ppears to undergo metabolism in whole animals in the andom walk from site of injection to site of action. We oelieve that correlation analysis can play a major role in "fine tuning" a reactive function such as SO_2F. This might be accomplished electronically or sterically; for example, a recent high ρ value of 2.79 has been reported[28] for the alkaline hydrolysis of para-substituted benzenesulfonyl fluorides. By placing proper substituents on the inhibitor with the SO_2F function, one could develop maximum stability with respect to metabolism compatible with reasonable irreversible enzyme inhibition. At each of Baker's four steps in inhibitor design, correlation analysis, coupled with cluster analysis for substituent selection,[3] can play a crucial role in drug development at the enzymic level.

The role of substituents in metabolism[5] and the random walk process must also be considered in making the transition from in vitro work to in vivo whole animal studies. It is clear from Baker's triazine study[8] that gaining more inhibitory in vitro activity by increasing MR is not likely to be valuable in whole animal studies. MR seems to model the most nonspecific kind of interaction between enzyme and ligand. Baker did not distinguish[2a] clearly between hydrophobic and polar areas; indeed, this is difficult to do even using regression analysis.

One must make maximum use of the directional nature[23] of hydrophobic binding to ensure maximum interaction between ligand and pathogen enzyme and, if possible, minimize this type of interaction with the host enzyme. When maximum hydrophobicity has been attained in one part of the inhibitor, one must attach polar groups which will fall in the polar space of the enzyme or project into the aqueous phase to counterbalance the overall hydrophobicity of the potential drug. There are few examples where log P_0 for a set of drugs exceeds 4 (in vivo).

References and Notes

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Correlation Analysis of Baker's Studies on Enzyme Inhibition. 2. Chymotrypsin, Trypsin, Thymidine Phosphorylase, Uridine Phosphorylase, Thymidylate Synthetase, Cytosine Nucleoside Deaminase, Dihydrofolate Reductase, Malate Dehydrogenase, Glutamate Dehydrogenase, Lactate Dehydrogenase, and Glyceraldehyde-phosphate Dehydrogenase†,[1a]

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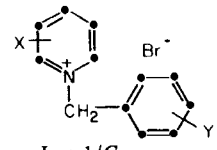
The inhibitory activity of 1058 inhibitors of the title enzymes has been formulated in 13 equations correlating chemical structure with inhibitory potency. Two types of regions in enzymes have been defined by means of π and molar refractivity constants. The use of indicator variables has been extensively developed to suggest special enzyme–ligand interactions. Several examples are given of the use of correlation equations in comparing structural features of different systems.

In the first paper in this series,[2] five correlation equations were presented which relate chemical structure and inhibitory activity of 578 reversible inhibitors of guanine deaminase, xanthine oxidase, dihydrofolate reductase, and complement. In this paper, most of the rest of Baker's studies during the period 1964–1972 are correlated by 13 equations describing the QSAR for 1053

† This paper is dedicated to the memory of Edward Smissman and Bernard R. Baker.

Table I. Inhibition Constants and Physicochemical Parameters for the Reversible Inhibition of α-Chymotrypsin by Benzylpyridinium Bromides



No.	X	Y	Log 1/C Obsd[a]	Log 1/C Calcd[b]	|Δ log 1/C|	π	I-1	I-2	I-3	% irreversible inact.	Ref
1	3-(3,4-$Cl_2C_6H_3OCH_2CONHCH_2$)	4-NO_2	3.33	3.55	0.22	1.65	0	0	0		8a
2	3-(3,4-$Cl_2C_6H_3OCH_2CONHCH_2$)	4-OCH_3	3.40	3.63	0.23	2.06	0	0	0		8a
3	3-(3,4-$Cl_2C_6H_3OCH_2CONHCH_2$)	H	3.42	3.64	0.22	2.08	0	0	0		8a
4	3-(3,4-$Cl_2C_6H_3OCH_2CONHCH_2$)	4-Cl, 3-SO_2F	3.70	3.86	0.16	3.16	0	0	0	100	8b
5	H	2-SO_2F	3.77	4.42	0.65	0.37	1	0	0	100	8c
6	3-(3,4-$Cl_2C_6H_3OCH_2CONH$)	4-NO_2	3.82	3.82	0.00	1.65	0	0	1		8a
7	3-(3,4-$Cl_2C_6H_3OCH_2CONH$)	H	3.92	3.91	0.01	2.08	0	0	1		8a
8[c]	3-(3,4-$Cl_2C_6H_3OCH_2CONHCH_2$)	3-Cl, 4-SO_2F	3.92	4.57	0.65	3.16	0	1	0	100	8b
9	3-(3,4-$Cl_2C_6H_3OCH_2CONH$)	4-CH_3	3.96	4.03	0.07	2.64	0	0	1		8a
10	H	4-SO_2F	3.96	3.99	0.03	0.37	0	1	0	93	8c
11	4-CH_3	4-SO_2F	4.01	4.11	0.10	0.93	0	1	0	95	8c
12	3-(3,4-$Cl_2C_6H_3OCH_2CONHCH_2$)	3-SO_2F	4.02	3.71	0.31	2.45	0	0	0	100	8a
13	3-CH_3CONH	4-SO_2F	4.02	4.07	0.05	−0.60	0	1	1	100	8a
14	3-(3,4-$Cl_2C_6H_3OCH_2CONH$)	4-OCH_3	4.05	3.91	0.14	2.06	0	0	1		8a
15	3-(3,4-$Cl_2C_6H_3OCH_2CONH$)	4-NO_2	4.07	3.82	0.25	1.65	0	0	1		8a
16	3-(3,4-$Cl_2C_6H_3OCH_2CONH$)	3,4-Cl_2	4.11	4.21	0.10	3.50	0	0	1		8a
17	4-$C_6H_5(CH_2)_2$	4-SO_2F	4.18	4.54	0.36	3.03	0	1	0	94	8c
18	4-$C_6H_5(CH_2)_3$	4-SO_2F	4.23	4.65	0.42	3.53	0	1	0	94	8c
19	3-(3,4-$Cl_2C_6H_3OCH_2CONH$)	3-SO_2F	4.29	3.99	0.30	2.45	0	0	1	100	8a
20	4-$C_6H_5CH_2$	4-SO_2F	4.30	4.41	0.11	2.38	0	1	0	94	8c
21	2,3-Benzo	4-SO_2F	4.30	4.27	0.03	1.69	0	1	0	88	8c
22[c]	4-$C_6H_5(CH_2)_3$	6-Cl, 2-SO_2F	4.32	5.22	0.90	4.24	1	0	0	92	8c
23	3-(3,4-$Cl_2C_6H_3OCH_2CONHCH_2$)	3-Cl, 2-SO_2F	4.43	5.00	0.57	3.16	1	0	0	100	8b
24	4-$C_6H_5(CH_2)_4$	4-SO_2F	4.43	4.75	0.32	4.03	0	1	0	95	8c
25[c]	4-(3,4-$Cl_2C_6H_3CH_2CH_2$)	2-SO_2F	4.48	5.26	0.78	4.45	1	0	0	87	8c
26[c]	3-(3,4-$Cl_2C_6H_3OCH_2CONH$)	3-Cl, 2-SO_2F	4.55	5.27	0.72	3.16	1	0	1	100	8b
27	H	6-Cl, 2-SO_2F	4.55	4.56	0.01	1.08	1	0	0	97	8c
28	3-(3,4-$Cl_2C_6H_3CH_2CH_2$)	4-SO_2F	4.64	4.84	0.20	4.45	0	1	0	92	8c
29	4-(3,4-$Cl_2C_6H_3CH_2CH_2$)	4-SO_2F	4.66	4.84	0.18	4.45	0	1	0	90	8c
30	3-(3,4-$Cl_2C_6H_3OCH_2CONHCH_2$)	2-Cl, 4-SO_2F	4.70	4.57	0.13	3.16	0	1	0	100	8b
31	4-[3,4-$Cl_2C_6H_3(CH_2)_4$]	4-SO_2F	4.70	5.05	0.35	5.45	0	1	0	85	8c
32	3,4-Benzo	6-Cl, 2-SO_2F	4.72	4.84	0.12	2.40	1	0	0	96	8c
33	2-(3,4-$Cl_2C_6H_3CH_2CH_2$)	4-SO_2F	4.77	4.84	0.07	4.45	0	1	0	85	8c
34	3-(3,4-$Cl_2C_6H_3OCH_2CONHCH_2$)	4-SO_2F	4.80	4.42	0.38	2.45	0	1	0	100	8a
35	4-$C_6H_5(CH_2)_4$	6-Cl, 2-SO_2F	4.80	5.32	0.52	4.74	1	0	0	100	8c
36	3-(3,4-$Cl_2C_6H_3OCH_2CONH$)	4-SO_2F	4.82	4.70	0.12	2.45	0	1	1	100	8a
37	3-(3,4-$Cl_2C_6H_3OCH_2CONH$)	3-Cl, 4-SO_2F	4.85	4.85	0.00	3.16	0	1	1	84	8b
38	3-(3,4-$Cl_2C_6H_3OCH_2CONH$)	2-SO_2F	4.89	5.12	0.23	2.45	1	0	1	100	8b
39[c]	3-(3,4-$Cl_2C_6H_3OCH_2CONH$)	4-Cl, 3-SO_2F	4.89	4.14	0.75	3.16	0	0	1	100	8b
40	4-[3,4-$Cl_2C_6H_3O(CH_2)_3$]	4-SO_2F	4.89	4.93	0.04	4.90	0	1	0	90	8c
41	3-(3,4-$Cl_2C_6H_3OCH_2CONH$)	2-Cl, 4-SO_2F	4.92	4.85	0.07	3.16	0	1	1	100	8b

42	3-(3,4-$Cl_2C_6H_3OCH_2CONH$)	4-Cl, 2-SO_2F	4.92	5.27	0.35	3.16	1	0	1	100	8b
43	4-C_6H_5	4-SO_2F	4.96	4.40	0.56	2.33	0	1	0	94	8c
44	3-$C_6H_5(CH_2)_2$	6-Cl, 2-SO_2F	5.14	5.12	0.02	3.74	1	0	0	89	8c
45	2-(3,4-$Cl_2C_6H_3CH_2CH_2$)	2-SO_2F	5.18	5.26	0.08	4.45	1	0	0	100	8c
46	3-$C_6H_5(CH_2)_4$	4-SO_2F	5.19	4.75	0.44	4.03	0	1	0	89	8c
47	2-[3,4-$Cl_2C_6H_3(CH_2)_4$]	4-SO_2F	5.21	5.05	0.16	5.45	0	1	0	82	8c
48	3-(3,4-$Cl_2C_6H_3OCH_2CONH$)	5-Cl, 2-SO_2F	5.22	5.27	0.05	3.16	1	0	1	100	8b
49	3-(3,4-$Cl_2C_6H_3OCH_2CONH$)	6-Cl, 2-SO_2F	5.24	5.27	0.03	3.16	1	0	1	100	8b
50	2,3-Benzo	6-Cl, 2-SO_2F	5.25	4.84	0.41	2.40	1	0	0	91	8c
51	3-(3,4-$Cl_2C_6H_3OCH_2CONHCH_2$)	4-Cl, 2-SO_2F	5.36	5.00	0.36	3.16	1	0	0	100	8b
52	3-(3,4-$Cl_2C_6H_3OCH_2CONHCH_2$)	6-Cl, 2-SO_2F	5.36	5.00	0.36	3.16	1	0	0	100	8b
53	3-[3,4-$Cl_2C_6H_3(CH_2)_4$]	4-SO_2F	5.38	5.05	0.33	5.45	0	1	0	94	8c
54	3-$C_6H_5(CH_2)_4$	6-Cl, 2-SO_2F	5.47	5.32	0.15	4.74	1	0	0	86	8c
55	2-[3,4-$Cl_2C_6H_3(CH_2)_4$]	2-SO_2F	5.47	5.47	0.00	5.45	1	0	0	100	8c
56	3-(3,4-$Cl_2C_6H_3OCH_2CONHCH_2$)	5-Cl, 2-SO_2F	5.48	5.00	0.48	3.16	1	0	0	100	8b
57	3-[3,4-$Cl_2C_6H_3(CH_2)_4$]	2-SO_2F	5.48	5.47	0.01	5.45	1	0	0	100	8c
58	3-[3,4-$Cl_2C_6H_3(CH_2)_4$]	6-Cl, 2-SO_2F	5.48	5.62	0.14	6.16	1	0	0	100	8c
59	3-(3,4-$Cl_2C_6H_3OCH_2CONHCH_2$)	2-SO_2F	5.49	4.85	0.64	2.45	1	0	0	100	8b
60	3-(3,4-$Cl_2C_6H_3CH_2CH_2$)	2-SO_2F	5.52	5.26	0.26	4.45	1	0	0	83	8c
61	4-[3,4-$Cl_2C_6H_3(CH_2)_4$]	2-SO_2F	5.55	5.47	0.08	5.45	1	0	0	96	8c

[a] Calculated from results of Baker et al.[8] [b] Calculated using eq 1. [c] These points not used in deriving equations.

