl; $N(Hept)_2$	(E)	P1		2.54	2.43	0.11	8
607	2-Br; $N(Hept)_2$	(E)	P1		2.50	2.49	0.01	8
608	7-Cl; $N(Hept)_2$	(E)	P1		2.50	2.47	0.02	34
609	7-Cl; $N(Hex)_2$	(E)	P1		2.39	2.52	0.13	34
610	3′-CF_3; $N(Hept)_2$	(E)	P1		2.34	2.61	0.27	34
611	—; $N(Pent)_2$	(E)	P1		2.33	2.26	0.07	34
612	8-Br; $N(Hept)_2$	(E)	P1		2.27	2.58	0.31	8
613	7-Cl; $N(Bu)_2$	(E)	P1		2.26	2.50	0.24	34
614	7-Br; $N(Bu)_2$	(E)	P1		2.15	2.54	0.39	34
615	7-Cl; $N(Pent)_2$	(E)	P1		2.14	2.53	0.39	34
616	—; $N(Bu)_2$	(E)	P1		2.06	2.21	0.15	34
617	—; $N(Hex)_2$	(E)	P1		2.03	2.28	0.25	34
618	7-Cl; $N(Pr)_2$	(E)	P1		2.02	2.45	0.43	34
619	7,8-$(CH{=}CH)_2$; $N(Hept)_2$	(E)	P1		2.28	2.21	0.07	34
620	5-CF_3; $N(Hept)_2$	(E)	P3		2.58	2.52	0.06	34
621	5-CF_3; $N(Bu)_2$	(E)	P3		2.23	2.56	0.33	34
622	5-Br; $N(Hex)_2$	(E)	P4		2.39	2.54	0.15	34
623	5-Cl; $N(Bu)_2$	(E)	P4		2.30	2.50	0.20	34
624	5-Br; $N(Bu)_2$	(E)	P4		2.23	2.54	0.31	34
625	—; $N(Hex)_2$	(E)	P4		2.20	2.28	0.08	34
626	—; $N(Hept)_2$	(E)	P4		2.19	2.26	0.07	34
627	—; $N(Bu)_2$	(E)	P4		2.09	2.21	0.12	34
628	—; $N(Hept)_2$	(E)	P2N		2.47	2.27	0.20	34
629	5,7-Cl_2; $N(Bu)_2$	(E)	P2N		2.42	2.71	0.29	34
630	5,7-Cl_2; $N(Bu)_2$	(E)	P3N		2.57	2.71	0.14	34
631	—; $N(Hept)_2$	(E)	P3N		2.33	2.27	0.06	34
632	6-Br; $N(Hept)_2$	(E)	P3N		2.12	2.56	0.44	34
633	3-Cl; $N(Hept)_2$	(E)	P5N		2.48	2.53	0.05	34
634	—; $N(Hept)_2$	(E)	P5N		2.25	2.27	0.02	34
635	3-Cl; $N(Hept)_2$	(E)	P7N		2.31	2.53	0.22	34
636	4′-Cl; $N(Bu)_2$	(E)	Q6N		2.11	2.08	0.03	34
637	8-Cl; $N(Bu)_2$	(E)	Q5		2.16	2.39	0.23	34
638	6,8,4′-Cl_3; $N(Et)_2$	(E)	Q2P3		2.47	2.40	0.07	34
639	6,8,4′-Cl_3; $N(Hept)_2$	(E)	Q2P3		2.43	2.17	0.26	34
640	6,8,4′-Cl_3; $N(Bu)_2$	(E)	Q2P3		2.32	2.41	0.09	34
641	7,4′-Cl_2; $N(Bu)_2$	(E)	Q2P3		2.20	2.24	0.04	34
642	7,4′-Cl_2; $N(Et)_2$	(E)	Q2P3		2.11	2.18	0.07	34
643	8-Cl; $N(Bu)_2$	(E)	Q2P5		2.47	2.55	0.08	34
644	8-Cl; $N(Bu)_2$	(E)	Q2P6		2.51	2.55	0.04	34
645	6,4′-Cl_2; $N(Et)_2$	(E)	Q2P8		2.12	2.18	0.06	34
646	6,4′-Cl_2; $N(Hept)_2$	(E)	Q2P8		2.34	2.08	0.26	34

[a] Calculated using eq 7c, 8c, and 9. [b] Calculated using eq 10. [c] (1) C. Hansch and J. Fukunaga, *CHEMTECH.*, **7**, 120 (1977). (2) A. Markovac and M. P. LaMontagne, *J. Med. Chem.*, 19, 978 (1976). (3) B. P. Das, M. E. Nuss, and D. W. Boykin, Jr., *ibid.*, **17**, 516 (1974). (4) B. P. Das, J. A. Campbell, F. B. Samples, R. A. Wallace, L. K. Whisenant, R. W. Woodard, and D. W. Boykin, Jr., *ibid.*, **15**, 370 (1972). (5) B. P. Das and D. W. Boykin, Jr., *ibid.*, 16, 413 (1973). (6) B. P. Das, R. T. Cunningham, and D. W. Boykin, Jr., *ibid.*, 16, 1361 (1973). (7) J. S. Gillespie, Jr., S. P. Acharya, D. A. Shamblee, and R. E. Davis, *ibid.*, **18**, 1223 (1975). (8) J. T. Traxler, L. O. Krbechek, R. R. Riter, R. G. Wagner, and C. W. Huffman, *ibid.*, 14, 90 (1971). (9) P. N. Craig, *ibid.*, **15**, 144 (1972). (10) H. R. Munson, Jr., R. E. Johnson, J. M. Sanders, C. J. Ohnmacht, and R. E. Lutz, *ibid.*, **18**, 1232 (1975). (11) E. R. Atkinson and A. J. Puttick, *ibid.*, **13**, 537 (1970). (12) D. W. Boykin, Jr., A. R. Patel, and R. E. Lutz, *ibid.*, 11, 273 (1968). (13) E. R. Atkinson and A. J. Puttick, *ibid.*, 11, 1223 (1968). (14) J. S. Gillespie, Jr., R. J. Rowlett, Jr., and R. E. Davis, *ibid.*, 11, 425 (1968). (15) T. Singh and J. H. Biel, *ibid.*, 13, 541 (1970). (16) W. T. Colwell, V. Brown, P. Christie, J. Lange, C. Reece, K. Yamamoto, and D. W. Henry, *ibid.*, **15**, 771 (1972). (17) C. R. Wetzel, J. R. Shanklin, Jr., and R. E. Lutz, *ibid.*, 16, 528 (1973). (18) A. J. Saggiomo, S. Kano, T. Kikuchi, K. Okubo, and M. Shinbo, *ibid.*, **15**, 989 (1972). (19) P. Blumbergs, M.-S. Ao, M. P. LaMontagne, A. Markovac, J. Novotny, C. H. Collins, and F. W. Starks, *ibid.*, **18**, 1122 (1975). (20) R. M. Pinder and A. Burger, *ibid.*, 11, 267 (1968). (21) C. J. Ohnmacht, A. R. Patel, and R. E. Lutz, *ibid.*, 14, 926 (1971). (22) K. C. Rice, B. J. Boone, A. B. Rubin, and T. J. Rauls, *ibid.*, 19, 887 (1976). (23) M. Loy and M. M. Joullie, *ibid.*, 16, 549 (1973). (24) P. A. Cruickshank and W. E. Hymans, *ibid.*, 17, 468 (1974). (25) E. R. Atkinson, *ibid.*, 17, 1012 (1974). (26) A. Markovac, M. P. LaMontagne, P. Blumbergs, A. B. Ash, and C. L. Stevens, *ibid.*, **15**, 918 (1972). (27) P. Blumbergs, M. P. LaMontagne, A. Markovac, J. G. Moehring, A. B. Ash, and C. L. Stevens, *ibid.*, **15**, 808 (1972). (28) M. P. LaMontagne, A. Markovac, and M.-S. Ao, *ibid.*, 16, 1040 (1973). (29) M. P. LaMontagne, *ibid.*, 16, 68 (1973). (30) R. B. Fugitt and R. M. Roberts, *ibid.*, 16, 875 (1973). (31) E. R. Atkinson and F. E. Granchelli, *ibid.*, 17, 1009 (1974). (32) A. R. Patel, C. J. Ohnmacht, D. P. Clifford, A. S. Crosby, and R. E. Lutz, *ibid.*, 14, 198 (1971). (33) M. P. LaMontagne, A. Markovac, and P. Blumbergs, *ibid.*, 17, 519 (1974). (34) Walter Reed Army Institute. (35) L. C. Washburn and D. E. Pearson, *J. Med. Chem.*, 17, 676 (1974). (36) J. T. Traxler, M. J. Moats, E. P. Lira, and C. W. Huffman, *J. Pharm. Sci.*, 64, 1943 (1975). (37) P.-L. Chien, D. J. McCaustland, W. H. Burton, and C. C. Cheng, *J. Med. Chem.*, **15**, 28 (1972). (38) E. A. Nodiff, A. J. Saggiomo, M. Shinbo, E. H. Chen, H. Otomasu, Y. Kondo, T. Kikuchi, B. L. Verma, S. Matsuura, K. Tanabe, M. P. Tyagi, and S. Morosawa, *ibid.*, **15**, 775 (1972). (39) P.-L. Chien and C. C. Cheng, *ibid.*, **16**, 1093 (1973). (40) E. L. Stogryn, *ibid.*, 17, 563 (1974).