Table II. Squared Correlation Matrix Showing Degree of Collinearity (r^2) between the Important Variables Used in α-Chymotrypsin Correlation Analysis

	π	MR	*I*-1	*I*-2	*I*-3
π	1.00	0.29	0.05	0.00	0.09
MR		1.00	0.00	0.07	0.04
I-1			1.00	0.42	0.02
I-2				1.00	0.02
I-3					1.00

Table III. Development of QSAR for α-Chymotrypsin

Intercept	π-X,Y	*I*-1	*I*-2	*I*-3	*r*	*s*	$F_{1,X}$
3.79	0.28				0.642	0.485	38
3.69	0.23	0.62			0.800	0.383	34
3.41	0.19	1.05	0.62		0.877	0.310	29
3.21	0.21	1.13	0.71	0.28	0.895	0.291	8.1

inhibitors of 11 different enzymes. In the two papers, 18 equations give the QSAR for 1631 enzyme inhibitor interactions with 14 different enzymes. In all, the data from over 100 papers by Baker's group are organized in a coherent manner which gives a quick overview of a vast amount of work.

While the equations are not perfect correlations and the ground covered by Baker leaves a good deal to be desired in the mapping of the various binding site regions, they do give an immediately comprehendable view of a huge enzymic structure–activity study. One can clearly see from the correlation equations what has been done as well as what needs to be done to further develop a given system. Baker's inhibitors are so complex, so numerous, and scattered through so many papers that we have yet to encounter someone who has made a serious effort to integrate his studies or even read all of the papers.

Method. The substituent constants employed in this work are from our recent compilation[3] or were calculated from these values. Many examples of such calculations have been reported.[4-7] Three new values were determined: $\pi_{NHCH_2C_6H_5}$ = 1.00 (from log $P_{C_6H_5NHCH_2C_6H_5}$ = 3.13); π_{OH} = −1.23 and π_{NH_2} = −0.16 (from log $P_{2\text{-pyridone}}$ = −0.58; log $P_{2\text{-aminopyridine}}$ = 0.49); and pyridine = 0.65. These values were used for 4- and 6-OH and NH_2 pyrimidines of Table XXI. The data for the correlations are contained in Tables I, IV, VII, IX, XII, XV, XVIII, XXI, XXIV, XXVII, XXX, and XXXIII, the degree of collinearity among the pertinent variables is presented in Tables II, V, VIII, X, XIII, XVI, XIX, XXII, XXV, XXVIII, XXXI, and XXXIV, and the stepwise development of the "best" equations is displayed in Tables III, VI, XI, XIV, XVII, XX, XXIII, XXVI, XXIX, XXXII, and XXXV.

C in the correlation equations is the molar concentration of inhibitor causing 50% inhibition of the enzyme. [S]/[I]-0.5 refers to ratio of the concentration of substrate [S] to inhibitor [I] which gives 50% inhibition.

All of the data come from Baker's papers on chymotrypsin,[8] trypsin,[9] thymidine phosphorylase[10] (*E. coli*), uridine phosphorylase[11] (Walker 256), thymidylate synthetase,[12] cytosine nucleoside deaminase,[13] dihydrofolate reductase,[14] malate dehydrogenase,[15] glutamate dehydrogenase,[15] lactate dehydrogenase,[15] and glyceraldehyde-phosphate dehydrogenase.[15]

Results

α-Chymotrypsin. We have been especially interested in the interaction of ligands with chymotrypsin, a proteolytic enzyme which hydrolyzes a wide variety of simple

Table IV. Constants Used for Deriving Eq 2 for Chymotrypsin

$$R^1-\overset{\overset{O}{\|}}{C}-R^2$$

No.	R^1	R^2	Log 1/C Obsd[a]	Log 1/C Calcd[b]	$\lvert\Delta$ log 1/C$\rvert$	MR_{R_1,R_2}	*I*-1	*I*-2	*I*-3	*I*-4	Ref
1	4-CN-$C_6H_4OCH_2$	CH_3	1.47	2.01	0.54	4.32	0.0	0.0	0.0	0.0	8d
2	$C_6H_5OCH_2$	$NHCH_3$	1.60	1.99	0.39	4.25	0.0	0.0	0.0	0.0	8d
3	3-CN-$C_6H_4OCH_2$	CH_3	1.66	2.01	0.35	4.32	0.0	0.0	0.0	0.0	8d
4	4-CH_3-$C_6H_4OCH_2$	CH_3	1.72	1.99	0.27	4.25	0.0	0.0	0.0	0.0	8d
5	4-CH_3O-$C_6H_4OCH_2$	CH_3	1.77	2.05	0.28	4.47	0.0	0.0	0.0	0.0	8d
6	$C_6H_5(CH_2)_2$	$N(C_2H_5)_2$	1.77	2.43	0.66	5.95	0.0	0.0	0.0	0.0	8d
7	$C_6H_5CH_2NH$	OC_2H_5	1.82	2.12	0.30	4.72	0.0	0.0	0.0	0.0	8d
8	$C_6H_5(CH_2)_2$	CH_3	1.82	1.94	0.12	4.04	0.0	0.0	0.0	0.0	8d
9	3-COO^--$C_6H_4OCH_2$	NHC_6H_5	1.89	1.83	0.06	6.72	0.0	0.0	0.0	1.0	8g
10	$C_6H_5OCH_2$	CH_3	1.92	1.87	0.05	3.79	0.0	0.0	0.0	0.0	8d
11	3-CH_3-$C_6H_4OCH_2$	CH_3	1.92	1.99	0.07	4.25	0.0	0.0	0.0	0.0	8d
12	4-$C_5H_4N(CH_2)_2$	NHC_6H_5	2.04	2.49	0.45	6.23	0.0	0.0	0.0	0.0	8g
13	2-$C_5H_4N(CH_2)_2$	NHC_6H_5	2.07	2.49	0.42	6.23	0.0	0.0	0.0	0.0	8g
14	$C_6H_5CH_2$	CH_3	2.10	1.80	0.30	3.57	0.0	0.0	0.0	0.0	8d
15	$C_6H_5(CH_2)_2$	$N(CH_3)C_6H_5$	2.10	2.65	0.55	6.94	0.0	0.0	0.0	0.0	8d
16	3-$C_5H_4N(CH_2)_2$	NHC_6H_5	2.11	2.49	0.38	6.23	0.0	0.0	0.0	0.0	8g
17	4-C_5H_4NCH=CH	NHC_6H_5	2.19	2.51	0.32	6.30	0.0	0.0	0.0	0.0	8g
18	2-$NO_2C_6H_4OCH_2$	CH_3	2.22	2.04	0.18	4.42	0.0	0.0	0.0	0.0	8d
19	2-COO^--$C_6H_4OCH_2$	NHC_6H_5	2.27	1.83	0.44	6.72	0.0	0.0	0.0	1.0	8g
20	$C_6H_5OCH_2$	NHC_6H_4-4-COO^-	2.28	2.25	0.03	6.73	0.0	0.0	1.0	0.0	8f
21	$C_6H_5OCH_2$	NHC_6H_4-3-COO^-	2.28	2.25	0.03	6.73	0.0	0.0	1.0	0.0	8g
22	$C_6H_5OCH_2$	C_6H_5	2.30	2.38	0.08	5.76	0.0	0.0	0.0	0.0	8d
23	2,3-$(CH=CH)_2$-$C_6H_5OCH_2$	CH_3	2.30	2.27	0.03	5.33	0.0	0.0	0.0	0.0	8d
24	$C_6H_5SCH_2$	CH_3	2.30	2.03	0.27	4.39	0.0	0.0	0.0	0.0	8d
25	3-NO_2-$C_6H_4OCH_2$	CH_3	2.31	2.04	0.27	4.42	0.0	0.0	0.0	0.0	8d
26	$C_6H_5OCH_2$	NHC_6H_4-4-OCH_2COO^-	2.32	2.39	0.07	7.41	0.0	0.0	1.0	0.0	8g
27	$C_6H_5OCH_2$	NHC_6H_4-4-CH_2COO^-	2.35	2.34	0.01	7.19	0.0	0.0	1.0	0.0	8g
28	$C_6H_5OCH_2$	NHC_6H_4-2-COO^-	2.37	2.25	0.12	6.73	0.0	0.0	1.0	0.0	8g
29	4-NO_2-$C_6H_4OCH_2$	CH_3	2.40	2.04	0.36	4.42	0.0	0.0	0.0	0.0	8d
30	C_6H_5CH=CH	OC_2H_5	2.40	2.11	0.29	4.67	0.0	0.0	0.0	0.0	8d
31	$C_6H_5(CH_2)_2$	OC_2H_5	2.40	2.12	0.28	4.72	0.0	0.0	0.0	0.0	8d
32	4-Cl-$C_6H_4OCH_2$	CH_3	2.41	2.83	0.42	4.29	0.0	1.0	0.0	0.0	8d
33	4-NO_2-C_6H_4CH=CH	CH_3	2.44	2.09	0.35	4.62	0.0	0.0	0.0	0.0	8d
34	$C_6H_5OCH_2$	$N(CH_3)C_6H_5$	2.46	2.60	0.14	6.69	0.0	0.0	0.0	0.0	8d
35	4,6-Cl_2-2-COO^--$C_6H_2OCH_2$	NHC_6H_5	2.51	2.87	0.36	7.72	0.0	1.0	0.0	1.0	8g
36	3-C_5H_4NCH=CH	NHC_6H_5	2.52	2.51	0.01	6.30	0.0	0.0	0.0	0.0	8g
37	2-C_5H_4NCH=CH	NHC_6H_5	2.52	2.51	0.01	6.30	0.0	0.0	0.0	0.0	8g
38	$C_6H_5OCH_2$	NHC_6H_5	2.59	2.49	0.10	6.22	0.0	0.0	0.0	0.0	8d
39	$C_6H_5OCH_2$	$NH(CH_2)_2C_6H_5$	2.64	2.70	0.06	7.15	0.0	0.0	0.0	0.0	8d
40	4-CH_3O-$C_6H_4OCH_2$	C_6H_5	2.72	2.54	0.18	6.44	0.0	0.0	0.0	0.0	8d
41	3,4-$(CH=CH)_2$-$C_6H_3OCH_2$	CH_3	2.74	2.28	0.46	5.33	0.0	0.0	0.0	0.0	8d
42	2-$C_6H_5C_6H_4OCH_2$	CH_3	2.80	2.49	0.31	6.22	0.0	0.0	0.0	0.0	8d
43	4-Cl-2-COO^--$C_6H_3OCH_2$	NHC_6H_5	2.82	2.76	0.06	7.22	0.0	1.0	0.0	1.0	8g
44	5-Cl-2-COO^--$C_6H_3OCH_2$	NHC_6H_5	2.82	2.76	0.06	7.22	0.0	1.0	0.0	1.0	8g
45	2-$C_9H_6N(CH_2)_2$	NHC_6H_5	2.85	2.82	0.03	7.77	0.0	0.0	0.0	0.0	8g
46	$C_6H_5OCH_2$	$N(CH_3)C_6H_4$-4-NO_2	2.92	2.73	0.19	7.32	0.0	0.0	0.0	0.0	8d
47	4-Br-2-COO^--$C_6H_3OCH_2$	NHC_6H_5	2.96	2.83	0.13	7.51	0.0	1.0	0.0	1.0	8g
48	3-Cl-$C_5H_4OCH_2$	CH_3	2.96	2.83	0.13	4.29	0.0	1.0	0.0	0.0	8d
49	$C_6H_5OCH_2$	$NHCH_2C_6H_5$	2.96	2.60	0.36	6.69	0.0	0.0	0.0	0.0	8d
50	4-Cl-2-COO^--$C_6H_3OCH_2$	$NHCH_2C_6H_4$-4-$NHCONHC_6H_4$-4'-SO_2F	3.00	3.57	0.57	12.15	0.0	1.0	0.0	1.0	8h
51	3,4-Cl_2-$C_6H_3OCH_2$	CH_3	3.12	2.96	0.16	4.79	0.0	1.0	0.0	0.0	8d
52	4-Cl-2-COO^--$C_6H_3OCH_2$	NHC_6H_4-3-$NHCONHC_6H_4$-4'-SO_2F	3.15	3.51	0.36	11.69	0.0	1.0	0.0	1.0	8h
53	$C_6H_5OCH_2$	$NHCH_2C_6H_4$-2-Cl	3.19	3.53	0.34	7.19	0.0	1.0	0.0	0.0	8d
54	4-Cl-2-COO^--$C_6H_4OCH_2$	$NHCH_2C_6H_4$-3-$NHCONHC_6H_4$-4'-SO_2F	3.23	3.57	0.34	12.15	0.0	1.0	0.0	1.0	8h
55	$C_6H_5OCH_2$	NHC_6H_4-3-Cl	3.28	3.43	0.15	6.72	0.0	1.0	0.0	0.0	8d
56	2,3-$Cl_2C_6H_3OCH_2$	CH_3	3.28	2.96	0.32	4.79	0.0	1.0	0.0	0.0	8d
57	3,4-$Cl_2C_6H_3OCH_2$	NHC_6H_4-4-OCH_2COO^-	3.29	3.42	0.13	8.41	0.0	1.0	1.0	0.0	8g
58	3-Cl-$C_6H_4OCH_2$	NHC_6H_4-4-$COCH_2Cl$	3.30	3.74	0.44	8.24	0.0	1.0	0.0	0.0	8e
59	4-Cl-$C_6H_4OCH_2$	C_6H_5	3.30	3.32	0.02	6.26	0.0	1.0	0.0	0.0	8d
60	2-COO^--C_6H_3OCH	$NHCH_2C_6H_4$-4-$NHCONHC_6H_3$-4'-CH_3-3'-SO_2F	3.32	3.62	0.30	12.61	0.0	1.0	0.0	1.0	8h
61	$C_6H_5OCH_2$	$NHCH_2C_6H_4$-4'-Cl	3.36	3.53	0.17	7.19	0.0	1.0	0.0	0.0	8d
62	4-Cl-2-COO^--$C_6H_3OCH_2$	$NHCH_2C_6H_4$-3-$NHCONHC_6H_3$-4'-CH_3-3'-SO_2F	3.40	3.62	0.22	12.61	0.0	1.0	0.0	1.0	8h
63	$C_6H_5OCH_2$	NHC_6H_4-4-Br	3.46	3.49	0.03	7.01	0.0	1.0	0.0	0.0	8d
64	$C_6H_5OCH_2$	$NHCH_2C_6H_4$-4-NO_2	3.46	2.73	0.73	7.32	0.0	0.0	0.0	0.0	8d
65	3-Cl-$C_6H_4OCH_2$	NHC_6H_4-4-SO_2F	3.46	3.59	0.13	7.49	0.0	1.0	0.0	0.0	8e
66	4-Cl-2-COO^--$C_6H_3OCH_2$	$NHCH_2C_6H_4$-3-$NHCONHC_6H_3$-3'-Cl-4'-SO_2F	3.52	3.62	0.10	12.65	0.0	1.0	0.0	1.0	8h