Table III. Partition Coefficient (Log P) of Aromatic Methanolamines

		partition coefficient (log P)		
	R	phenanthrene[a] (A)	2-phenylquinoline[b] (B)	2,6-diphenylpyridine[c] (C)
1	$-CH_2NMe_2$	0.65	1.08	2.25
2	$-CH_2NEt_2$	0.94	1.37	2.54
3	$-CH_2NPr_2$	1.69	2.12	3.29
4	$-CH_2NBu_2$	2.57	3.00[d]	4.17[e]
5	$-CH_2NPen_2$	3.58	4.01	5.18
6	$-CH_2NHex_2$	4.51	4.94	6.11
7	$-CH_2NHep_2$	5.51	5.94	7.11
8	$-CH_2NHMe$	0.55[f]	0.98	2.15
9	$-CH_2NHEt$	0.99	1.42	2.59
10	$-CH_2NHPr$	1.43	1.86	3.03
11	$-CH_2NHBu$	1.87	2.30	3.47
12	$-CH_2NHPen$	2.37[g]	2.80	3.97
13	2-piperidinyl	1.58	2.01	3.18

[a] Unless otherwise noted, log P values were measured from 0.1 N HCl solution. [b] Calculated by adding the difference (Δlog P) obtained from the corresponding analogues in the phenanthrenes to the log P values of B-4·HCl measured in pH 7.4 phosphate buffer solution. [c] Calculated by adding the difference (Δ log P) obtained from the corresponding analogues in the phenanthrenes to the log P values of C-4·HCl. [d] Measured in pH 7.4 phosphate buffer solution. [e] Calculated by adding the difference (Δ log P) in log P values of 2,6-diphenylpyridine between those measured in 0.1 N HCl and in pH 7.4 phosphate buffer solution to the log P value of C-3·HCl in 0.1 N HCl solution: log P C-3·HCl (7.4 buffer) = log P C-3·HCl (0.1 N HCl) − log P 2,6-Ph_2Pyr (0.1 N HCl) + log P 2,6-Ph_2Pyr (7.4 buffer) = 1.11 − 1.98 + 5.04 = 4.17. [f] Log P A-8·HCl = log P A-9·HCl (0.99) − 0.44 = 0.55. [g] Log P A-12·HCl = log P A-11·HCl (1.87) + 0.50 = 2.37.

by the procedure of Duncan et al.[22a] and compound **4** by the method of Nodiff et al.[22b] All compounds were checked for purity by thin-layer chromatography. Carbon–hydrogen analyses of the new compounds gave values which agreed within 0.4% with the theoretical values.

Bilinear Model. Kubinyi[23] has recently developed a new approach to deal with the "parabolic" dependence of log $1/C$ on log P. In his model, the a log $P - b(\log P)^2$ of biological QSAR are replaced by a' log $P - b'\log(\beta P + 1)$. This approach requires one more disposable parameter; namely, β. Nevertheless, Kubinyi has shown that the bilinear model often yields more significant correlations than the symmetrical parabolic model. We therefore replaced the log P terms of eq 7c and 10 with the above bilinear log P terms and refit the data. The usual least-squares method cannot be employed. We have used an algorithm provided by Kubinyi.

Results

The parameters necessary for the formulation of eq 7–10 are shown in Table II (supplementary material). Two calculated log $1/C$ are given for each congener. One value is given for each congener calculated using eq 10 for all antimalarials. An additional value for comparison is shown for the phenanthrenes (1–217) obtained from eq 7c, the quinolines (218–433) from eq 8c, and the pyridines (434–491) from eq 9.

The symbol E after the formula for the antimalarial means that log $1/C$ was obtained by extrapolation; these compounds did not produce cures. A (1) or (2) following the formula indicates the highest number of cures produced by these compounds; all other congeners achieved at least three cures. The definition of the symbols for the aromatic nuclei, as well as the number of each type occurring in the data set, is given in Table IV.

Phenanthrenes. To formulate the QSAR in this report, we have employed our previously outlined approach for dealing with large data sets and many variables.[24] Stepwise regression has not been employed; instead, we have generated all possible equations.

In reexamining the phenanthrenes, we have factored the data into two sets of congeners: those which achieved three cures (eq 7a) and those which achieved less than three cures (eq 7b). Then the two data sets were combined to yield a single QSAR (eq 7c). Three data points (18, **148**, and **156**) were omitted in deriving eq 7c; when these are included, essentially the same equation is obtained with $r = 0.912$, $s = 0.258$, and log $P_0 = 3.8$.

$$\log 1/C = 0.860(\pm0.15)\Sigma\sigma + 0.212(\pm0.07)\Sigma\pi + 0.171(\pm0.16)\log P - 0.023(\pm0.016)(\log P)^2 - 0.162(\pm0.20)\text{c-side} + 0.260(\pm0.15)CNR_2 - 0.141(\pm0.09)AB + 2.559(\pm0.34) \quad (7a)$$

$$n = 176;\ r = 0.857;\ s = 0.240;\ \log P_0 = 3.8\ (0.8\text{–}4.5)$$

$$\log 1/C = 0.665(\pm0.28)\Sigma\sigma + 0.005(\pm0.12)\Sigma\pi + 0.046(\pm0.24)\log P - 0.004(\pm0.02)(\log P)^2 - 0.176(\pm0.20)\text{c-side} + 0.222(\pm0.23)CNR_2 + 2.326(\pm0.53) \quad (7b)$$

$$n = 38;\ r = 0.791;\ s = 0.188;\ \log P_0 = -0.4\ (\pm\infty)$$

$$\log 1/C = 0.827(\pm0.13)\Sigma\sigma + 0.163(\pm0.07)\Sigma\pi + 0.187(\pm0.14)\log P - 0.024(\pm0.014)(\log P)^2 - 0.225(\pm0.15)\text{c-side} + 0.315(\pm0.13)CNR_2 - 0.103(\pm0.09)AB - 0.639(\pm0.10) <3\text{-cures} + 2.613(\pm0.30) \quad (7c)$$

$$n = 214;\ r = 0.925;\ s = 0.239;\ \log P_0 = 3.9\ (2.4\text{–}4.5)$$

Equation 7a is a good correlation compared to our earlier equations in terms of s, although the correlation coefficient is lower because the amount of variance in log $1/C$ has been reduced by removal of the less active compounds. In this expression, $\Sigma\sigma$ and $\Sigma\pi$ refer to substituents on the phenanthrene ring. The indicator variable c-side takes the value of 1 for congeners having a cycloalkyl group attached to the side-chain nitrogen atom; its negative coefficients show that these compounds on the average are slightly less active than normal alkyl chains, other factors being equal. The variable CNR_2 is given the value of 1 for those analogues having an extra CH_2 between the CHOH and NR_2 of the side chain; its positive coefficient suggests increased activity may be the result of hydrophobic or dispersion forces. The variable AB is assigned a value of 1 when two ring substituents are adjacent to each other, the value of 2 when two such pairs are present, and the value of 3 when there are three such adjacencies (e.g., 2, 3, 4, 5). The small negative effect of this term may reflect the loss in hydrophobicity due to groups being placed next to each other; for example, the difference between simple additive and observed $\Sigma\pi$ for 3,4-dibromobenzene is 0.21.[18]

The same terms, except for AB, have been used to derive eq 7b. Since there are no examples of adjacent ring substituents in this subset of phenanthrenes, this term had to be omitted. The single most important variable, $\Sigma\sigma$, has roughly the same weight in both eq 7a and 7b. The indicator variables c-side and CNR_2 are also in good agreement; however, the $\Sigma\pi$ and log P terms are not very

Table IV. Symbols for Aryl Groups of Compounds of Table II

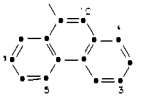
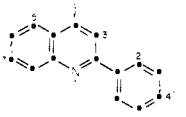
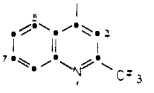
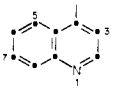
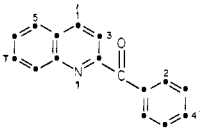
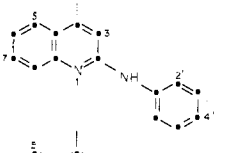
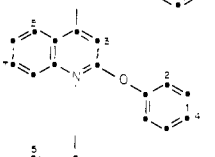
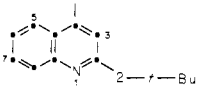
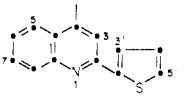
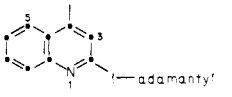
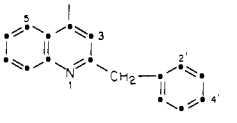
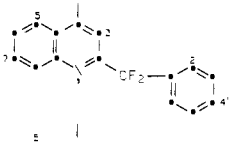
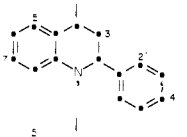
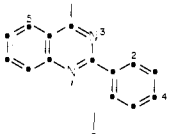
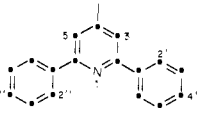
no.	compounds	no. of congeners[a]	symbols in Table II
1		217 (21)	P
2		133 (12)	Q2P
3		24 (1)	Q2F
4		18 (7)	Q
5		8	Q2COP
6		4	Q2NP
7		7 (2)	Q2OP
8		7 (3)	Q2TB
9		5 (1)	Q2TH
10		3 (1)	Q2AD
11		2	Q2CH2P
12		2	Q2CF2P
13		2	Q2P4H
14		1	Q2P3N
15		58 (3)	PY