Table IV (*Continued*)

No.	R^1	R^2	Log 1/C Obsd[a]	Log 1/C Calcd[b]	|Δ log 1/C|	MR_{R_1,R_2}	*I*-1	*I*-2	*I*-3	*I*-4	Ref
67	4-Cl-2-COO⁻-$C_6H_3OCH_2$	$NHCH_2C_6H_4$-4-$NHCONHC_6H_4$-3'-SO_2F	3.52	3.57	0.05	12.15	0.0	1.0	0.0	1.0	8h
68	$C_6H_5OCH_2$	NHC_6H_4-4-Cl	3.52	3.43	0.09	6.72	0.0	1.0	0.0	0.0	8d
69	3,4-Cl_2-$C_6H_3OCH_2$	$NHCH_2C_6H_4$-3-$NHCOCH_2Br$	3.57	4.03	0.46	9.86	0.0	1.0	0.0	0.0	8f
70	4-Cl-2-COO⁻-$C_6H_3OCH_2$	NHC_6H_4-3-$NHCONHC_6H_3$-4'-CH_3-3'-SO_2F	3.59	3.57	0.02	12.15	0.0	1.0	0.0	1.0	8h
71	3-Cl-$C_6H_4OCH_2$	NHC_6H_5	3.59	3.43	0.16	6.72	0.0	1.0	0.0	0.0	8g
72	$C_6H_5OCH_2$	$NHCH_2C_6H_4$-3-Cl	3.62	3.53	0.09	7.19	0.0	1.0	0.0	0.0	8d
73	4-Cl-2-COO⁻-$C_6H_3OCH_2$	$NHCH_2C_6H_4$-4-$NHCONHC_6H_3$-2'-Cl-5'-SO_2F	3.64	3.62	0.02	12.65	0.0	1.0	0.0	1.0	8h
74	3,4-Cl_2-$C_6H_3OCH_2$	NHC_6H_4-4-Cl	3.68	3.64	0.04	7.72	0.0	1.0	0.0	0.0	8d
75	3-Cl-$C_6H_4OCH_2$	NHC_6H_4-4-CN	3.70	3.54	0.16	7.25	0.0	1.0	0.0	0.0	8f
76	3,4-Cl_2-$C_6H_3OCH_2$	NHC_6H_4-3-$COCH_2Cl$	3.72	3.84	0.12	8.74	0.0	1.0	0.0	0.0	8e
77	3-Cl-$C_6H_4OCH_2$	$NHCH_2C_6H_5$	3.72	3.53	0.19	7.19	0.0	1.0	0.0	0.0	8d
78	3-Cl-$C_6H_4OCH_2$	NHC_6H_4-3-$COCH_2Cl$	3.74	3.74	0.00	8.24	0.0	1.0	0.0	0.0	8e
79	4-Cl-2-COO⁻-$C_6H_3OCH_2$	$NHCH_2C_6H_4$-3-$NHCONHC_6H_3$-2'-Cl-5'-SO_2F	3.80	3.62	0.18	12.65	0.0	1.0	0.0	1.0	8h
80	3-Cl-$C_6H_4OCH_2$	$NHCH_2C_6H_4$-2-$NHCOCH_2Br$	3.80	3.94	0.14	9.36	0.0	1.0	0.0	0.0	8f
81	4-Cl-2-COO⁻-$C_6H_3OCH_2$	NHC_6H_4-3-$NHCONHC_6H_4$-3'-SO_2F	3.82	3.51	0.31	11.69	0.0	1.0	0.0	1.0	8g
82	3,4-Cl_2-$C_6H_3OCH_2$	$NHCH_2C_6H_4$-4-Cl	3.85	3.73	0.12	8.19	0.0	1.0	0.0	0.0	8d
83	3,4-Cl_2-$C_6H_3OCH_2$	$NHCH_2C_6H_4$-3-Cl	3.89	3.73	0.16	8.19	0.0	1.0	0.0	0.0	8d
84	3-Cl-$C_6H_4OCH_2$	NHC_6H_4-4-Cl	3.96	3.54	0.42	7.22	0.0	1.0	0.0	0.0	8d
85	3-Cl-$C_6H_4OCH_2$	NHC_6H_4-3-$NHCOCH_2Br$	4.00	3.86	0.14	8.90	0.0	1.0	0.0	0.0	8e
86	3-Cl-$C_6H_4OCH_2$	NHC_6H_3-2-OCH_3-5-SO_2F	4.04	4.47	0.43	8.17	1.0	1.0	0.0	0.0	8h
87	3-Cl-$C_6H_4OCH_2$	$NHCH_2C_6H_4$-2-$NHCOC_6H_4$-4'-SO_2F	4.05	4.24	0.19	11.31	0.0	1.0	0.0	0.0	8f
88	3-Cl-$C_6H_4OCH_2$	$NHCH_2C_6H_4$-2-$NHCONHC_6H_4$-3'-SO_2F	4.05	4.28	0.23	11.65	0.0	1.0	0.0	0.0	8f
89	3-Cl-$C_6H_4OCH_2$	$NHCH_2C_6H_4$-4-$NHCOCH_2Br$	4.05	3.94	0.11	9.36	0.0	1.0	0.0	0.0	8f
90	4-Cl-2-COO⁻-$C_6H_3OCH_2$	$NHCH_2C_6H_4$-3-$NHCONHC_6H_4$-3'-SO_2F	4.09	3.57	0.52	12.15	0.0	1.0	0.0	1.0	8h
91	4-Cl-2-COO⁻-$C_6H_3OCH_2$	NHC_6H_4-3-$NHCONHC_6H_3$-2'-Cl-5'-SO_2F	4.10	3.57	0.53	12.19	0.0	1.0	0.0	1.0	8h
92	3-Cl-$C_6H_4OCH_2$	$NHCH_2C_6H_4$-3-$NHCONHC_6H_4$-3'-SO_2F	4.15	4.28	0.13	11.65	0.0	1.0	0.0	0.0	8f
93	3-Cl-$C_6H_4OCH_2$	$NHCH_2C_6H_4$-3-$NHCOC_6H_4$-4'-SO_2F	4.17	4.24	0.07	11.31	0.0	1.0	0.0	0.0	8f
94	3-Cl-$C_6H_4OCH_2$	NHC_6H_4-4-$CH_2NHCONHC_6H_4$-3'-SO_2F	4.22	4.28	0.06	11.65	0.0	1.0	0.0	0.0	8f
95	3-Cl-$C_6H_4OCH_2$	$NHCH_2C_6H_4$-4-$NHCOC_6H_4$-4'-SO_2F	4.22	4.24	0.02	11.31	0.0	1.0	0.0	0.0	8f
96	3-Cl-$C_6H_4OCH_2$	$NHCH_2C_6H_4$-2-$NHCOC_6H_4$-3'-SO_2F	4.28	4.24	0.04	11.31	0.0	1.0	0.0	0.0	8f
97	3-Cl-$C_6H_4OCH_2$	NHC_6H_4-2-SO_2F	4.38	4.33	0.05	7.49	1.0	1.0	0.0	0.0	8e
98	3-Cl-$C_6H_4OCH_2$	NHC_6H_4-3-SO_2F	4.44	4.33	0.11	7.49	1.0	1.0	0.0	0.0	8h
99	3,4-Cl_2-$C_6H_3OCH_2$	$NHCH_2C_6H_4$-3-$NHCOC_6H_4$-3'-SO_2F	4.46	4.30	0.16	11.81	0.0	1.0	0.0	0.0	8f
100	3-Cl-$C_6H_4OCH_2$	$NHCH_2C_6H_4$-3-$NHCOC_6H_4$-3'-SO_2F	4.46	4.24	0.22	11.31	0.0	1.0	0.0	0.0	8f
101	3,4-Cl_2-$C_6H_3OCH_2$	NHC_6H_4-2-SO_2F	4.70	4.43	0.27	7.99	1.0	1.0	0.0	0.0	8e
102	3-Cl-$C_6H_4OCH_2$	$NHCH_2C_6H_4$-4-$NHCOC_6H_4$-3'-SO_2F	4.74	4.24	0.50	11.31	0.0	1.0	0.0	0.0	8f
103	3,4-Cl_2-$C_6H_3OCH_2$	$NHCH_2C_6H_4$-3-$NHCOC_6H_4$-4'-SO_2F	4.85	4.30	0.55	11.81	0.0	1.0	0.0	0.0	8f

[a] Calculated from results of Baker et al.[8d-h] [b] Calculated using eq 2.

Table V. Squared Correlation Matrix for Variables of Eq 2

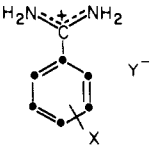
	I-2	$MR_{R_1R_2}$	$\pi_{R_1R_2}$	*I*-4	*I*-1	*I*-3	$(MR_{R_1R_2})^2$
I-2	1.00	0.43	0.02	0.10	0.03	0.04	0.39
$MR_{R_1R_2}$		1.00	0.03	0.28	0.00	0.00	0.98
$\pi_{R_1R_2}$			1.00	0.24	0.10	0.29	0.03
I-4				1.00	0.01	0.01	0.31
I-1					1.00	0.00	0.00
I-3						1.00	0.01
$(MR_{R_1R_2})^2$							1.00

Table VI. Development of QSAR for Eq 2 for RC(=O)R Inhibition of Chymotrypsin

Intercept	*I*-2	$MR_{R_1R_2}$	*I*-4	*I*-1	*I*-3	$(MR_{R_1R_2})^2$	*r*	*s*	$F_{1,X}$[a]
2.27	1.41						0.823	0.485	212
1.67	1.03	0.11					0.862	0.435	25.1
1.31	0.99	0.18	−0.84				0.921	0.335	70.0
1.27	0.90	0.18	−0.79	0.80			0.938	0.301	25.3
1.27	0.86	0.19	−0.82	0.79	−0.29		0.941	0.294	5.10
0.67	0.83	0.35	−0.77	0.74	−0.36	−0.01	0.944	0.290	4.20

[a] $F_{1,60;\alpha\,0.001} = 12$; $F_{1,60;\alpha\,0.05} = 4.00$.

Table VII. Inhibition Constants and Physicochemical Parameters for the Reversible Inhibition of Trypsin by Benzamidines