Table IV (*Continued*)

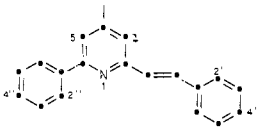
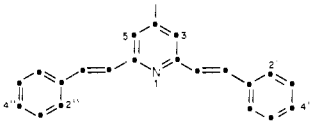
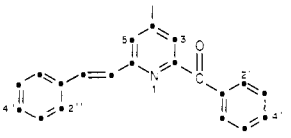
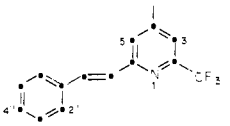
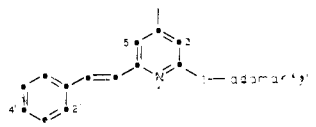
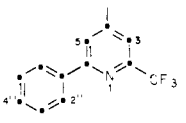
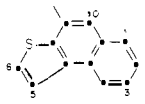
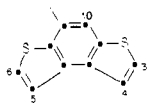
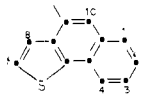
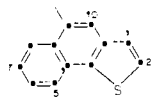
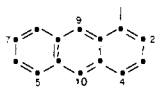
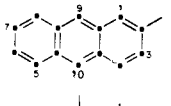
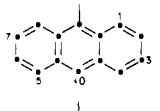
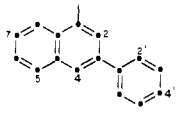
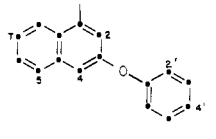
no.	compounds	no. of congeners[a]	symbols in Table II
16		2	PY2VP
17		3 (1)	PY22VP
18		1	PY2COP
19		1	Y2VP
20		1	PY2AD
21		8 (1)	Y
22		19	T7
23		4	T17
24		6 (1)	T5
25		5	T3
26		11	A1
27		2	A2
28		11 (1)	A9
29		15	N2P
30		5	N2OP

Table IV (*Continued*)

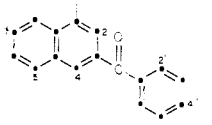
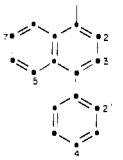
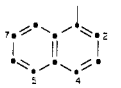
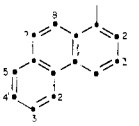
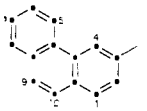
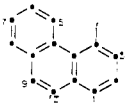
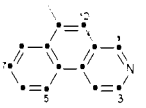
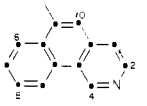
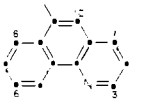
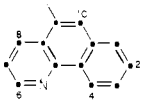
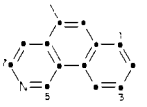
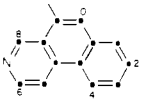
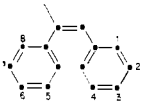
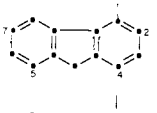
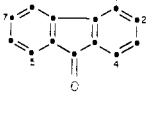
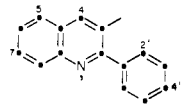
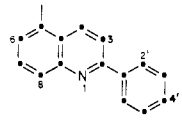
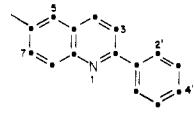
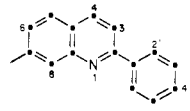
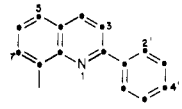
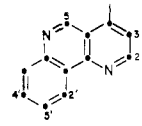
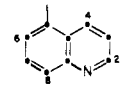
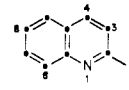
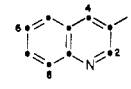
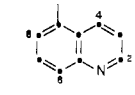
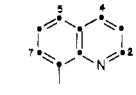
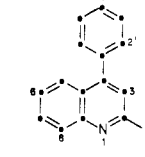
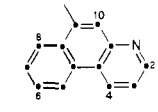
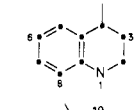
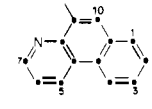
no.	compounds	no. of congeners[a]	symbols in Table II
31		1	N2COP
32		1	N4P
33		2 (4)	N
34		20	P1
35		2	P3
36		6 (1)	P4
37		2	P2N
38		3 (1)	P3N
39		1	P4N
40		4	P5N
41		1 (1)	P6N
42		1	P7N
43		1	DPE
44		1	FH2
45		1	FCO

Table IV (*Continued*)

no.	compounds	no. of congeners[a]	symbols in Table II
46		5	Q2P3
47		2	Q2P5
48		1 (4)	Q2P6
49		1 (1)	Q2P7
50		3 (2)	Q2P8
51		1	Q6N
52		1	Q5
53		(6)	Q2
54		(9)	Q3
55		(2)	Q5
56		(8)	Q8
57		(3)	Q4P2
58		(1)	P1N
59		(1)	Q4H
60		(4)	P8N

[a] Figures in parentheses are number of congeners in Table XIII.

Table V. Development of Equation 7c for Phenanthrenes

intercept	$\Sigma\sigma$	<3-cures	$\Sigma\pi$	CNR_2	$(\log P)^2$	c-side	$\log P$	AB	r	s	$F_{1,X}$[a]
2.68	1.38								0.794	0.382	361
3.07	1.00	−0.75							0.891	0.286	170
2.97	0.82	−0.70	0.14						0.901	0.274	18.9
2.94	0.80	−0.70	0.15	0.32					0.910	0.262	21.0
3.02	0.75	−0.69	0.19	0.35	−0.005				0.917	0.253	15.8
3.03	0.76	−0.66	0.19	0.35	0.005	−0.23			0.920	0.248	8.37
2.63	0.79	−0.67	0.15	0.32	−0.025	−0.23	0.20		0.923	0.244	7.90
2.58	0.83	−0.66	0.15	0.31	0.026	−0.24	0.21	0.10	0.925	0.242	5.22

[a] $F_{1,120(\alpha=0.001)} = 11.4$; $F_{1,120(\alpha=0.005)} = 8.18$; $F_{1,120(\alpha=0.025)} = 5.15$.

Table VI. Squared (r^2) Correlation Matrix for Equation 7c for Phenanthrenes

	$\log P$	c-side	$\Sigma\pi$	$\Sigma\sigma$	CNR_2	AB	<3-cures
$\log P$	1.00	0.01	0.05	0.00	0.01	0.00	0.00
c-side		1.00	0.01	0.00	0.00	0.01	0.03
$\Sigma\pi$			1.00	0.46	0.01	0.14	0.21
$\Sigma\sigma$				1.00	0.00	0.17	0.22
CNR_2					1.00	0.01	0.00
AB						1.00	0.03
<3-cures							1.00

significant, as can be seen from their 95% confidence intervals, and log P_0 cannot be calculated with any confidence.

When the data sets of eq 7a and 7b are combined using indicator variables <3-cures for the points of eq 7b, eq 7c can be formulated. The coefficients of eq 7c are in good agreement with those of eq 7a, and the goodness of fit, as judged by s, has not been decreased by the addition of the 38 poor data points.

There are some important advantages to combining eq 7a and 7b into eq 7c, although at first this might seem to be a dubious procedure since eq 7a and 7b are not essentially identical. In fact, however, congeners **180**–**217** as a group are well fit by eq 7c. Only 10 of the 38 congeners have deviations from eq 7c higher than the standard deviation of eq 7c. The standard deviation for the group is 0.227, which is less than that for the whole group of 214 congeners; therefore, this poorly active subset does conform to the same structure–activity relationship as the larger group of highly active compounds. One cannot ascertain this without combining the two data sets, because the limited range in log $1/C$ for compounds **180**–**217** provides little perspective.

Including these less important molecules has important benefits for the drug designer. With a better spread in data, one can now place much better confidence limits on log P_0 and the confidence limits on the intercept can also be tightened. From the point of view of molecular bookkeeping, we can more easily keep track of a more diverse set of molecules.

The negative coefficient with the <3-cures term of eq 7c reflects the fact that the dose–response curve rises more steeply in the region where one is simply extending the lifespan of the mice. It appears to change slope sharply in the region where the majority of the mice are beginning to be cured.

A data point of particular interest is **163**. This congener contains the bulky 3,6-di-*tert*-butyl groups; nevertheless, it is moderately well fit, showing that rather bulky substituents can be placed on the phenanthrene ring without undue loss of activity.

The development of eq 7c is given in Table V and the correlation among its variables is shown in Table VI.

Quinolines. As with the phenanthrenes, we have factored the quinolines to obtain equations for congeners producing at least three cures (eq 8a) and those producing

three or more cures

$$\log 1/C = 0.621(\pm0.15)\Sigma\sigma + 0.365(\pm0.16)\Sigma\pi + 0.365(\pm0.16)\log P - 0.043(\pm0.017)(\log P)^2 - 0.400(\pm0.19)\text{c-side} + 0.476(\pm0.19)\text{MR-4'-Q} + 0.341(\pm0.25)\text{Me-6,8-Q} + 0.248(\pm0.15)\text{2-Pip} + 2.060(\pm0.15) \quad (8a)$$

$n = 122$; $r = 0.834$; $s = 0.274$; $\log P_0 = 4.23$ (3.7–4.7)

extrapolated cures

$$\log 1/C = 0.176(\pm0.16)\Sigma\sigma + 0.071(\pm0.11)\Sigma\pi + 0.088(\pm0.09)\log P - 0.005(\pm0.01)(\log P)^2 + 0.330(\pm0.17)\text{MR-4'-Q} + 0.073(\pm0.21)\text{Me-6,8-Q} + 0.018(\pm0.17)\text{2-Pip} + 2.156(\pm0.17) \quad (8b)$$

$n = 87$; $r = 0.744$; $s = 0.184$; $\log P_0 = 9.5$ ($\pm\infty$)

all quinolines

$$\log 1/C = 0.541(\pm0.13)\Sigma\sigma + 0.155(\pm0.10)\Sigma\pi + 0.228(\pm0.10)\log P - 0.026(\pm0.012)(\log P)^2 - 0.181(\pm0.13)\text{c-side} - 0.695(\pm0.10)\text{<3-cures} + 0.365(\pm0.15)\text{MR-4'-Q} + 0.232(\pm0.20)\text{Me-6,8-Q} + 0.130(\pm0.11)\text{2-Pip} + 2.492(\pm0.22) \quad (8c)$$

$n = 216$; $r = 0.898$; $s = 0.296$; $\log P_0 = 4.37$ (3.7–5.2)

one, two, or no cures (eq 8b). These two sets were then merged to afford eq 8c. Seven data points (**218**, **298**, **306**, **308**, **333**, **336**, and **337**) were excluded in the formulation of eq 8a.

All data points are included in the formulation of eq 8c.

Equation 8a has several variables not present in eq 7c. The term in MR-4′-Q is assigned MR values for substituents in the 4′ position of the 2-phenyl ring. Since MR gives a better correlation than π for these substituents, this suggests that dispersion forces and/or a conformational change due to steric effects may be behind the increased inhibitory power of such groups. Although there are many examples of 3′ substitution with several different types of substituents, these congeners are well fit without being included in a $\Sigma\pi$ or the MR term. The evidence is good that 3′ substituents are only involved in an electronic effect and the overall hydrophobic character (log P). The Me-6,8-Q term takes the value of 1 for quinolines with methyl groups in the 6 and 8 positions and the value of 0.5 when only one such group is present. Its positive coefficient brings out an activating effect of Me in these positions which is not produced by other groups, such as Cl. It is not clear why such groups are activating in quinoline while nothing in the phenanthrene series corresponds to this. In the case of the quinolines, the 2-Pip

Table VII. Development of Equation 8c for Quinolines

intercept	<3-cures	Σπ	Σσ	MR-4'-Q	Me-6, 8-Q	c-side	log P	(log P)²	2-Pip	r	s	$F_{1,X}$[a]
3.55	−1.04									0.774	0.419	320
3.19	−0.91	0.38								0.833	0.367	65.9
3.04	−0.75		0.55	0.50						0.861	0.338	
2.94	−0.72		0.68	0.48	0.48					0.876	0.321	24.8
2.89	−0.72	0.15	0.56	0.44	0.36					0.882	0.315	9.38
2.92	−0.70	0.16	0.54	0.42	0.31	−0.17				0.886	0.310	6.52
2.62	−0.70	0.21	0.43	0.38		−0.25	0.22	−0.027		0.891	0.305	
2.49	−0.70	0.20	0.46	0.36		−0.20	0.24	−0.027	0.16	0.895	0.300	8.15
2.49	−0.70	0.16	0.54	0.37	0.23	−0.18	0.23	−0.026	0.13	0.898	0.296	5.33

[a] $F_{1,120(\alpha=0.001)} = 11.4$; $F_{1,120(\alpha=0.005)} = 8.18$; $F_{1,120(\alpha=0.01)} = 6.85$; $F_{1,120(\alpha=0.025)} = 5.15$.

Table VIII. Squared (r^2) Correlation Matrix for Equation 8c for Quinolines

	<3-cures	Σπ	Σσ	MR-4'-Q	Me-6,8-Q	2-Pip	log P	c-side
<3-cures	1.00	0.09	0.13	0.11	0.00	0.02	0.12	0.03
Σπ		1.00	0.25	0.03	0.01	0.04	0.21	0.00
Σσ			1.00	0.00	0.19	0.04	0.05	0.00
MR-4'-Q				1.00	0.01	0.02	0.22	0.02
Me-6,8-Q					1.00	0.06	0.00	0.02
2-Pip						1.00	0.23	0.05
log P							1.00	0.00
c-side								1.00

Table IX. Development of Equation 9 for Pyridines

intercept	<3-cures	Σσ	AB	NBrPy	$(\log P)^2$	log P	r	s	$F_{1,X}$[a]
3.67	−0.97						0.692	0.406	51.5
2.83		1.15	−0.75				0.864	0.286	58.2
3.02	−0.41	0.95	−0.58				0.896	0.255	15.1
2.98	−0.37	0.91	−0.54	0.37			0.919	0.228	14.5
3.08	−0.30	0.99	−0.57	0.35	−0.005		0.926	0.221	4.64
1.72	−0.29	0.95	−0.58	0.37	−0.046	0.49	0.933	0.212	5.58

[a] $F_{1,40(\alpha=0.001)} = 12.0$; $F_{1,40(\alpha=0.025)} = 5.42$; $F_{1,40(\alpha=0.05)} = 4.08$.

group in the side chain seems to be *slightly* more active than other types of alkylamino groups; this is brought out by the 2-Pip indicator variable.

The AB variable was not significant in the quinoline set and, since only three examples of congeners with an extra CH_2 in the side chain are present in the quinolines, these points were dropped at this stage of the correlation analysis; however, they were parameterized by CNR_2 in the overall equation and are reasonably well fit.

The correlation with eq 8a is not as good as that of eq 7a; however, the agreement between the coefficients for the variable common to each equation is not bad.

Equation 8b is rather meaningless when one considers the confidence limits on the various parameters. The major reason for this is that there is very little variance in the data ($\sigma^2 = 0.069$ compared to 0.229 for eq 8a). However, when eq 8a and 8b are merged to produce eq 8c, the 87 extrapolated log $1/C$ values do not distort the shape of eq 8c. Equation 8c is much like eq 8a, except that one term, <3-cures, is needed to merge the two sets. The coefficient with this term is close in size to that in eq 7c.

That the 87 congeners of eq 8b conform to the QSAR of the more active quinolines can be seen from their good fit to eq 8c. The standard deviation of these 87 compounds from eq 8b is 0.184, which is less than the standard deviation (0.296) for eq 8c.

The most surprising aspect of eq 8a and 8c is the $\sum\sigma$ term. Our first approach was to factor σ into two terms, one for substitutents on the 2-phenyl moiety and one for substituents on the quinoline ring. Doing so yielded an equation with two electronic terms with identical coefficients. Merging these two terms did not reduce the quality of the correlation. This is a most important discovery which was observed in a less dramatic way with the X and Y substituents on I. This relationship between the electronic effect of the substituents and biological activity must be incorporated into any molecular mechanism of activity. The development of eq 8c is given in Table VII and the intercorrelation of the variables is shown in Table VIII.