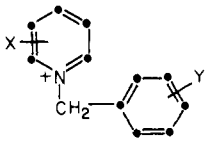
No.	X	Log 1/C Obsd[a]	Log 1/C Calcd[b]	|Δ log 1/C|	π	σ⁻	% irreversible inact.	Ref
1[c]	4-CON(CH$_3$)C$_6$H$_5$	3.10	4.00	0.90	0.86	0.63		9a
2[c]	4-O(CH$_2$)$_4$OC$_6$H$_4$-4′-NHCOC$_6$H$_4$-4″-NHCOC$_6$H$_4$-4‴-SO$_2$F	3.22	5.45	2.23	3.95	−0.27		9b
3	4-COCH$_3$	3.44	3.51	0.07	−0.55	0.87		9a
4	H	4.49	4.46	0.03	0.00	0.00		9a
5	4-O(CH$_2$)$_3$OC$_6$H$_5$	4.82	5.18	0.36	2.50	−0.27		9a
6	4-O(CH$_2$)$_3$C$_6$H$_4$-4′-NHCOCH$_2$Br	5.04	5.12	0.08	2.12	−0.27	0	9b
7	4-O(CH$_2$)$_3$C$_6$H$_5$	5.10	5.30	0.20	3.11	−0.27		9a
8	3-O(CH$_2$)$_3$OC$_6$H$_5$	5.12	4.82	0.30	2.49	0.10		9a
9	3-O(CH$_2$)$_4$OC$_6$H$_4$-4′-NHCONHC$_6$H$_4$-4″-SO$_2$F	5.14	5.24	0.10	4.76	0.10	6	9c
10	4-O(CH$_2$)$_3$OC$_6$H$_4$-4′-NHCOC$_6$H$_4$-4″-SO$_2$F	5.21	5.28	0.07	3.03	−0.27	44	9b
11	4-O(CH$_2$)$_4$OC$_6$H$_4$-4′-NHCOCH$_2$Br	5.27	5.19	0.08	2.55	−0.27	18	9b
12	4-O(CH$_2$)$_2$OC$_6$H$_4$-3′-NHCONHC$_6$H$_4$-4″-SO$_2$F	5.32	5.43	0.11	3.83	−0.27	15	9c
13	4-O(CH$_2$)$_4$OC$_6$H$_4$-4′-NHCOC$_6$H$_4$-3″-SO$_2$F	5.35	5.36	0.01	3.46	−0.27	40	9b
14	4-O(CH$_2$)$_4$OC$_6$H$_4$-3′-NHCOC$_6$H$_4$-4″-SO$_2$F	5.36	5.36	0.00	3.46	−0.27	96	9c
15	4-O(CH$_2$)$_2$OC$_6$H$_4$-3′-NHCONHC$_6$H$_3$-4″-CH$_3$-3″-SO$_2$F	5.39	5.53	0.14	4.39	−0.27	76	9c
16	4-O(CH$_2$)$_4$OC$_6$H$_4$-4′-NHCOC$_6$H$_4$-4″-SO$_2$F	5.39	5.36	0.03	3.46	−0.27	31	9b
17	4-O(CH$_2$)$_3$OC$_6$H$_4$-4′-NHCONHC$_6$H$_4$-4″-SO$_2$F	5.40	5.52	0.12	4.33	−0.27	0	9c
18	4-O(CH$_2$)$_2$OC$_6$H$_4$-3′-NHCONHC$_6$H$_4$-3″-SO$_2$F	5.44	5.43	0.01	3.83	−0.27	96	9c
19	4-O(CH$_2$)$_3$OC$_6$H$_4$-4′-NHCOC$_6$H$_4$-3″-SO$_2$F	5.47	5.28	0.19	3.03	−0.27	54	9b
20	4-O(CH$_2$)$_4$OC$_6$H$_4$-4′-NHCONHC$_6$H$_4$-3″-SO$_2$F	5.49	5.60	0.11	4.76	−0.27	37	9b
21	4-O(CH$_2$)$_2$OC$_6$H$_4$-3′-NHCOC$_6$H$_4$-4″-SO$_2$F	5.52	5.19	0.33	2.53	−0.27	91	9c
22	4-O(CH$_2$)$_4$OC$_6$H$_4$-4′-NHCONHC$_6$H$_3$-2″-OCH$_3$-5″-SO$_2$F	5.55	5.60	0.05	4.74	−0.27	6	9c
23	4-O(CH$_2$)$_4$OC$_6$H$_3$-2′-Cl-4′-NHCONHC$_6$H$_4$-3″-SO$_2$F	5.60	5.73	0.13	5.47	−0.27	41	9c
24	4-O(CH$_2$)$_4$OC$_6$H$_4$-4′-NHCONHC$_6$H$_3$-4″-OCH$_3$-3″-SO$_2$F	5.60	5.60	0.00	4.74	−0.27	48	9c
25	4-O(CH$_2$)$_4$OC$_6$H$_3$-2′-Cl-4′-NHCONHC$_6$H$_4$-4″-SO$_2$F	5.62	5.73	0.11	5.47	−0.27	0	9c
26	4-O(CH$_2$)$_4$OC$_6$H$_4$-4′-NHCONHC$_6$H$_3$-4″-CH$_3$-3″-SO$_2$F	5.64	5.70	0.06	5.32	−0.27	38	9c
27	4-O(CH$_2$)$_4$OC$_6$H$_4$-4′-NHCONHC$_6$H$_3$-4″-OC$_2$H$_5$-3″-SO$_2$F	5.66	5.69	0.03	5.24	−0.27	41	9c
28	4-O(CH$_2$)$_2$OC$_6$H$_4$-3′-NHCONHC$_6$H$_3$-2″-Cl-5″-SO$_2$F	5.74	5.56	0.18	4.54	−0.27	100	9c
29	4-O(CH$_2$)$_4$OC$_6$H$_4$-4′-NHCONHC$_6$H$_3$-2″-Cl-4″-SO$_2$F	5.80	5.73	0.06	5.47	−0.27	78	9c
30	4-O(CH$_2$)$_4$OC$_6$H$_4$-4′-NHCONHC$_6$H$_3$-3″-CH$_3$-4″-SO$_2$F	5.80	5.70	0.10	5.32	−0.27	0	9c
31	4-O(CH$_2$)$_4$OC$_6$H$_4$-4′-NHCONHC$_6$H$_3$-2″-Cl-5″-SO$_2$F	5.82	5.73	0.09	5.47	−0.27	76	9c
32	4-O(CH$_2$)$_4$OC$_6$H$_4$-4′-NHCONHC$_6$H$_4$-4″-SO$_2$F	5.85	5.60	0.25	4.76	−0.27	0	9c
33	4-O(CH$_2$)$_4$OC$_6$H$_3$-3-CH$_3$-4′-NHCONHC$_6$H$_4$-4″-SO$_2$F	5.85	5.70	0.15	5.32	−0.27	0	9c

[a] Calculated from results of Baker et al.[9] [b] Calculated using eq 3. [c] These points not used in deriving equations.

Table VIII. Squared Correlation Matrix Showing Degree of Collinearity (r^2) between the Important Variables Used in Trypsin Correlation Analysis of Eq 5

	π	MR	σ⁻
π	1.00	0.80	0.36
MR		1.00	0.40
σ⁻			1.00

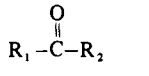
amide, peptide, and ester linkages. In the present report, two correlation equations for two types of inhibitors have been formulated from the data in Tables I and IV.



(causing 50% inhibition of α-chymotrypsin)

$$\log 1/C = 0.208\ (\pm 0.06)\ \pi_{X,Y} + 1.135\ (\pm 0.23)\ (I\text{-}1) + 0.710\ (\pm 0.23)\ (I\text{-}2) + 0.276\ (\pm 0.19)\ (I\text{-}3) + 3.210\ (\pm 0.26) \quad (1)$$

n 56 r 0.895 s 0.291



(causing 50% inhibition of α-chymotrypsin)

$$\log 1/C = 0.355\ (\pm 0.16)\ MR_{R_1,R_2} - 0.0099\ (\pm 0.0096)\ (MR_{R_1,R_2})^2 + 0.738\ (\pm 0.31)\ (I\text{-}1) + 0.826\ (\pm 0.16)\ (I\text{-}2) - 0.359\ (\pm 0.26)\ (I\text{-}3) - 0.771\ (\pm 0.18)\ (I\text{-}4) + 0.665\ (\pm 0.62) \quad (2)$$

n 103 r 0.944 s 0.290

Substituting $MR_{X,Y}$ for $\pi_{X,Y}$ in eq 1 gives a correlation with $r = 0.869$ despite the fact that the collinearity between $\pi_{X,Y}$ and $MR_{X,Y}$ is not unusually high. The explanation of this may be that the true vector for this space lies between π and MR; that is, the space is not very homogeneous and is not well modeled by either vector but is about as well fit by one as the other. This question should be examined using a set of substituents completely orthogonal with respect to π and MR. To do the job properly, one should study a set of relatively small substituents to explore space near the two rings and a set of larger functions to compare more distant enzymic space.

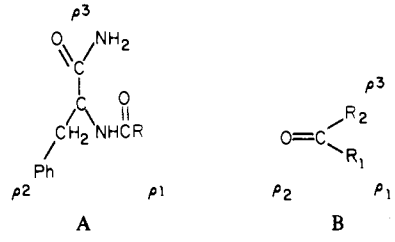
A most interesting aspect of eq 1 is I-1 which accounts for the effect of SO_2F in the 2 position of the benzyl ring. Activity is enhanced about 14-fold over the cases where SO_2F is in the 3 position or absent. A similar effect was observed for the inhibition of complement, an enzyme conglomerate[7] composed of hydrolases. It has been suggested that 2-SO_2F is favorably disposed in the ortho position to react with the hydroxyl of a serine moiety.[7] A smaller beneficial effect for SO_2F in the 4 position is

parameterized by I-2. No special effect is seen for 3-SO_2F despite the fact that by virtue of the rotation of the phenyl, 3-substituents can come into contact with a greater variety of enzyme space than 4-substituents. Indicator variable I-3 accounts for those cases where the nitrogen atom of an amide is attached directly to the pyridine ring. The slightly increased activity of these congeners is probably due to electron donation by the amide nitrogen to the pyridinium ring. The QSAR of the benzylpyridinium inhibitors of chymotrypsin is quite different from other inhibitors,[16a] and suggests that these positively charged molecules may be interacting at a site removed from the hydrolytically active site. Table II shows that except for (π, MR) and (I-1, I-2), the other vectors are quite orthogonal. The development of the QSAR for eq 1 is shown in Table III.

Equation 2 correlates a set of 103 ketones, amides, and esters inhibiting chymotrypsin. R_2 represents the Me of methyl ketones or NHR or OR of amides and esters. In the large majority of cases, $R_1 = XC_6H_4OCH_2-$. In eq 2, MR_{R_1,R_2} represents the sum of molar refractivities for the two groups attached to the carbonyl moiety. The exponential term in MR indicates that very large groups produce less effective inhibition. Equation 2 is not a very significant improvement over the equation lacking $(MR)^2$ ($F_{1,96} = 7.5$), since it reduces the variance in log $1/C$ by only 1%. I-1 takes the value of 1 for cases where $R_2 = NHC_6H_4SO_2F$. The SO_2F function increases activity by a factor of about 5. I-2 is a rather unusual parameter in terms of our experience; it assumes the value of 1 for cases where there are one or two halogens on the aromatic rings of R_1 and R_2. Strangely, the effect of halogen (mostly Cl) is not additive. In some instances there are three halogens (**74**, **82**, and **83**). These congeners are as well predicted as the cases where only one halogen is present on either ring. One could postulate that a substituent the size of Cl might be just the right size to produce a favorable (for inhibition) conformational change; however, it seems strange that the same effect could be obtained from either R group. I-3 and I-4 parameterize the presence of a COO^- on R_2 and R_1, respectively.

The highly hydrophilic COO^- has a deleterious effect on the potency of the congeners containing it as the negative coefficients with these terms indicate. The smaller negative coefficient with I-3 for R_2 indicates that the COO^- function is better accommodated on the amide and ester moieties than on the phenoxy group. It suggests different binding areas for R_1 and R_2.

In an earlier study on ligands interacting with chymotrypsin, we found the Hein–Niemann system of labeling space about an asymmetric center to be helpful in structure–activity analysis. In the diagram shown for



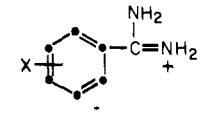
binding an acylphenylalanine amide, ρ_H space is behind the plane of the page. ρ_2 space is clearly hydrophobic. Correlation equations have a 1.2 (±0.2) π term for hydrophobic bonding in this space. The ρ_1 and ρ_2 areas are different; binding in ρ_1 was correlated with MR and the little data available for ρ_3 interaction were highly collinear with respect to π and MR so that no clean decision could be made about ρ_3 space.[16a] However, the coefficients with π and MR terms for ρ_3 space interaction are small, suggesting polar space. Correlation eq 3 for a limited set of

$$\log [S]/[I]\ 0.5 = 0.80\ (\pm 0.28)\ \pi + 0.46\ (\pm 0.45)\ \sigma + 0.87\ (\pm 0.40)\ X - 1.96\ (\pm 0.24) \quad (3)$$

$$n \quad r \quad s$$
$$15 \quad 0.913 \quad 0.261$$

phenoxyacetones [$XC_6H_4OCH_2C(=O)CH_3$] was formulated from Baker's work. The electronic term in this equation is of very marginal importance as one can see from its confidence limits. X is an indicator variable for three examples where phenyl ketones rather than methyl ketones were used. S/I in this expression is the substrate/inhibitor ratio. It was postulated that even though the coefficient with the π term was lower than any others studied, it still probably indicates binding in ρ_2 space; this now seems unlikely. On the basis of the much larger data set, binding as in B would place X and Y in MR space; while this would rationalize the results, there is no proof that these compounds are necessarily acting in the ρ_1–ρ_2–ρ_3 region. Inhibition may be occurring from another point in the enzyme. The fact that one does not obtain an improved correlation by factoring $MR_{R_1R_2}$ into MR_{R_1} and MR_{R_2} suggests that the two types of space involved are very similar. The orthogonality of π and MR for the R_1COR_2 congeners with poor correlation when π is used in place of MR supports the idea that ρ_2 space is not involved.

Trypsin. Trypsin is a proteolytic enzyme similar to chymotrypsin. The following QSAR (eq 4 and 5) have been formulated from the data in Table VII.



(causing 50% inhibition of trypsin)

$$\log 1/C = 0.270\ (\pm 0.06)\ \pi + 4.330\ (\pm 0.23) \quad (4)$$

$$n \quad r \quad s$$
$$31 \quad 0.874 \quad 0.234$$

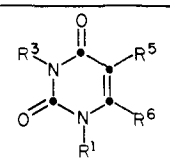
$$\log 1/C = 0.184\ (\pm 0.05)\ \pi - 0.978\ (\pm 0.32)\ \sigma^- + 4.463\ (\pm 0.16) \quad (5)$$

$$n \quad r \quad s$$
$$31 \quad 0.949 \quad 0.155$$

The two-variable equation is a significant improvement over the equation in π alone: $F_{1,28} = 38.1$; $F_{1,28;\ \alpha\ 0.001} = 13.5$. Two data points of Table VII have not been used in the formulation of the QSAR; these are the two least active congeners, one of which (1) has a unique attachment to the benzene ring. The use of MR in place of π in eq 5 also gives a high correlation. The small coefficients with these terms suggest that "true" hydrophobic interactions are probably not involved. The result is similar to that found for chymotrypsin. The poorly independent nature of π and σ can be seen in Table VIII. A better data set is needed for more firm conclusions.