Table X. Squared (r^2) Correlation Matrix for Parameters of Equation 9 for Pyridines

	<3-cures	Σσ	AB	NBrPy	log P	Σπ
<3-cures	1.00	0.10	0.13	0.04	0.03	0.07
Σσ		1.00	0.11	0.01	0.09	0.71
AB			1.00	0.02	0.01	0.35
NBrPy				1.00	0.00	0.00
log P					1.00	0.05
Σπ						1.00

2,6-Diphenylpyridines. There are 58 examples of 2,6-diphenylpyridines (**434–491**) in Table II. The "best" QSAR for these is eq 9. One unique point not included

$$\log 1/C = 0.953(\pm0.19)\sum\sigma - 0.289(\pm0.19)\text{<3-cures} - 0.583(\pm0.14)\text{AB} + 0.371(\pm0.17)\text{NBrPy} - 0.485(\pm0.42)\log P - 0.046(\pm0.04)(\log P)^2 + 1.718(\pm1.2) \quad (9)$$

$$n = 57;\ r = 0.933;\ s = 0.212;\ \log P_0 = 5.3\ (3.0\text{–}5.9)$$

in eq 9 contains an additional CH_2 in the side chain. This point is included in the final equation where the CNR_2 term accounts for this structural variation. The development of eq 9 is given in Table IX and the relationships between its variables are presented in Table X. One new parameter has been introduced (NBrPy) which does not occur in the phenanthrene or quinoline equations. This

Table XI. Development of Equation 10 for All Congeners

intercept	<3-cures	$\Sigma\sigma$	$\Sigma\pi$	Py	Q2P-378	MR-4′-Q	CNR_2	AB	Me-6, 8-Q	c-side	log P	(log P)^2	NBr-Py	2-Pip	r	s	$F_{1,X}$[a]
3.68	-1.15														0.791	0.425	1077
3.26	-0.92	0.63													0.860	0.355	283
3.19	-0.90	0.55	0.11												0.867	0.347	30.3
3.13	-0.87	0.45	0.19	0.28											0.873	0.340	25.7
3.12	-0.86	0.47	0.19	0.27	-0.51										0.877	0.335	20.5
3.04	-0.82	0.49	0.20	0.33	-0.64	0.26									0.881	0.330	22.7
3.03	-0.82	0.47	0.21	0.35	-0.64	0.28	0.35								0.886	0.324	23.1
3.02	-0.82	0.51	0.21	0.35	-0.71	0.36	0.33	-0.15							0.890	0.319	21.2
3.00	-0.81	0.56	0.19	0.32	-0.68	0.31	0.33	-0.15	0.31						0.892	0.317	11.7
3.01	-0.81	0.56	0.19	0.32	-0.70	0.32	0.33	-0.15	0.30	-0.16					0.894	0.314	9.7
2.77	-0.80	0.53	0.19	0.33	-0.71	0.35	0.32	-0.15		-0.19	0.15	-0.017			0.895	0.312	
2.74	-0.80	0.58	0.17	0.30	-0.69	0.30	0.32	-0.15	0.30	-0.18	0.15	-0.017			0.897	0.310	11.0
2.74	-0.79	0.58	0.17	0.27	-0.69	0.30	0.32	-0.15	0.29	-0.18	0.15	-0.018	0.16		0.898	0.309	2.79
2.69	-0.80	0.58	0.17	0.27	-0.67	0.28	0.32	-0.14	0.25	-0.17	0.17	-0.019	0.17	0.08	0.898	0.309	2.48

[a] $F_{1,120;\alpha=0.001} = 11.4$; $F_{1,120;\alpha=0.005} = 8.18$; $F_{1,120;\alpha=0.1} = 2.75$.

Table XII. Squared (r^2) Correlation Matrix for Parameters of Equation 10

	<3-cures	$\Sigma\sigma$	Me-6, 8-Q	$\Sigma\pi$	Py	Q2P378	MR-4′-Q	AB	CNR_2	c-side	log P	2-Pip	NBrPy
<3-cures	1.00	0.17	0.00	0.09	0.02	0.01	0.00	0.02	0.00	0.01	0.02	0.01	0.01
$\Sigma\sigma$		1.00	0.11	0.22	0.03	0.00	0.02	0.04	0.01	0.00	0.04	0.05	0.01
Me-6,8-Q			1.00	0.00	0.01	0.00	0.05	0.00	0.00	0.01	0.00	0.12	0.00
$\Sigma\pi$				1.00	0.19	0.00	0.00	0.02	0.00	0.00	0.01	0.02	0.03
Py					1.00	0.00	0.04	0.00	0.00	0.00	0.06	0.01	0.15
Q2P378						1.00	0.04	0.00	0.00	0.00	0.00	0.00	0.00
MR-4′-Q							1.00	0.08	0.01	0.00	0.01	0.03	0.01
AB								1.00	0.00	0.00	0.03	0.01	0.00
CNR_2									1.00	0.00	0.00	0.00	0.00
c-side										1.00	0.01	0.01	0.00
log P											1.00	0.12	0.01
2-Pip												1.00	0.00
NBrPy													1.00

indicator variable takes the value of 1 for branched alkyl groups attached to the side-chain nitrogen. The side chain of the 2,6-diphenylpyridines may be positioned on the receptor somewhat differently from the phenanthrenes and quinolines so that branching increases inhibitory power.

No $\Sigma\pi$ term appears in eq 9. In this sense, the 2,6-diphenylpyridines resemble the 2-phenylquinolines where $\Sigma\pi$ does not include substituents on the 2-phenyl moiety. However, the MR-4′ variable does not improve the correlation with the pyridines, which is probably due to the high collinearity between $\Sigma\sigma$ and MR-4′. The larger coefficient with $\Sigma\sigma$ is no doubt due to this collinearity and/or the collinearity between $\Sigma\pi$ and $\Sigma\sigma$. The coefficient with $\Sigma\sigma$ (0.95) in eq 9 is close to the sum of the coefficients for $\Sigma\sigma$ and MR-4′-Q in eq 8c (0.54 + 0.37 = 0.91) (this is not a strict comparison, since MR and σ are not equiscalar).

The interecept of the pyridine equation is much lower than that of the phenanthrene or quinoline equations; however, the confidence limits on it are so large that we cannot assume the difference to be significant.

The log P and log P_0 terms also differ from those of the other antimalarial equations, but again the confidence limits are so wide that a true difference cannot be inferred with any surety.

There are only two examples of 2,6-diphenylpyridines with cycloalkyl groups on the side-chain nitrogen (c-side); hence, this parameter was not included in eq 9. These points are so parameterized in the overall equation.

Overall QSAR. Equations 7–9 embrace the first 491 compounds of Table II. Beyond this, there are 155 miscellaneous compounds of "similar" structure (see Table IV for classification of the nuclei). In order to formulate the most general structure–activity picture, all of the congeners of Table II have have been fit to eq 10 and no data points were excluded.

$$\log 1/C = 0.575(\pm0.09)\Sigma\sigma + 0.173(\pm0.05)\Sigma\pi + 0.171(\pm0.07)\log P - 0.019(\pm0.008)(\log P)^2 - 0.168(\pm0.10)\text{c-side} + 0.321(\pm0.14)CNR_2 - 0.140(\pm0.06)\text{AB} - 0.795(\pm0.06)\text{<3-cures} + 0.281(\pm0.11)\text{MR-4′-Q} + 0.252(\pm0.18)\text{Me-6,8-Q} + 0.081(\pm0.10)\text{2-Pip} + 0.166(\pm0.19)\text{NBrPy} - 0.674(\pm0.22)\text{Q2P378} + 0.272(\pm0.11)\text{Py} + 2.689(\pm0.17) \quad (10)$$

$$n = 646;\ r = 0.898;\ s = 0.309;\ \log P_0 = 4.50\ (4.0\text{–}5.0)$$

The last two terms of eq 10 do not occur in the QSAR of the three other subsets. The indicator variable Py takes the value of 1 for pyridine derivatives. The small positive weighting factor with this term indicates that, other parameters being equal, pyridines are intrinsically more active than the phenanthrenes or quinolines.

The variable Q2P378 is given the value of 1 for 2-phenylquinolines in which the side chain is attached at positions 3, 7, or 8. These congeners are about five times less active than when the side chain is attached to positions 4–6. Care must be taken in interpreting this term, since there are only two data points supporting the term where the side chain is attached to position 5 and one example each when the side chain is at position 6 or 7.

The development of eq 10 is given in Table XI and the interrelationship of its variables in Table XII. Equation 10 is a robust expression with an average of 46 data points per variable. There is over a 1000-fold range in the ac-

tivities of Table II and eq 10, with a standard deviation of 0.3, indicates that these activities can, on the average, be predicted within a factor of ±2. Considering the fact that many of the more lipophilic congeners are quite insoluble and, hence, difficult to administer and that the range in structural modification is large, eq 10 is about as good as one could expect. For comparison, we have placed the log $1/C$ values calculated by eq 10 and eq 7c, 8c, and 9c in Table II.

Discussion

Phenanthrenes. One of the most serious obstacles to developing comprehensive correlation equations for the antimalarials was the problem of formulating a log $1/C$ value for those congeners which did not achieve a cure rate of at least 3 out of 5 mice; the problem was especially acute with those congeners which did not achieve any cures. Using an indicator variable to parameterize such a heterogeneous group of congeners having low activity might seem to be a dubious procedure; however, the coefficient with the <3-cure terms in eq 7c, 8c, and 10 are in rather good agreement. The coefficient with this indicator variable in eq 9 does not agree well with the others, but there are only 11 congeners in this case which did not reach the 3-cure level. The best evidence for the use of the <3-cures indicator variable is the fact that the compounds in eq 10 which did not achieve 3 cures are as well fit as the others.

The negative coefficient with this term shows that compounds which do not attain 3 cures are less effective than one would expect from our mode of extrapolation. We believe the techniques employed with these less active compounds may be useful in other QSAR studies.

The use of the <3-cures variable shows that the initial dose–response curve rises more rapidly in the "extending-life" region and then flattens out somewhere between 2 and 3 cures. This might well have been anticipated, since eliminating all microbes to achieve a cure is much more difficult than extending the life of the mice for a certain number of days. What is of greatest interest is that the QSAR for the two processes are quite similar; this is particularly valuable to know since, in much drug research and especially in cancer chemotherapy, one often finds no cures for a whole set of congeners. Our results *suggest* that QSAR formulated with weakly active compounds are of value in designing congeners with curative power.