Thymidine Phosphorylase (from *E. coli*). This enzyme catalyzes the phosphorylysis of the nucleoside

Table IX. Constants Used for Deriving Eq 6 for Thymidine Phosphorylase (*E. coli*)



No.	Substituents	Log S/I Obsd[a]	Log S/I Calcd[b]	$\lvert\Delta$ log $S/I\rvert$	π-1,3	π-6	π-ortho	π-meta	I-1	I-2	I-3	I-4	Ref
1	1-CH_3	−2.30	−1.66	0.64	0.50	0.0	0.0	0.0	0.0	0.0	0.0	0.0	10a
2	1-$(CH_2)_3OH$	−1.90	−1.71	0.19	0.34	0.0	0.0	0.0	0.0	0.0	0.0	0.0	10a
3	1-$(CH_2)_2OH$	−1.85	−1.84	0.01	−0.16	0.0	0.0	0.0	0.0	0.0	0.0	0.0	10a
4	1-$(CH_2)_5OH$	−1.85	−1.44	0.41	1.34	0.0	0.0	0.0	0.0	0.0	0.0	0.0	10a
5	1-$(CH_2)_4OH$	−1.78	−1.57	0.21	0.84	0.0	0.0	0.0	0.0	0.0	0.0	0.0	10a
6	1-$(CH_2)_3C_6H_4$-4′-COOH	−1.78	−2.12	0.34	−1.20	0.0	0.0	0.0	0.0	0.0	0.0	0.0	10b
7	1-$CH_2C_6H_4$-2′-$NHCOCH_2Br$	−1.43	−1.36	0.07	1.64	0.0	0.0	0.0	0.0	0.0	0.0	0.0	10b
8	1-C_4H_9	−1.34	−1.26	0.08	2.00	0.0	0.0	0.0	0.0	0.0	0.0	0.0	10a
9	1-$(CH_2)_3C_6H_5$-5-CH_2OH	−1.32	−0.95	0.37	3.16	0.0	0.0	0.0	0.0	0.0	0.0	0.0	10c
10	1-C_4H_9-5-$CH_2OC_2H_5$	−1.32	−1.26	0.06	2.00	0.0	0.0	0.0	0.0	0.0	0.0	0.0	10c
11	1-*i*-C_5H_{11}	−1.30	−1.18	0.12	2.30	0.0	0.0	0.0	0.0	0.0	0.0	0.0	10b
12	1-c-C_5H_9	−1.28	−1.22	0.06	2.14	0.0	0.0	0.0	0.0	0.0	0.0	0.0	10b
13	1-$(CH_2)_3C_6H_5$-5-CH_2O-*i*-C_5H_{11}	−1.20	−0.95	0.25	3.16	0.0	0.0	0.0	0.0	0.0	0.0	0.0	10c
14	1-$CH_2C_6H_4$-3′-$NHCOCH_2Br$	−1.20	−1.36	0.16	1.64	0.0	0.0	0.0	0.0	0.0	0.0	0.0	10b
15	1-$CH_2C_6H_4$-4′-$CONH_2$	−1.18	−1.66	0.48	0.52	0.0	0.0	0.0	0.0	0.0	0.0	0.0	10b
16	1-*i*-C_6H_{13}	−1.18	−1.04	0.14	2.80	0.0	0.0	0.0	0.0	0.0	0.0	0.0	10b
17	1-C_5H_{11}	−1.15	−1.12	0.03	2.50	0.0	0.0	0.0	0.0	0.0	0.0	0.0	10b
18	1-$(CH_2)_3C_6H_5$	−1.11	−0.95	0.16	3.16	0.0	0.0	0.0	0.0	0.0	0.0	0.0	10b
19	3-CH_2CN-5-Br-6-$CH_2C_6H_5$	−1.00	−1.09	0.09	−0.57	2.01	0.0	0.0	0.0	1.0	0.0	0.0	10f
20	1-$(CH_2)_3C_6H_5$-5-$CH_2OC_2H_5$	−1.00	−0.95	0.05	3.16	0.0	0.0	0.0	0.0	0.0	0.0	0.0	10c
21	5-N=NC_6H_5-6-C_6H_5	−0.90	−0.49	0.41	0.0	1.96	0.0	0.0	1.0	0.0	0.0	1.0	10i
22	6-CH_3	−0.90	0.10	1.00	0.0	0.50	0.0	0.0	1.0	0.0	0.0	0.0	10d
23	5-NH_2	−0.85	0.02	0.87	0.0	0.0	0.0	0.0	1.0	0.0	0.0	0.0	10e
24	1-$(CH_2)_2C_6H_5$	−0.80	−1.08	0.28	2.66	0.0	0.0	0.0	0.0	0.0	0.0	0.0	10b
25	5-$SO_2NC_5H_{10}$-6-CH_3	−0.78	−0.73	0.05	0.0	0.50	0.0	0.0	1.0	0.0	0.0	1.0	10c
26	1-$CH_2C_6H_5$-6-CH_3	−0.78	−1.17	0.39	2.01	0.50	0.0	0.0	0.0	0.0	0.0	0.0	10k
27	1-$(CH_2)_3C_6H_5$-5-$CH_2CH=CH_2$	−0.78	−0.95	0.17	3.16	0.0	0.0	0.0	0.0	0.0	0.0	0.0	10c
28	1-$CH_2C_6H_5$	−0.76	−1.26	0.50	2.01	0.0	0.0	0.0	0.0	0.0	0.0	0.0	10b
29	5-$SO_2NC_5H_{10}$-6-$(CH_2)_2C_6H_5$	−0.70	−0.38	0.32	0.0	2.66	0.0	0.0	1.0	0.0	0.0	1.0	10f
30	1-$(CH_2)_3C_6H_5$-5-C_6H_5	−0.70	−0.95	0.25	3.16	0.0	0.0	0.0	0.0	0.0	0.0	0.0	10c
31	1-$(CH_2)_3C_6H_5$-6-C_5H_{11}	−0.63	−0.54	0.09	3.16	2.50	0.0	0.0	0.0	0.0	0.0	0.0	10c
32	6-NHC_6H_{11}	−0.60	0.27	0.87	0.0	1.54	0.0	0.0	1.0	0.0	0.0	0.0	10h
33	1-$(CH_2)_4C_6H_5$	−0.60	−0.81	0.21	3.66	0.0	0.0	0.0	0.0	0.0	0.0	0.0	10b
34	Uracil	−0.59	0.02	0.61	0.0	0.0	0.0	0.0	1.0	0.0	0.0	0.0	10d
35	5-$COCH_3$	−0.52	0.02	0.54	0.0	0.0	0.0	0.0	1.0	0.0	0.0	0.0	10e
36	5-N=NC_6H_5-6-CH_3	−0.51	−0.73	0.22	0.0	0.50	0.0	0.0	1.0	0.0	0.0	1.0	10i
37[c]	5-Br-6-$CH_2C_6H_4$-4′-$NHCOCH_3$	−0.48	0.72	1.20	0.0	1.04	0.0	0.0	1.0	1.0	0.0	0.0	10j
38	1-$(CH_2)_3C_6H_5$-6-$CH_2C_6H_5$	−0.48	−0.08	0.40	3.16	2.01	0.0	0.0	0.0	1.0	0.0	0.0	10c
39	3-$(CH_2)_3C_6H_5$-6-$CH_2C_6H_5$	−0.48	−0.08	0.40	3.16	2.01	0.0	0.0	0.0	1.0	0.0	0.0	10e
40	1-$(CH_2)_3C_6H_5$-6-C_3H_7	−0.48	−0.70	0.22	3.16	1.50	0.0	0.0	0.0	0.0	0.0	0.0	10c
41	5-COO^-	−0.48	0.02	0.50	0.0	0.0	0.0	0.0	1.0	0.0	0.0	0.0	10e
42	6-C_3H_7	−0.40	0.26	0.66	0.0	1.50	0.0	0.0	1.0	0.0	0.0	0.0	10d
43[c]	5-Br-6-$CH_2C_6H_4$-4′-$NHCOCH_2Br$	−0.38	0.82	1.20	0.0	1.64	0.0	0.0	1.0	1.0	0.0	0.0	10j
44	5-Br-6-$CH_2C_6H_4$-4′-SO_2NH_2	−0.36	0.58	0.94	0.0	0.19	0.0	0.0	1.0	1.0	0.0	0.0	10f
45	1-$(CH_2)_5C_6H_5$	−0.32	−0.68	0.36	4.16	0.0	0.0	0.0	0.0	0.0	0.0	0.0	10b
46	1-$(CH_2)_3C_6H_5$-6-C_6H_5	−0.32	−0.63	0.31	3.16	1.96	0.0	0.0	0.0	0.0	0.0	0.0	10c
47	5-C_6H_5	−0.30	0.02	0.32	0.0	0.0	0.0	0.0	1.0	0.0	0.0	0.0	10d
48	5-CH_3	−0.28	0.02	0.30	0.0	0.0	0.0	0.0	1.0	0.0	0.0	0.0	10d
49	6-$CH_2C_6H_4$-4′-$NHCOCH_3$	−0.23	0.72	0.95	0.0	1.04	0.0	0.0	1.0	1.0	0.0	0.0	10j
50	5-Br-6-C_6H_5	−0.23	0.34	0.57	0.0	1.96	0.0	0.0	1.0	0.0	0.0	0.0	10f
51	5-$CH_2C_6H_5$-6-C_6H_5	−0.20	0.34	0.54	0.0	1.96	0.0	0.0	1.0	0.0	0.0	0.0	10d
52	6-C_6H_4-4′-NO_2	−0.18	0.29	0.47	0.0	1.68	0.0	0.0	1.0	0.0	0.0	0.0	10d
53	5-F	−0.11	0.02	0.13	0.0	0.0	0.0	0.0	1.0	0.0	0.0	0.0	10e
54	6-COC_6H_5	−0.08	0.19	0.27	0.0	1.05	0.0	0.0	1.0	0.0	0.0	0.0	10g
55	6-CF_3	−0.08	0.16	0.24	0.0	0.88	0.0	0.0	1.0	0.0	0.0	0.0	10e
56	6-C_5H_{11}	−0.04	0.42	0.46	0.0	2.50	0.0	0.0	1.0	0.0	0.0	0.0	10d
57	6-$(CH_2)_3C_6H_5$	−0.04	0.53	0.57	0.0	3.16	0.0	0.0	1.0	0.0	0.0	0.0	10d
58	5-Br-6-$CH_2C_6H_3$-3′-NO_2-4′-$NHCOCH_3$	−0.04	0.69	0.73	0.0	2.25	0.0	−0.28	1.0	1.0	0.0	0.0	10j
59	5-$SO_2NC_5H_{10}$-6-CH=CHC_6H_5	0.06	−0.36	0.42	0.0	2.77	0.0	0.0	1.0	0.0	0.0	1.0	10f
60	5-$CH_2C_6H_5$-6-CF_3	0.12	0.16	0.04	0.0	0.88	0.0	0.0	1.0	0.0	0.0	0.0	10i
61	6-NH_2	0.17	−0.18	0.35	0.0	−1.23	0.0	0.0	1.0	0.0	0.0	0.0	10g
62	5-N=N-C_6H_5-6-$CH_2C_6H_5$	0.20	0.05	0.15	0.0	2.01	0.0	0.0	1.0	1.0	0.0	1.0	10i
63	5-NO_2-6-CH=CHC_6H_5	0.21	0.47	0.26	0.0	2.77	0.0	0.0	1.0	0.0	0.0	0.0	10f
64	5-C_5H_{11}-6-C_3H_7	0.22	0.26	0.04	0.0	1.50	0.0	0.0	1.0	0.0	0.0	0.0	10d
65	6-$(CH_2)_2C_6H_5$	0.22	0.45	0.23	0.0	2.66	0.0	0.0	1.0	0.0	0.0	0.0	10d
66	5-Br-6-$(CH_2)_2C_6H_5$	0.24	0.45	0.21	0.0	2.66	0.0	0.0	1.0	0.0	0.0	0.0	10f
67	5-C_5H_{11}-6-CF_3	0.28	0.16	0.12	0.0	0.88	0.0	0.0	1.0	0.0	0.0	0.0	10i
68	6-SO_2CH_3	0.28	−0.25	0.53	0.0	−1.63	0.0	0.0	1.0	0.0	0.0	0.0	10i
69	5-$(CH_2)_3C_6H_5$-6-CF_3	0.30	0.16	0.14	0.0	0.88	0.0	0.0	1.0	0.0	0.0	0.0	10i

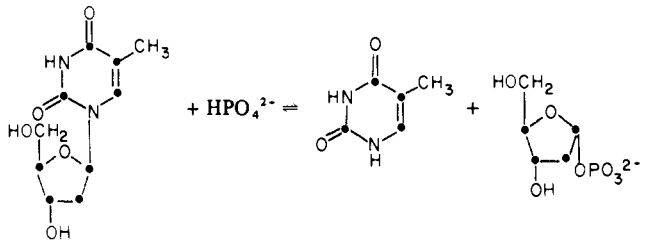
Table IX (*Continued*)