In the development of eq 7c (Table V), two variables, $\sum\sigma$ and <3-cures, account for 79.4% of the variance in the data. The $\sum\pi$ term accounts for 1.7% and the other five variables for an additional 6.1%. The log P + (log P)^2 terms at the optimum log P add 0.37 to log $1/C$. It is only for very high and low log P values that these terms become critical. There are 14 examples (**76**, **84**, **114**, **119**, **124**, **129**, **138**, **142**, **143**, **146**, **150**, **182**, **190**, and **191**) where log $P \geq$ 7, and all but one of these are tightly fit by eq 7c. When log P is 7, the contribution to log $1/C$ is 0.13, other factors being constant; it is –0.04 at 8 and becomes –0.26 at 9. The highest log P in the phenanthrene series is 8.09 and the lowest log P is 0.83 so that a good test of the limits of log P has not been made.

One of the uses of QSAR is to bring out compounds with unusual activity which can serve as leads for new modifications. Looking over the activity of congeners **1**–**219** of Table II predicted by eq 7c, we find only five examples (**1**, **2**, **18**, **180**, and **195**) which are *underpredicted* by 0.5 or more. There is nothing special about any of these compounds. The high deviations are probably due to testing aberrations. The molecule most widely out of line is **18**, which has a single 2-CF_3 group. While this is the only such example, there are several examples of compounds with a single Br or Cl in the 2 position which are well fit. Compound **18** does not suggest any new line of approach to more active congeners. Compounds **1** and **2** are three to four times more active than expected, but they are similar to compounds **3**, **6**, and **10**, which are well fit. Compound **196** has a 1-OH group, but so does compound **202**, and the latter shows no unusual activity. It would be interesting to retest these compounds to see if this high activity is indeed real.

Adding in terms $(\sum\sigma)^2$ and $(\sum\pi)^2$ to eq 7c did not improve the correlation; hence, we are left with the impression that activity can still be increased by adding relatively small, strong electron-withdrawing lipophilic substituents. The best substituent of this type would be $-SO_2CF_3$ with $\pi = 0.55$ and $\sigma_p = 0.93$. Placing three such substituents in the 1, 3, 5, or 7 position and using $CH_2OHCH_2CH_2N(Bu)_2$ as a side chain would give a compound with a calculated log $1/C$ of 5.72. With four such groups, activity of 6.5 is predicted, provided that $\sum\sigma$ continues to affect activity in a linear fashion from the present highest value of 1.63 up to 3.72. Since the SO_2CF_3 is particularly stable metabolically, this would be a practical molecule to test.

Quinolines. The striking aspect of eq 8c for the quinolines is that all of the parameters common to eq 7c and 8c, except $\sum\sigma$ and the standard deviation, are almost identical. The close agreement between intercepts underlines the bioisosteric character of the two ring systems. The majority of the quinolines are substituted 2-phenylquinolines. Log P for phenanthrene is 4.46 and it is 3.90 for 2-phenylquinoline; hence, the two ring systems are almost isolipophilic. What is surprising is that, this being so, the quinolines are not intrinsically more active than the phenanthrenes because of the electronegative character of the ring nitrogen atom. Since electron withdrawal by substituents is so clearly important in eq 7c, one would expect sp^2 ring nitrogen atoms to enhance activity, other factors being equal. Of course, substituting an aromatic CH with an N results in a large drop in hydrophobicity; for example, log $P_{naphthalene}$ = 3.37 while log $P_{quinoline}$ = 2.03. Nevertheless, the almost identical intercepts of eq 7c and 8c show that isolipophilic phenanthrenes and quinolines yield bioisosteric antimalarials. Moreover, there are many miscellaneous congeners of Table II (supplementary material) with one or two ring nitrogen atoms which are well fit by eq 10. The expected increase in activity by the electronegativity of the aromatic nitrogen atom in the heterocyclic antimalarials of this report must somehow be offset by some repulsive interaction between these nitrogen atoms and some part of the receptor site.

Another unexpected aspect of the electronic effect is that substituents attached directly to the quinoline ring or to the 2-phenyl moiety have the same effect on activity. This is an important clue to the mechanism of action of these antimalarials. There is evidence that antimalarials act by intercalation with DNA;[24,26] if this is so, then the role of electron withdrawal by substituents might be that of promoting electron donation from DNA bases to the aromatic ring of the arylcarbinols. This effect might be more or less the same from the quinoline ring or its 2-phenyl substituent. Of course, such an argument could be made for any active site, and it is not necessary to invoke intercalation with DNA.

Table XIII. Inactive Congeners

no.	substituent	symbol	log 1/C calcd[a]	MR-4′-Q	log P	ref[b]
1	7,4′-F_2; $N(C_2H_4)_2NEt$	Q2P	2.36	0.09	3.32	34
2	7,8-$(CH=CH)_2$, 3,2′,4′-Me_3; NBu_2	Q2P	2.24	0.57	6.00	22
3	6-Cl, 4′-Me; 2-Pip	Q2OP	2.80	0.57	3.40	34
4	6-OMe; quinuclidine-5-Et	Q	1.86	0.00	2.31	34
5	2-CONHPH, 8,3′-$(CF_3)_2$; 2-Pip	Q	3.14	0.00	2.30	34
6	6-$OCHMeCH_2OH$; quinuclidine-5-Et	Q	1.86	0.00	2.31	34
7	2-*t*-Bu, 6-Cl; 2-Pip	Q2TB	2.55	0.00	2.74	34
8	—; $NHC(Me)_2CH_2C(Me)_3$	A9	2.26	0.00	3.46	34
9	4-Cl; $N(Et)_2$	N	2.24	0.00	0.56	34
10	4-Cl; $N(Bu)_2$	N	2.43	0.00	2.19	34
11	4-Cl; $N(Dec)_2$	N	2.28	0.00	8.13	34
12	6-Cl; $N(Bu)_2$	N	2.51	0.00	2.19	34
13	5-Br, 7,8-$(CH=CH)_2$; $N(Hept)_2$	P4	2.41	0.00	7.69	34
14	6-Br; $N(Hept)_2$	P3N	2.65	0.00	4.89	34
15	6,8-Cl_2; $N(Bu)_2$	Q2	2.71	0.00	2.46	34
16	6,8-Cl_2; $N(Hex)_2$	Q2	2.79	0.00	4.40	34
17	6-OMe, 7-Cl; $N(Bu)_2$	Q2	2.31	0.00	1.73	34
18	4-OMe, 6,8-Cl_2; $N(Bu)_2$	Q2	2.77	0.00	2.44	34
19	4-OMe, 6,8-Cl_2; $N(Hex)_2$	Q2	2.85	0.00	4.38	34
20	4,6-$(OMe)_2$, 7-Cl; $N(Bu)_2$	Q2	2.37	0.00	1.71	34
21	7,4′-Cl_2; $N(Hept)_2$	Q3	1.97	0.00	5.40	34
22	8-Cl; $N(Hex)_2$	Q5	2.52	0.00	3.69	34
23	4-Me, 5-Cl; $N(Hept)_2$	Q8	1.85	0.00	5.25	34
24	6,8-Cl_2, 4′-Cl; $N(Bu)_2$	Q4P2	2.91	0.00	5.13	34
25	6-OMe, 7-Cl, 4′-Cl; $N(Bu)_2$	Q4P2	2.59	0.00	4.40	34
26	6-C_6H_5, 4′-Cl; $N(Bu)_2$	Q4P2	2.72	0.00	5.67	34
27	—; $N(CH_2CH_2CO_2H)_2$	P	1.99	0.00	0.60	1
28	—; $N(allyl)_2$	P	1.99	0.00	0.59	1
29	—; $N(c\text{-}C_6H_{11})CH_2CH_2OH$	P	1.99	0.00	2.00	1
30	6-Br; 2-quinuclidinyl	P	2.44	0.00	2.98	34
31	6-Br; 3-azabicyclo[3.2.2]nonane	P	2.47	0.00	3.74	37
32	7,4′-Cl_2; $N(C_2H_4)_2O$	Q2P	2.53	0.60	1.14	13
33	7,4′-F_2; $N(C_2H_4)_2O$	Q2P	2.00	0.09	0.00	13
34	7,4′-F_2; $N(C_2H_4)_2NC_6H_5$	Q2P	2.39	0.09	4.26	13
35	3,2′-C_2H_4; N-Pip	Q2P	2.20	0.10	3.51	34
36	6,8-Cl_2, 3′-OH; $N(Bu)_2$	Q2P	2.87	0.10	3.75	34
37	6-OMe, 3′,4′-Cl_2; $N(Oct)_2$	Q2P	2.35	0.60	8.34	14
38	4′-Me; 2-Pip	Q2OP	2.50	0.57	2.69	4
39	6-OMe; 2-Pip-5-CH=CHBr	Q	2.05	0.00	1.71	34
40	2-*i*-Pr; 2-Pip	Q	2.20	0.00	1.58	34
41	—; $N(Hept)_2$	P1N	2.27	0.00	4.03	34
42	6,8-Me_2; 2-Pip	Q3	1.84	0.00	1.17	34
43	8-Cl; $N(CH_2)_6$	Q2P6	2.46	0.10	3.62	34
44	6-Me; $N(CH_2)_6$	Q2P8	1.63	0.10	3.47	34
45	—; $N(c\text{-}C_6H_{11})CH_2CH_2CN$	P	2.01	0.00	2.27	1
46	—; $N(CH_2CH_2CN)_2$	P	1.70	0.00	0.37	1
47	3,6-$(CF_3)_2$; 4-Pip	P	3.11	0.00	3.34	39
48	10-OMe; $N(Bu)_2$	P	2.05	0.00	2.55	35
49	2,6-$(SO_2Me)_2$; $N(Bu)_2$	P	1.89	0.00	−0.69	2
50	3-COOH, 6-CF_3; 2-Pip	P	2.77	0.00	2.14	38
51	3,6-$(CF_3)_2$; $CH_2N(Non)_2$	P	2.93	0.00	9.77	16
52	3,6-$(CF_3)_2$; NH_2	P	3.04	0.00	2.19	39
53	6,8,4′-Cl_3; $N(C_2H_4)_2NC_6H_5$	Q2P	2.87	0.60	6.11	34
54	7,4′-Cl_2; $N(C_2H_4)_2NC_6H_5$	Q2P	2.73	0.60	5.40	34
55	7,4′-F_2; NH-1-adamantyl	Q2P	2.38	0.09	3.84	13
56	3-Br; $N(Bu)_2$	Q2P	2.58	0.10	3.86	10
57	2-CF_3; 2-Pip	Q2F	2.36	0.00	0.93	34
58	2-*t*-Bu; 2-Pip	Q2TB	2.24	0.00	2.03	34
59	8-CF_3; 2-Pip	Q4H	2.60	0.00	1.12	32
60	—; 2-Pip	Q	1.98	0.00	0.05	34
61	2-C-Hex; 2-Pip	Q	2.29	0.00	2.56	34
62	4′,4″-Br_2; $N(Hept)_2$	PY	2.46	0.00	8.83	27
63	3′,4′,3″,4″-Cl_4; $N(Hept)_2$	PY	2.40	0.00	9.95	27
64	2,2′-$(CF_3)_2$; $N(Bu)_2$	Y	3.16	0.00	3.97	28
65	4′,4″-$(CF_3)_2$; NHBu	PY22VP	3.08	0.00	6.67	29
66	—; N-Pip	T5	1.96	0.00	1.73	6
67	—; $N(Hept)_2$	P6N	2.27	0.00	4.03	34
68	—; $N(Hept)_2$	P8N	2.27	0.00	4.03	34
69	3-Br; $N(Hept)_2$	P8N	2.55	0.00	4.89	34
70	3-Cl; $N(Hept)_2$	P8N	2.53	0.00	4.74	34
71	1,3-Cl_2, 7-Me; $N(Hept)_2$	P8N	2.74	0.00	6.01	34
72	4,6,8-Cl_3; $N(Bu)_2$	Q3	2.50	0.00	3.17	34
73	4,7-Cl_2; $N(Bu)_2$	Q3	2.03	0.00	2.46	34
74	4-Cl, 8-CF_3; $N(Bu)_2$	Q3	2.19	0.00	2.63	34
75	4-Cl, 8-C_6H_5; $N(Bu)_2$	Q3	2.19	0.00	3.71	34
76	6,8-Cl_2; $N(Bu)_2$	Q3	2.20	0.00	2.46	34

Table XIII (*Continued*)

no.	substituent	symbol	log 1/C calcd[a]	MR-4′-Q	log P	ref[b]
77	8-CF_3; $N(Bu)_2$	Q3	1.88	0.00	1.92	34
78	4-Cl, 6,8-Me_2; $N(Bu)_2$	Q3	2.17	0.00	2.87	34
79	6,8-Cl_2; $N(Bu)_2$	Q5	2.71	0.00	2.46	34
80	6-Cl; $N(Et)_2$	Q8	1.58	0.00	0.12	34
81	6-Cl; $N(Bu)_2$	Q8	1.80	0.00	1.75	34
82	4-Me, 5-Cl; $N(Et)_2$	Q8	1.58	0.00	0.68	34
83	4-Me, 5-Cl; $N(Bu)_2$	Q8	1.77	0.00	2.31	34
84	4-Me, 6-Cl; $N(Et)_2$	Q8	1.66	0.00	5.25	34
85	4-Me, 6-Cl; $N(Bu)_2$	Q8	1.85	0.00	2.31	34
86	4-Me, 6-Cl; $N(Hept)_2$	Q8	1.93	0.00	525	34
87	8-Cl; $N(Hex)_2$	Q2P6	2.61	0.10	5.65	34
88	8-Me; $N(CH_2)_6$	Q2P6	2.30	0.10	3.47	34
89	8,4′-Me_2; $N(CH_2)_6$	Q2P6	2.30	0.57	4.03	34
90	4′-Cl; $N(CH_2)_6$	Q2P7	1.72	0.60	3.62	34
91	—; $N(CH_2)_6$	Q2P8	1.42	0.10	2.91	34
92	2-adamant-1-yl, 6,8-Cl_2; 2-Pip-NCOMe	Q2AD	2.87	0.00	4.29	34
93	2-*t*-Bu; $CH(CH_2OH)N(Et)_2$	Q2TB	*c*			34
94	6-Br; 2-Pip-N-COOEt	P	*c*			34
95	3,6-$(CF_3)_2$; NHCH(COOMe)-*i*-Pr	P	*c*			34
96	—; $C(CH_2OH)N(Et)_2$	Q2TH	*c*			34
97	—; $N(CH_2CH_2CH_2NH_2)_2$	P	*c*			34
98	—; $N(CH_2CCH)_2$	P	*c*			34
99	6-Br; 2-Pip-NCOPr:OCOBu	P	*c*			34
100	6-Br; $NHCH_2$-2-Pip-N-Me	P	*c*			34
101	6-Br; $N(C_2H_4)_2N(CH_2)_3N(Me)_2$	P	*c*			34
102	6-Br; $N[(CH_2)_2N(Et_2)]_2$	P	*c*			34
103	4′,4″-Cl_2; N(Bu)Succ	PY	*c*			34

[a] Calculated using eq 10. [b] See footnote *c*, Table II. [c] Variations in these side chains are so unusual that we were not able to make reasonable estimates of log *P*; hence, we have not been able to give a calculated log 1/*C*.

The quinolines differ from the phenanthrenes in a number of ways. The most important difference is that accounted for by the MR-4′-Q variable. The rather large coefficient (compared to that with $\sum\pi$) with this term suggests a role for dispersion forces or steric effects by substituents in the 4′ position on the 2-phenyl group. These substituents are better correlated by MR than by π. MR could be modeling binding by 4′ substituents to the active site and/or the production of a conformational change in the site. No such effect is apparent in the phenanthrene series. In addition, it was found that better results are obtained by not including π or MR for 3′ substituents; hence, both 3′ and 4′ substituents appear to be positioned outside of the hydrophobic region of the active site into which substituents on the phenanthrene ring fall (as modeled by $\sum\pi$).

Other differences between quinolines and phenanthrenes are accounted for by the Me-6,8-Q and 2-Pip terms. The former term brings out the special activating effect of methyl groups in either the 6 or 8 position. The activating effect of such methyl groups was also noticed by Pinder and Burger.[25] The 2-Pip side chain seems to confer some small extra activity on quinolines not seen with the phenanthrenes.

The small contribution of the AB term present in the phenanthrenes does not have a significant role in the quinolines. The poorer correlation with the quinolines may mask this small effect.

The <3-cures term in eq 8c is more significant because 87 of the 219 quinolines produce less than 3 cures, while only 38 out of 217 phenanthrenes failed to achieve 3 cures. The anomalous position of $\sum\sigma$ in the development of eq 8c compared to eq 7c requires comment. In the case of the phenanthrenes, the better spread in π values may allow a better separation of the roles of π and σ. We have a mean and standard deviation in the phenanthrenes for $\sum\pi$ of 1.52 ± 0.80 and 0.67 ± 0.38 for $\sum\sigma$, while a somewhat lower variance is seen with the quinolines in the corresponding figures: $\sum\pi$ = 0.79 ± 0.55 and $\sum\sigma$ = 0.38 ± 0.44.

It should be possible to make a more potent quinoline by adding two SO_2CF_3 groups to the quinoline ring and placing one in the 4′ position. This combination with a $CHOHCH_2$-2-Pip side chain has a calculated log 1/*C* of 5.52.

2,6-Diphenylpyridines. A most notable difference between eq 9 for the pyridines and eq 7c and 8c for the phenanthrenes and quinolines is that eq 9 does not contain a $\sum\pi$ term. In addition, its coefficient with $\sum\sigma$ is larger than that for eq 7c and 8c, which is probably due to the high collinearity between $\sum\pi$ and $\sum\sigma$ (see Table X). The $\sum\sigma$ term in eq 9 may account for the hydrophobic effect as well as the electronic effect of the substituents; however, one must recall that the 2-phenyl group in the pyridines is analogous to the 2-phenyl group in the quinolines and that no parameterization was made in eq 8c for the hydrophobic effect of 3′ and 4′ substituents.