No.	Substituents	Log S/I Obsd[a]	Log S/I Calcd[b]	|Δ log S/I|	π-1,3	π-6	π-ortho	π-meta	I-1	I-2	I-3	I-4	Ref
70	6-$CH_2C_6H_4$-4'-NH_2	0.32	0.68	0.36	0.0	0.78	0.0	0.0	1.0	1.0	0.0	0.0	10d
71	5-Br-6-$(CH_2)_3C_6H_5$	0.33	0.53	0.20	0.0	3.16	0.0	0.0	1.0	0.0	0.0	0.0	10f
72	5-Br	0.35	0.02	0.33	0.0	0.0	0.0	0.0	1.0	0.0	0.0	0.0	10e
73	6-$CH_2C_6H_4$-4'-SO_2NH_2	0.38	0.58	0.20	0.0	0.19	0.0	0.0	1.0	1.0	0.0	0.0	10f
74	5-Br-6-C_3H_7	0.46	0.26	0.20	0.0	1.50	0.0	0.0	1.0	0.0	0.0	0.0	10f
75	6-$CHOHC_6H_5$	0.48	0.10	0.38	0.0	0.54	0.0	0.0	1.0	0.0	0.0	0.0	10g
76	5-C_6H_4-4'-Cl-6-CF_3	0.49	0.16	0.33	0.0	0.88	0.0	0.0	1.0	0.0	0.0	0.0	10i
77	6-$NH(CH_2)_2C_6H_5$	0.49	0.38	0.11	0.0	2.21	0.0	0.0	1.0	0.0	0.0	0.0	10g
78	5-$(CH_2)_2C_6H_5$-6-CF_3	0.60	0.16	0.44	0.0	0.88	0.0	0.0	1.0	0.0	0.0	0.0	10i
79	5-NO_2	0.66	0.02	0.64	0.0	0.0	0.0	0.0	1.0	0.0	0.0	0.0	10e
80	6-$CH_2C_6H_5$	0.66	0.88	0.22	0.0	2.01	0.0	0.0	1.0	1.0	0.0	0.0	10d
81	6-$NHCH(C_6H_5)CH_2C_6H_5$	0.71	0.57	0.14	0.0	3.43	0.0	0.0	1.0	0.0	0.0	0.0	10h
82	6-NHC_6H_4-4'-t-C_4H_9	0.74	1.74	1.00	0.0	3.35	0.0	0.0	1.0	0.0	1.0	0.0	10h
83	5-Br-6-$CH_2C_6H_4$-4'-NO_2	0.77	0.83	0.06	0.0	1.73	0.0	0.0	1.0	1.0	0.0	0.0	10f
84	6-$N(CH_2C_6H_5)_2$	0.78	0.52	0.26	0.0	3.12	0.0	0.0	1.0	0.0	0.0	0.0	10h
85	5-NO_2-6-CH_3	0.80	0.10	0.70	0.0	0.50	0.0	0.0	1.0	0.0	0.0	0.0	10e
86	6-$CH_2C_6H_4$-3'-$NHCOCH_2Br$	0.82	0.58	0.24	0.0	2.01	0.0	−0.37	1.0	1.0	0.0	0.0	10j
87	6-$N(CH_3)C_6H_5$	0.85	0.35	0.50	0.0	2.02	0.0	0.0	1.0	0.0	0.0	0.0	10g
88[c]	5-N=N-C_6H_5-6-C_5H_{11}	0.85	−0.40	1.25	0.0	2.50	0.0	0.0	1.0	0.0	0.0	1.0	10i
89	6-$N(CH_3)CH_2C_6H_5$	0.88	0.28	0.60	0.0	1.65	0.0	0.0	1.0	0.0	0.0	0.0	10h
90	6-$CH_2C_6H_4$-4'-F	0.89	0.90	0.01	0.0	2.15	0.0	0.0	1.0	1.0	0.0	0.0	10j
91	5-NO_2-6-C_3H_7	0.89	0.26	0.63	0.0	1.50	0.0	0.0	1.0	0.0	0.0	0.0	10f
92	5-$(CH_2)_4C_6H_5$-6-CF_3	0.92	0.16	0.76	0.0	0.88	0.0	0.0	1.0	0.0	0.0	0.0	10i
93	6-NHC_6H_5	1.00	1.42	0.42	0.0	1.37	0.0	0.0	1.0	0.0	1.0	0.0	10g
94	6-$CH_2C_6H_4$-4'-CH_3	1.02	0.96	0.06	0.0	2.51	0.0	0.0	1.0	1.0	0.0	0.0	10g
95	6-$NHCH(C_6H_5)_2$	1.04	0.49	0.55	0.0	2.93	0.0	0.0	1.0	0.0	0.0	0.0	10h
96	6-$N(C_2H_5)CH_2C_6H_5$	1.04	0.37	0.67	0.0	2.15	0.0	0.0	1.0	0.0	0.0	0.0	10h
97	6-$CH_2C_6H_3$-3'-NO_2-4'-F	1.06	0.68	0.38	0.0	2.15	0.0	−0.28	1.0	1.0	0.0	0.0	10j
98	6-$CH_2C_6H_3$-3'-NO_2-4'-$NHCOCH_3$	1.12	0.69	0.43	0.0	2.23	0.0	−0.28	1.0	1.0	0.0	0.0	10j
99	6-$NHCH(CH_3)C_6H_5$	1.15	0.23	0.92	0.0	1.30	0.0	0.0	1.0	0.0	0.0	0.0	10h
100	6-$SO_2C_6H_5$	1.15	1.24	0.09	0.0	0.27	0.0	0.0	1.0	0.0	1.0	0.0	10g
101	6-$CH_2C_6H_4$-4'-$NHCOCH_2Br$	1.19	0.82	0.37	0.0	1.64	0.0	0.0	1.0	1.0	0.0	0.0	10j
102	5-i-6-$CH_2C_6H_5$	1.22	0.88	0.34	0.0	2.01	0.0	0.0	1.0	1.0	0.0	0.0	10f
103	6-NHC_6H_4-2'-OC_2H_5	1.23	1.84	0.61	0.0	1.37	0.38	0.0	1.0	0.0	1.0	0.0	10h
104	6-OC_6H_5	1.24	1.53	0.29	0.0	2.08	0.0	0.0	1.0	0.0	1.0	0.0	10g
105	6-NHC_6H_4-4'-CH_3	1.28	1.50	0.22	0.0	1.87	0.0	0.0	1.0	0.0	1.0	0.0	10h
106	6-NHC_6H_4-2'-OCH_3	1.30	1.39	0.09	0.0	1.37	−0.02	0.0	1.0	0.0	1.0	0.0	10h
107	6-NHC_6H_4-4'-C_2H_5	1.43	1.58	0.15	0.0	2.37	0.0	0.0	1.0	0.0	1.0	0.0	10h
108	6-NHC_6H_4-4'-Cl	1.46	1.58	0.12	0.0	2.35	0.0	0.0	1.0	0.0	1.0	0.0	10h
109	6-$CH_2C_6H_4$-4'-NO_2	1.48	0.83	0.65	0.0	1.73	0.0	0.0	1.0	1.0	0.0	0.0	10d
110	5-Br-6-$CH_2C_6H_4$-4'-NH_2	1.55	0.68	0.87	0.0	0.78	0.0	0.0	1.0	1.0	0.0	0.0	10f
111	6-$NHCH_2C_6H_4$-4'-Cl	1.56	1.47	0.09	0.0	1.71	0.0	0.0	1.0	0.0	1.0	0.0	10h
112	6-NHC_6H_4-3'-CH_3	1.56	1.82	0.26	0.0	1.37	0.0	0.50	1.0	0.0	1.0	0.0	10h
113	6-NHC_6H_4-4'-Br	1.60	1.60	0.00	0.0	2.50	0.0	0.0	1.0	0.0	1.0	0.0	10h
114	5-Br-6-$CH_2C_6H_5$	1.60	0.88	0.72	0.0	2.01	0.0	0.0	1.0	1.0	0.0	0.0	10f
115	6-NHC_6H_4-4'-C_4H_9	1.73	1.74	0.01	0.0	3.37	0.0	0.0	1.0	0.0	1.0	0.0	10h
116	6-$NHCH_2C_6H_4$-2',5'-$(CH_3)_2$	1.78	2.00	0.22	0.0	1.50	0.50	0.0	1.0	0.0	1.0	0.0	10h
117	6-$NHCH_6H_4$-4'-OC_2H_5	1.78	1.48	0.30	0.0	1.75	0.0	0.0	1.0	0.0	1.0	0.0	10h
118	6-NHC_6H_4-3'-Cl	1.81	2.03	0.22	0.0	1.64	0.0	0.71	1.0	0.0	1.0	0.0	10h
119	6-$NHCH_2C_6H_5$	1.82	1.36	0.46	0.0	1.00	0.0	0.0	1.0	0.0	1.0	0.0	10g
120	6-NHC_6H_3-2',5'-$(CH_3)_2$	1.98	2.06	0.08	0.0	1.87	0.50	0.0	1.0	0.0	1.0	0.0	10h
121	6-SC_6H_5	2.00	1.57	0.43	0.0	2.32	0.0	0.0	1.0	0.0	1.0	0.0	10g
122[c]	6-$CH_2C_6H_4$-3'-NO_2	2.07	0.65	1.42	0.0	2.01	0.0	−0.28	1.0	1.0	0.0	0.0	10j
123[c]	5-Br-6-$CH_2C_6H_3$-3'-NO_2-4'-NH_2	2.10	0.65	1.45	0.0	1.99	0.0	−0.28	1.0	1.0	0.0	0.0	10j
124	6-NHC_6H_4-2'-C_2H_5	2.11	2.54	0.43	0.0	1.37	1.0	0.0	1.0	0.0	1.0	0.0	10h
125	6-NHC_6H_4-2'-CH_3	2.11	1.98	0.13	0.0	1.37	0.50	0.0	1.0	0.0	1.0	0.0	10h
126[c]	6-$CH_2C_6H_3$-3'-NO_2-4'-NH_2	2.20	0.65	1.55	0.0	1.99	0.0	−0.28	1.0	1.0	0.0	0.0	10j
127	6-$NHCH_2C_6H_4$-2'-Cl	2.26	2.16	0.10	0.0	1.0	0.71	0.0	1.0	0.0	1.0	0.0	10h
128	6-$NH(2\text{-}C_{10}H_7)$	2.26	2.06	0.20	0.0	2.03	0.0	0.66	1.0	0.0	1.0	0.0	10h
129	6-NHC_6H_4-2'-Cl	2.28	2.26	0.02	0.0	1.66	0.71	0.0	1.0	0.0	1.0	0.0	10h
130	6-NHC_6H_4-4'-C_6H_5	2.32	1.74	0.58	0.0	3.33	0.0	0.0	1.0	0.0	1.0	0.0	10h
131	6-NHC_6H_3-2',6'-$(CH_3)_2$	2.34	2.06	0.28	0.0	1.87	0.50	0.0	1.0	0.0	1.0	0.0	10h
132	6-$NH(1\text{-}C_{10}H_7)$	2.40	2.69	0.29	0.0	1.37	0.66	0.66	1.0	0.0	1.0	0.0	10h
133	6-NHC_6H_3-2',4'-$(CH_3)_2$	2.43	2.06	0.37	0.0	1.87	0.50	0.0	1.0	0.0	1.0	0.0	10h
134	6-$NHCH_2C_6H_4$-3'-Cl	2.52	1.93	0.59	0.0	1.00	0.0	0.71	1.0	0.0	1.0	0.0	10h
135	6-NHC_6H_4-3'-C_6H_5	2.63	3.00	0.37	0.0	1.37	0.0	1.96	1.0	0.0	1.0	0.0	10h
136	6-NHC_6H_3-2',3'-$(CH_3)_2$	2.65	2.38	0.27	0.0	1.37	0.50	0.50	1.0	0.0	1.0	0.0	10h
137	6-NHC_6H_4-2',3'-Cl_2	3.04	2.86	0.17	0.0	1.83	0.71	0.71	1.0	0.0	1.0	0.0	10h
138	6-NH(2-Anthranyl)	3.04	2.70	0.34	0.0	2.69	0.0	1.32	1.0	0.0	1.0	0.0	10h
139	6-$NHCH_2(1\text{-}C_{10}H_7)$	3.28	2.63	0.65	0.0	1.00	0.66	0.66	1.0	0.0	1.0	0.0	10k
140	6-$NHCH_2(1\text{-}C_{10}H_5$-6',7'-$Cl_2)$	3.57	4.01	0.44	0.0	1.00	1.37	1.37	1.0	0.0	1.0	0.0	10k
141	6-$NHCH_2[1\text{-}C_{10}H_5$-6',7'-$(CH_3)_2]$	3.60	3.60	0.00	0.0	1.00	1.16	1.16	1.0	0.0	1.0	0.0	10k
142	6-$NHCH_2(1\text{-}C_{10}H_6$-7'-Cl)	3.76	3.43	0.33	0.0	1.00	1.37	0.66	1.0	0.0	1.0	0.0	10k

[a] Calculated from results of Baker et al.[10] [b] Calculated using eq 6. [c] These molecules not used in deriving equations.