All Congeners. Two new variables not needed in the preceding equations are required in eq 10. The variable Py is assigned the value of 1 for all pyridines and the variable Q2P378 is assigned the value of 1 for 2-phenylquinolines with side chains attached at positions 3, 7, and 8. The corresponding quinolines with side chains at positions 4–6 are given the value of 0 for Q2P378. The negative coefficent with Q2P378 shows that aromatic nuclei cannot be placed on the active site in just any fashion; certain configurations are more effective, although almost any aromatic nucleus appears to give congeners with some activity.

In Table II (supplementary material) one can compare the results obtained with eq 10 for all congeners with those of the specialized eq 7c, 8c, and 9 for the phenanthrenes, quinolines, and pyridines. Although these three specialized equations give somewhat better results, the agreement in general is quite good. Equation 10 would be as good a guide for the synthesis of new compounds as eq 7c and 8c. Equation 9 might be misleading because of high collinearity between $\sum\pi$ and $\sum\sigma$.

Inactive Congeners. Almost all structure–activity

studies turn up compounds which show little or no activity even though they are closely related structurally to active compounds. Attempts are being made to deal with such derivatives by using discriminate analysis or pattern recognition. We believe, however, that the lack of activity of such molecules should, where possible, be rationalized in terms of the QSAR. Undue weight should not in general be accorded such compounds, since their borderline activity often means that their activities are at *best* less accurately known.

In the present study we have placed such molecules in Table XIII along with their calculated log $1/C$ values (eq 10) and their physiochemical parameters. Compounds 1–**26** showed a mean survival time (Δt_{ms}) of from 2–11 days; most were in the range of 3–6 days. Compounds **27**–**44** produced a Δt_{ms} of between 1 and 2 days. The remaining 48 derivatives can be considered to be inactive, since their Δt_{ms} was less than 1 day. Excluding compound **80**, which is reported to be very toxic to mice, the average of their predicted log $1/C$ values is 2.34. This of course is reassuring, since they are, as expected from eq 10, weakly active and predicted to be near the bottom of the scale in Table II (supplementary material). The least active compound in Table II has a log $1/C$ of 1.97.

Most of the compounds in the inactive group have calculated values near the borderline of 2. Notable exceptions are compounds **5**, **47**, **52**, **64**, and **65**, which have predicted log $1/C$ of 3 or more. Compound **52** is unique in that it has no alkyl group attached to the side-chain amino group; such alkyl groups appear to be essential for activity. Compounds **64** and **65** were tested only up to 160 mg/kg instead of the usual 640; they may well show activity at higher doses. Compound **5** is a unique structure with a 2-$CONHC_6H_5$ substituent on the quinoline ring; it would be interesting to know if this group is generally deactivating or if it is just a fluke. Compounds **47** and **64** are also unique structures.

Compounds **15**–**20** and **24**–**26** are another group having a special feature. The side chain in these compounds is attached to the 2 position of the quinoline ring; such an attachment essentially destroys activity. Other compounds with unique structures are **67**–**71**.

A number of compounds having more or less "normal" structures and rather large log $1/C$ values are **3** (2.80), **36** (2.87), **50** (2.78), **51** (2.93), and **53** (2.87). It is possible that activity in some of these compounds was missed because of difficulty in testing. Many of the compounds discussed in this report are highly insoluble and difficult to test.

Two other general types of arylmethanols which have always turned out to be inactive are those with a pyridine moiety[25] serving as the basic group in the side chain and bis compounds[26] in which two aryl units are joined together by connection through the side chain via a diamine.

All in all, we feel that the more or less inactive compounds of Table XIII are reasonably well accounted for when those with unique structural features for which no parameterization is present in eq 10 can be set aside. Certainly there are no bad surprises where high activity was found and low predicted or where high activity was predicted (log $1/C > 4$) and low was found. Nothing important would have been missed if one had been making new congeners on the basis of developing eq 10 and all of the compounds of Table XIII had simply not been made.

Kubinyi Bilinear Model. Using the technique outlined under Method, we have fit all active congeners to the bilinear model. Equation 11, obtained by this method, can be compared with eq 10. With the possible exception of log P_0, the parameters of eq 10 and 11 do not differ significantly. Since the bilinear model contains one more parameter than the parabolic model, eq 11 is less satisfactory than eq 10.

$$\log 1/C = 0.576(\pm0.09)\sum\sigma + 0.168(\pm0.05)\sum\pi + 0.105(\pm0.05)\log P - 0.167(\pm0.07)\log(\beta P + 1) 0.169(\pm0.10)\text{c-side} + 0.319(\pm0.136)CNR_2 - 0.139(\pm0.06)\text{AB} - 0.795(\pm0.06)\text{<3-cures} + 0.278(\pm0.11)\text{MR-4'-Q} + 0.252(\pm0.18)\text{Me-6,8-Q} + 0.084(\pm0.10)\text{2-Pip} + 0.151(\pm0.19)\text{NBrPy} - 0.683(\pm0.22)\text{Q2P378} + 0.267(\pm0.11)\text{Py} + 2.726(\pm0.15) \quad (11)$$

$n = 646$; $r = 0.898$; $s = 0.309$; $\log P_0 = 4.19$; $\log \beta = 3.959$

The drug-modification study of Table II (supplementary material) is most impressive. The best compounds are 1000 times as potent as quinine (**412**), which, with a log $1/C$ of 2.06, is almost at the bottom of the list. This large data set of complex drugs acting on a most complex organism in mice constitutes an excellent proving ground for developing our ideas about structure–activity relationships. While the result embodied in eq 10 is highly satisfying, it is unlikely to be the "last word" on this set of congeners; the complexity of the set is enormous. Moreover, we have had to make a number of assumptions in calculating log P values and in dealing with the electronic effects of substituents which no doubt have introduced some errors into our calculations. We may have overlooked interaction terms and we may even have missed indicator variables which would help in our analysis. The amount of information for correlation in Table II (supplementary material) is so huge that we have not been able to completely get it "into our heads", even after working with it off and on for several years; that is, there are so many variations on so many compounds that it is extremely difficult to keep in mind all of the various structural features for hypothesis testing. It was only by careful study of the residuals from the various correlation equations as they developed that various indicator variables began to show significance. Eventually, the commonality came to light and merging the sets became feasible. A kind of manageable order has been brought to the 646 molecules of Table II; also, the lack of activity of the compounds in Table XIII is accounted for moderately well.

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Supplementary Material Available: Substituent constants for Tables II and XIII and the method of calculating partition coefficients (77 pages). Ordering information is given on any current masthead page.

References and Notes

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Structure-Activity Relationships of Dimeric *Catharanthus* Alkaloids. 2. Experimental Antitumor Activities of N-Substituted Deacetylvinblastine Amide (Vindesine) Sulfates[1-3]

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While structure-activity relationships for vinblastine (VLB), vincristine, deacetyl-VLB, and deacetyl-VLB amide (vindesine, VDS) in several tumor and leukemia models have been reported previously,[3] the present study explores these relationships for a series of N-substituted vindesine analogues. These compounds were prepared from the reaction of deacetyl-VLB acid azide with the appropriate amines and were characterized by mass spectral analysis, ^1H and ^{13}C NMR spectra, electrometric titration, and infrared spectra. *N*-Alkylvindesines have reduced activity compared to that of VDS against the Gardner lymphosarcoma (GLS). *N*-β-Hydroxyethyl-VDS surpasses vindesine in its activity against the Ridgway osteogenic sarcoma and the GLS, whereas against the B16 melanoma it is less active than VDS. *N*-β-(4-Hydroxyphenethyl)-VDS, envisaged as a substrate for the enzyme tyrosinase, was shown to be more active than VDS against the B16 melanoma but has only marginal activity against the GLS. In terms of *collective* antitumor activity against the model systems used, vindesine emerges as the congener with optimum qualities. Bis(*N*-ethylidenevindesine) disulfide, the first example of a bridged bisvindesine and comparable to VDS in its antitumor profile, shows evidence of activity against a P388/VCR leukemia strain known to be resistant to maytansine as well as to vincristine.

Despite the relatively "minor" difference between the molecular structures of the *Catharanthus* alkaloids vinblastine (VLB, N_a-CH_3) and vincristine (VCR, N_a-CHO), substantial differences in the clinical usefulness and clinical toxicity of these two oncolytic agents have been noted.[3,5] Vindesine (VDS, 1, $R_1 = R_2 = H$), a chemically modified vinblastine product selected for clinical evaluation, provides an opportunity to explore the consequences of another "minor" structural change.[3]

The selection of VDS for trial in man depended on several factors. VDS possesses an experimental antitumor spectrum[3] which resembles that of VCR rather than that of the parent alkaloid VLB, while its toxicological profile[6] suggested a potential for reduced neurotoxicity relative to that of VCR. The relative ease with which a preparation of adequate purity could be secured also favored this choice.

Phase I and II clinical trial reports[7-13] indicate vindesine to be an active oncolytic agent. Clinically, vindesine appears to be less neurotoxic than VCR, and generally its administration has not had to be discontinued because of neurotoxicity.[13]

These preliminary clinical observations obtained with vindesine provide much needed feedback information for the design of further improved *Catharanthus* alkaloid modification products.

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