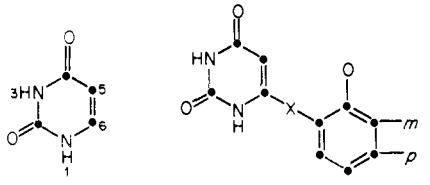
Table X. Squared Correlation Matrix for Variables Pertaining to Eq 6 for Thymidine Phosphorylase (*E. coli*)

Intercept	*I*-3	*I*-1	π_o	*I*-2	π_m	π-1,3	*I*-4	π-6	E_s-o
I-3	1.00	0.11	0.30	0.07	0.23	0.07	0.02	0.09	0.36
I-1		1.00	0.03	0.01	0.02	0.63	0.01	0.21	0.04
π_o			1.00	0.02	0.21	0.02	0.01	0.00	0.74
I-2				1.00	0.04	0.01	0.01	0.04	0.02
π_m					1.00	0.01	0.00	0.00	0.08
π-1,3						1.00	0.01	0.11	0.03
I-4							1.00	0.01	0.01
π-6								1.00	0.01
E_s-o									1.00



linkage.[17a] Baker used 5-fluorouracil-2'-deoxy ribonucleoside (FUDR) as a substrate in his studies in place of the natural thymidine analog. His interest was in finding inhibitors to prevent the detoxification of the FUDR with further catabolism of 5-FU by other enzymes to α-fluoro-β-alanine.[17b]

Certain tumors cannot detoxify FU or FUDR for lack of these catabolic enzymes. This could form the basis of cancer chemotherapy. The QSAR for uracils causing 50% inhibition of enzyme from *E. coli* B has been developed from the data in Table IX. Although eq 6 contains eight



C D

$$\log [S]/[I]\ 0.5 = 1.177\ (\pm 0.23)\ (I\text{-}3) + 1.814\ (\pm 0.32)\ (I\text{-}1) + 1.127\ (\pm 0.35)\ \pi_o + 0.536\ (\pm 0.22)\ (I\text{-}2) + 0.807\ (\pm 0.29)\ \pi_m + 0.269\ (\pm 0.12)\ (\pi\text{-}1,3) - 0.827\ (\pm 0.37)\ (I\text{-}4) + 0.163\ (\pm 0.08)\ (\pi\text{-}6) - 1.798\ (\pm 0.29) \quad (6)$$

$$n \quad r \quad s$$
$$136 \quad 0.948 \quad 0.431$$

terms, there are, on the average, 17 data points per term. In this expression *I*-3 refers to 6-X-C_6H_5 functions where X represents NH, $NHCH_2$, O, S, and SO_2. *I*-2 takes the value of 1 for the case where X = CH_2. All of these bridge atoms are electron releasing except SO_2. There is only one example of this unit and only one example of an S bridge. It may simply be fortuitous that these two congeners are well parameterized by *I*-3; other such congeners must be tested before this classification can be made with any certainty. The stereoelectronic character of the congeners where X = CH_2 does not allow such effective inhibition. It was thought possible that the electronic effect of the bridge atom would be a significant feature of X; however, the use of $\mathfrak{F}$ and/or $\mathfrak{R}$ to parameterize the electronic character of X did not result in a reduction in the variance of the data.

The indicator variable *I*-1 takes the value of 1 for those congeners where H is present on the nitrogens at the 1 and 3 positions. These congeners are, on the average, 65 times as active as those with substituents in one of these positions. This does not seem to be a steric effect since the size of the group has little import, but rather suggests a role for hydrogen bonding. The variables π_o and π_m refer to positions on the phenyl ring attached through X. It is assumed that only substituents on one side of this ring contact hydrophobic space; hence, 5- and 6-substituents are given a value of π_m or π_o of zero. These substituents, as well as para substituents, are included in π-6; the small coefficient with this term indicates little effect for such groups. It seemed likely that part of π_o might be steric in nature but an attempt to delineate a steric role for ortho substituents by using E_s-o did not result in an improved correlation. The high collinearity of E_s-o and π_o can be seen from Table X. A role for a steric effect of ortho substituents might be established with a better selection of substituents. Substituent space around the 1 and 3 positions does not appear to be truly hydrophobic as the low coefficient with relatively large confidence limits indicates. Large substituents in these positions do not destroy activity; they simply make very little contribution to inhibitory power and this is largely offset by the loss of the H atom on nitrogen (*I*-1). This suggests that these positions are essentially open to the surrounding solvent (high bulk tolerance with small substituents being as well fit as large groups) with some weak dispersion forces playing a small role. This might be due to weak interaction with a polar surface of the enzyme.

I-4 takes the value of 1 for the bridges 5-N=N- and 5-SO_2NH-. Only six congeners (three of each type) have been used in the derivation of the regression equations. Attempts to separate electronic effects of 5-substituents via $\mathfrak{F}$ and $\mathfrak{R}$ were also unsuccessful. *I*-4 is not a very important variable; it does, however, merit further study to see if it primarily represents a steric problem. It is difficult to visualize what properties the azo and sulfonyl groups have in common.

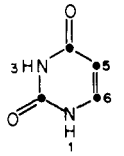
It is surprising that no role could be established for electronic effects of substituents in the 5 or 6 positions. A wide variation of substituents has been tested; there is considerable unaccounted for variance (*s* for eq 6 is 0.43). It is possible that a better purified enzyme and more careful testing might bring out an electronic role for the 5- and 6-functions.

Table XI. Development of QSAR for Eq 6 for Thymidine Phosphorylase (*E. coli*)

Intercept	*I*-3	*I*-1	π_o	*I*-2	π_m	π-1,3	*I*-4	π-6	*r*	*s*	$F_{1,X}$[a]
−0.16	2.24								0.761	0.856	185
−1.11	1.79	1.41							0.874	0.644	104
−1.11	1.38	1.41	1.27						0.899	0.582	30.6
−1.17	1.55	1.30	1.27	0.61					0.913	0.545	19.9
−1.17	1.38	1.31	1.02	0.65	0.76				0.925	0.510	19.1
−1.78	1.39	1.91	1.02	0.66	0.76	0.29			0.935	0.478	19.2
−1.78	1.31	1.98	1.02	0.63	0.77	0.29	−0.75		0.942	0.454	14.9
−1.80	1.18	1.81	1.13	0.54	0.81	0.29	−0.83	0.16	0.948	0.431	14.9

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

Uridine Phosphorylase (from Walker 256 Rat Tumor). Baker points out that uridine phosphorylase from different sources shows quite different responses to the same inhibitor.[17b] In this study enzyme from Walker 256 tumor was employed and the reaction inhibited by uracils was the cleavage of FUDR. Variable π-L in eq 7



$$\log 1/C = 0.413\ (\pm 0.08)\ (\pi\text{-}L) + 1.737\ (\pm 0.29)\ (I\text{-}1) + 0.560\ (\pm 0.25)\ (I\text{-}2) + 0.347\ (\pm 0.25)\ (I\text{-}3) + 0.565\ (\pm 0.26)\ (I\text{-}4) - 0.955\ (\pm 0.27) \quad (7)$$

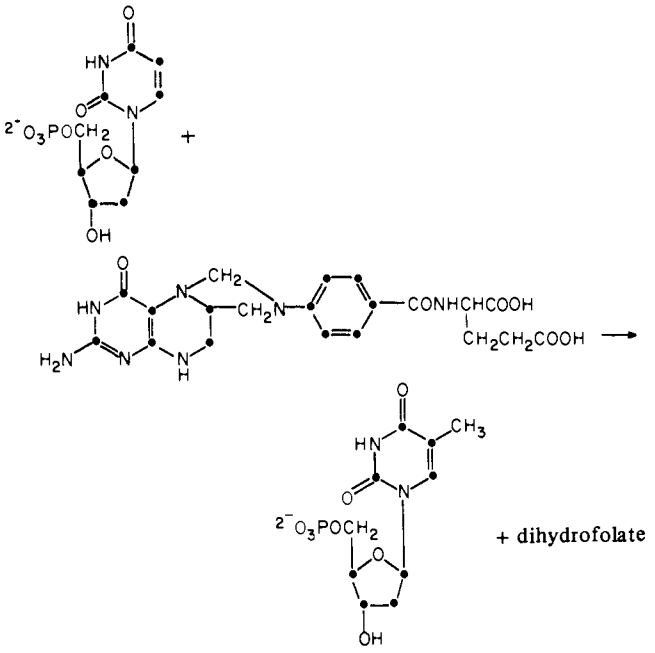
$$n \quad r \quad s$$
$$89 \quad 0.912 \quad 0.392$$

is the larger hydrophobic substituent in the 1 or 5 position. Such a mode of parameterization yields a better correlation than, say, π-1 + π-5 or π-L + π-S where π-S is the smaller of the two possible hydrophobic groups. Using the two variables π-1 and π-5 gives a rather good correlation with essentially equal coefficients with each term. The fact that π-L alone does a better job suggests that there is a preferred hydrophobic space near the 1 or 5 position which can be occupied by the more hydrophobic of the substituents by rotation of the uracil about its 3–6 axis. However, as can be seen in Table XIII, there is such a large amount of collinearity between π-1,5 and π-L, and π-1,5 and MR-L that firm statements about the nature of enzymic 1- and 5-space cannot be made without further study.

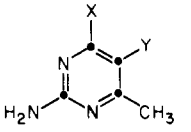
Table XIV shows the development of the Walker 256 uridine phosphorylase QSAR. The most important variable is the hydrophobic term π-L. Since the value of this term is 0.41 rather than in the range 0.1–0.2 and since π gives a better correlation than MR, it seems most likely that interaction of substituents is predominantly with hydrophobic space rather than polar space. The second most important variable is I-1, which takes a value of 1 for 5-$CH_2C_6H_5$ and 5-SC_6H_5 substituents. The large coefficient with this term suggests that these two groups appear to be of optimum size and configuration to cause a conformational change in the enzyme which is quite inhibitory. The contribution by I-1 is in addition to that made by the π-L component of these functions. Other large 5-substituents such as 5-COOEt, 5-Br, 5-NHC_6H_5, 5-N=NC_6H_5, and 5-$NHCH_2C_6H_5$ are adequately parameterized by π-L alone. The third most significant parameter, I-4, is the only parameter for substituents in the 6 position. I-4 takes the value of 1 only for 6-$NHCH_2R$. Groups such as 6-NHC_6H_5 and 6-$NHCHR_1R_2$ are not included. Since other large groups such as 6-$CH_2C_6H_4X$ do not make any contribution to inhibitory power, it is thought that substituents in the 6 position fall into aqueous space and do not make direct contact with the enzyme. If this is so, then 6-$NHCH_2R$ must make its contribution via an electronic effect. Attempts to justify this hypothesis by the use of $\mathfrak{F}$ and $\mathfrak{R}$ were not successful. I-2 takes the value of 1 for 1-$CH_2C_6H_5$; this group increases activity by a factor of about 4. The least important variable is I-3, which has a value of 1 for 1-H. An H on the 1 position makes a small contribution to inhibitory activity which might be ascribed to H-bonding.

Assuming the different reaction end points for eq 6 and 7 are comparable, a comparison of two different kinds (bacterial and mammalian) of pyrimidine nucleoside phosphorylase can be made, even though different sets of uracils were studied in each case. Hydrophobic interactions in different portions of enzymic space are important for each enzyme but the hydrophobic space does not appear to be large.

Thymidylate Synthetase (*E. coli* **B**). Thymidylate synthetase catalyzes the transfer of 1-carbon fragments; it is crucial for the synthesis of the DNA bases.



Equation 8, which is derived from the data in Table XV,

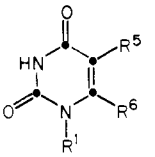


$$\log [S]/[I]\ 0.5 = 0.255\ (\pm 0.05)\ (\text{MR-Y}) + 0.905\ (\pm 0.29)\ (I\text{-}1) - 0.664\ (\pm 0.23)\ (I\text{-}2) - 2.910\ (\pm 0.32) \quad (8)$$

$$n \quad r \quad s$$
$$41 \quad 0.914 \quad 0.299$$

constitutes the QSAR for the 50% inhibition of thymidylate synthetase by 2-amino-6-methylpyrimidines. Baker employed the reactants shown in this equation. For the set of 43 congeners under consideration, X = OH, SH, H, NH_2, or $N(Me)_2$; only one congener was present for each of the cases where X = H, NH, or $N(Me)_2$. I-1 takes the value of 1 for X = SH. This result reminds us that thioinosinate binds to inosinate dehydrogenase fourfold better than the substrate inosinate; this is the reason for 6-mercaptopurine's use as an antitumor drug. I-2 assumes the value of 1 for functions of the type where Y = $(CH_2)_3N(R)C(=O)Z$ and where Z = CH_3, C_6H_5, or OC_6H_5. Two data points (**34** and **36**) have been dropped because they are poorly fit; however, including these does not make a significant change in the terms of eq 8. The positive coefficient with I-1 indicates that 4-SH functions are about eight times as effective in enzyme inhibition as 4-OH or 4-NH_2. The negative coefficient with I-2 brings out the fact that carbonyl groups attached to the nitrogen of the side chain result in about five times poorer inhibition. It is surprising that sulfonamides not parameterized by I-2 are well fit, indicating that they do not produce a deleterious effect on inhibition. Although there is a 500-fold range in the activity of the inhibitors, relatively little highly specific information has been gained. The most useful

Table XII. Constants Used for Deriving Eq 7 for Uridine Phosphorylase (Walker 256)



No.	Substituents	Log *S/I* Obsd[a]	Log *S/I* Calcd[b]	|Δ log *S/I*|	π-*L*	*I*-1	*I*-2	*I*-3	*I*-4	Ref
1	6-OC_6H_5	−1.32	−0.61	0.71	0.0	0.0	0.0	1.0	0.0	11a
2	6-$NHCH(CH_3)C_6H_5$	−1.30	−0.61	0.69	0.0	0.0	0.0	1.0	0.0	11a
3[c]	1-c-C_5H_9	−1.16	−0.07	1.09	2.14	0.0	0.0	0.0	0.0	11b
4	6-$CH_2C_6H_5$	−1.04	−0.61	0.43	0.0	0.0	0.0	1.0	0.0	11a
5	6-NH_2	−1.00	−0.61	0.39	0.0	0.0	0.0	1.0	0.0	11a
6	1-CH_3	−0.95	−0.75	0.20	0.50	0.0	0.0	0.0	0.0	11b
7	6-NHC_6H_3-2′,6′-$(CH_3)_2$	−0.94	−0.61	0.33	0.0	0.0	0.0	1.0	0.0	11a
8	6-CF_3	−0.92	−0.61	0.31	0.0	0.0	0.0	1.0	0.0	11c
9	H	−0.86	−0.61	0.25	0.0	0.0	0.0	1.0	0.0	11a
10	6-$(CH_2)_2C_6H_5$	−0.83	−0.61	0.22	0.0	0.0	0.0	1.0	0.0	11a
11	1-C_4H_9-5-Br	−0.81	−0.13	0.68	2.00	0.0	0.0	0.0	0.0	11b
12	6-$SO_2C_6H_5$	−0.81	−0.61	0.20	0.0	0.0	0.0	1.0	0.0	11a
13[c]	1-$(CH_2)_2C_6H_5$	−0.78	0.14	0.92	2.66	0.0	0.0	0.0	0.0	11b
14	6-NHC_4H_9	−0.68	−0.04	0.64	0.0	0.0	0.0	1.0	1.0	11a
15	1-$(CH_2)_2OC_6H_5$	−0.65	−0.12	0.53	2.01	0.0	0.0	0.0	0.0	11b
16	6-$(CH_2)_3C_6H_5$	−0.65	−0.61	0.04	0.0	0.0	0.0	1.0	0.0	11a
17	6-$NH(CH_2)_2C_6H_5$	−0.60	−0.04	0.56	0.0	0.0	0.0	1.0	1.0	11a
18	5-$CO_2C_2H_5$	−0.57	−0.40	0.17	0.51	0.0	0.0	1.0	0.0	11c
19	6-$N(CH_3)CH_2C_6H_5$	−0.57	−0.61	0.04	0.0	0.0	0.0	1.0	0.0	11a
20	6-$NHCH(C_6H_5)CH_2C_6H_5$	−0.57	−0.61	0.04	0.0	0.0	0.0	1.0	0.0	11a
21	1-C_3H_7	−0.57	−0.33	0.23	1.50	0.0	0.0	0.0	0.0	11b
22	1-$(CH_2)_3C_6H_5$	−0.37	0.30	0.67	3.03	0.0	0.0	0.0	0.0	11b
23	6-$NH(CH_2)_3C_6H_5$	−0.33	−0.04	0.29	0.0	0.0	0.0	1.0	1.0	11a
24	5-NHC_6H_5	−0.30	−0.04	0.26	1.37	0.0	0.0	1.0	0.0	11c
25	5-F	−0.28	−0.55	0.27	0.14	0.0	0.0	1.0	0.0	11c
26	1-C_4H_9-5-$SO_2NHC_4H_9$	−0.26	−0.13	0.13	2.00	0.0	0.0	0.0	0.0	11b
27	1-$CH_2C_6H_4$-3′-NO_2	−0.25	0.32	0.57	1.73	0.0	1.0	0.0	0.0	11b
28[c]	5-$CH_2C_6H_5$-6-CF_3	−0.22	1.96	2.18	2.01	1.0	0.0	1.0	0.0	11c
29	6-NHC_6H_3-2′,3′-$(CH_3)_2$	−0.18	−0.61	0.43	0.0	0.0	0.0	1.0	0.0	11a
30	5-N=N-C_6H_5-6-C_5H_{11}	−0.15	0.09	0.24	1.69	0.0	0.0	1.0	0.0	11a
31	5-Br-6-$NHCH_2C_6H_5$	−0.14	0.31	0.45	0.86	0.0	0.0	1.0	1.0	11a
32	5-$NH(CH_2)_2C_6H_5$	−0.13	0.06	0.19	1.61	0.0	0.0	1.0	0.0	11c
33	6-$NHCH_2C_6H_4$-4′-Cl	−0.10	−0.04	0.06	0.0	0.0	0.0	1.0	1.0	11a
34	6-$N(CH_2C_6H_5)_2$	−0.01	−0.61	0.60	0.0	0.0	0.0	1.0	0.0	11a
35	5-$NH(CH_2)_4C_6H_5$	0.00	0.47	0.47	2.61	0.0	0.0	1.0	0.0	11c
36	6-$NHCH_2C_6H_5$	0.00	−0.04	0.04	0.0	0.0	0.0	1.0	1.0	11a
37	6-NHC_6H_3-2′,3′-Cl_2	0.00	−0.61	0.61	0.0	0.0	0.0	1.0	0.0	11a
38	6-NHC_5H_{11}	0.01	−0.04	0.05	0.0	0.0	0.0	1.0	1.0	11a
39	6-$NHCH(C_6H_5)_2$	0.02	−0.61	0.63	0.0	0.0	0.0	1.0	0.0	11a
40	1-$CH_2C_6H_4$-4′-CH_3	0.03	0.64	0.61	2.51	0.0	1.0	0.0	0.0	11b
41	1-C_4H_9	0.06	−0.13	0.19	2.00	0.0	0.0	0.0	0.0	11b
42	6-$NHCH_2C_6H_4$-3′-Cl	0.08	−0.04	0.12	0.0	0.0	0.0	1.0	1.0	11a
43	5-Br-6-$CH_2C_6H_5$	0.08	−0.25	0.33	0.86	0.0	0.0	1.0	0.0	11a
44	1-$(CH_2)_3OC_6H_5$	0.12	0.08	0.04	2.51	0.0	0.0	0.0	0.0	11b
45	6-$NH(CH_2)_4C_6H_5$	0.15	−0.04	0.19	0.0	0.0	0.0	1.0	1.0	11a
46	5-$NHCH_2C_6H_5$	0.17	−0.19	0.36	1.0	0.0	0.0	1.0	0.0	11c
47	1-$CH_2C_6H_4$-3′-$NHCOCH_2Br$	0.19	0.28	0.09	1.64	0.0	1.0	0.0	0.0	11b
48	1-*i*-C_6H_{13}	0.19	0.20	0.01	2.80	0.0	0.0	0.0	0.0	11b
49	1-C_5H_{11}	0.20	0.08	0.12	2.50	0.0	0.0	0.0	0.0	11b
50	5-Br	0.20	−0.25	0.45	0.86	0.0	0.0	1.0	0.0	11c
51	6-$NHCH_2$-(1-$C_{10}H_7$)	0.22	−0.04	0.26	0.0	0.0	0.0	1.0	1.0	11a
52	6-$NHCH_2C_6H_4$-2′-Cl	0.22	−0.04	0.26	0.0	0.0	0.0	1.0	1.0	11a
53	1-*i*-C_5H_{11}	0.26	0.00	0.26	2.30	0.0	0.0	0.0	0.0	11b
54	5-$NH(CH_2)_3C_6H_5$	0.30	0.26	0.04	2.11	0.0	0.0	1.0	0.0	11c
55	6-$NH(CH_2)_3OC_6H_5$	0.30	−0.04	0.34	0.0	0.0	0.0	1.0	1.0	11a
56	5-OC_6H_5	0.32	0.25	0.07	2.08	0.0	0.0	1.0	0.0	11c
57	1-$(CH_2)_5OC_6H_5$	0.32	0.50	0.18	3.51	0.0	0.0	0.0	0.0	11b
58	1-$CH_2C_6H_4$-3′-OH	0.35	0.16	0.19	1.34	0.0	1.0	0.0	0.0	11b
59	1-CH_2-(2-$C_{10}H_7$)	0.40	0.98	0.58	3.33	0.0	1.0	0.0	0.0	11b
60	5-$CH_2OCH_2C_6H_5$	0.43	0.04	0.39	1.56	0.0	0.0	1.0	0.0	11c
61	1-$CH_2C_6H_5$	0.43	0.44	0.01	2.01	0.0	1.0	0.0	0.0	11b
62	5-Br-6-$CH_2C_6H_4$-3′-NO_2	0.43	−0.25	0.68	0.86	0.0	0.0	1.0	0.0	11a
63	5-$(CH_2)_2C_6H_5$	0.46	0.49	0.03	2.66	0.0	0.0	1.0	0.0	11c
64	1-C_4H_9-5-$SO_2NHC_6H_5$	0.46	−0.13	0.59	2.00	0.0	0.0	0.0	0.0	11b
65	1-CH_2-(1-$C_{10}H_7$)	0.52	0.98	0.46	3.33	0.0	1.0	0.0	0.0	11b
66	1-$(CH_2)_5C_6H_5$	0.61	0.71	0.10	4.03	0.0	0.0	0.0	0.0	11b
67	1-$(CH_2)_6C_6H_5$	0.66	0.92	0.26	4.53	0.0	0.0	0.0	0.0	11b
68	6-$NH(CH_2)_5C_6H_5$	0.67	−0.04	0.71	0.0	0.0	0.0	1.0	1.0	11a
69	1-$CH_2C_6H_4$-3′-Cl	0.74	0.73	0.01	2.72	0.0	1.0	0.0	0.0	11b

Table XII (*Continued*)

No.	Substituents	Log S/I Obsd[a]	Log S/I Calcd[b]	|Δ log S/I|	π-L	I-1	I-2	I-3	I-4	Ref
70	1-$CH_2C_6H_4$-2'-OCH_3	0.82	0.43	0.39	1.99	0.0	1.0	0.0	0.0	11b
71	1-$(CH_2)_3OC_6H_5$-5-$(CH_2)_4C_6H_5$	0.86	0.50	0.36	3.53	0.0	0.0	0.0	0.0	11c
72	5-$(CH_2)_3C_6H_5$	0.91	0.64	0.27	3.03	0.0	0.0	1.0	0.0	11c
73	1-$(CH_2)_4C_6H_5$	0.94	0.50	0.44	3.53	0.0	0.0	0.0	0.0	11b
74	1-$CH_2C_6H_4$-4'-OC_6H_5	1.02	1.30	0.28	4.09	0.0	1.0	0.0	0.0	11b
75	1-$(CH_2)_4OC_6H_5$	1.06	0.29	0.77	3.01	0.0	0.0	0.0	0.0	11b
76	1-$CH_2C_6H_4$-3'-CH_3	1.19	0.56	0.63	2.31	0.0	1.0	0.0	0.0	11b
77[c]	1-$CH_2C_6H_4$-3'-OCH_3	1.35	0.43	0.92	1.99	0.0	1.0	0.0	0.0	11b
78	1-$CH_2C_6H_3$-3',5'-$(CH_3)_2$	1.40	0.85	0.55	3.01	0.0	1.0	0.0	0.0	11b
79[c]	5-NO_2	1.43	−0.61	2.04	0.0	0.0	0.0	1.0	0.0	11c
80	1-$CH_2C_6H_4$-3'-$OCH_2C_6H_5$	1.52	1.31	0.21	4.12	0.0	1.0	0.0	0.0	11b
81	1-$CH_2C_6H_4$-3'-C_6H_5	1.60	1.79	0.19	5.29	0.0	1.0	0.0	0.0	11b
82	1-$CH_2C_6H_4$-3'-$O(CH_2)_4C_6H_5$	1.63	1.74	0.11	5.17	0.0	1.0	0.0	0.0	11b
83	1-$CH_2C_6H_4$-3'-OC_6H_5	1.63	1.30	0.33	4.09	0.0	1.0	0.0	0.0	11b
84	1-$CH_2C_6H_4$-3'-$O(CH_2)_2C_6H_5$	1.64	1.33	0.31	4.17	0.0	1.0	0.0	0.0	11b
85[c]	1-$CH_2C_6H_4$-3'-OC_2H_5	1.74	0.59	1.15	2.39	0.0	1.0	0.0	0.0	11b
86	5-CH_2-(1-$C_{10}H_7$)	1.76	2.50	0.74	3.33	1.0	0.0	1.0	0.0	11c
87	1-$CH_2C_6H_4$-3'-$O(CH_2)_3C_6H_5$	1.79	1.53	0.25	4.67	0.0	1.0	0.0	0.0	11b
88	1-CH_3-5-$CH_2C_6H_5$	1.81	1.61	0.20	2.01	1.0	0.0	0.0	0.0	11c
89	1-$(CH_2)_3OC_6H_5$-5-$CH_2C_6H_5$	1.85	1.82	0.03	2.51	1.0	0.0	0.0	0.0	11c
90	5-$CH_2C_6H_5$	1.88	1.96	0.08	2.01	1.0	0.0	1.0	0.0	11c
91	5-SC_6H_5	1.89	2.09	0.20	2.32	1.0	0.0	1.0	0.0	11c
92[c]	5-$(CH_2)_4C_6H_5$	2.00	0.85	1.15	3.53	0.0	0.0	1.0	0.0	11c
93	1,5-$(CH_2C_6H_5)_2$	2.19	2.17	0.02	2.01	1.0	1.0	0.0	0.0	11c
94	5-$CH_2C_6H_4$-4'-OCH_3	2.32	1.95	0.37	1.99	1.0	0.0	1.0	0.0	11c
95	5-$CH_2C_6H_4$-3'-OC_2H_5	2.46	2.12	0.34	2.39	1.0	0.0	1.0	0.0	11c
96	5-$CH_2C_6H_4$-3'-$OCH_2C_6H_5$	2.90	2.83	0.07	4.12	1.0	0.0	1.0	0.0	11c

[a] Calculated from results of Baker et al.[11] [b] Calculated using eq 7. [c] These molecules not used in deriving equations.

Table XIII. Squared Correlation Matrix for Variables of Eq 7 for Uridine Phosphorylase (Walker 256)

	π-1,5	MR-L	π-L	I-1	I-2	I-3	I-4
π-1,5	1.00	0.83	0.94	0.07	0.22	0.49	0.20
MR-L		1.00	0.89	0.05	0.28	0.39	0.22
π-L			1.00	0.03	0.25	0.46	0.20
I-1				1.00	0.01	0.01	0.02
I-2					1.00	0.35	0.05
I-3						1.00	0.13
I-4							1.00

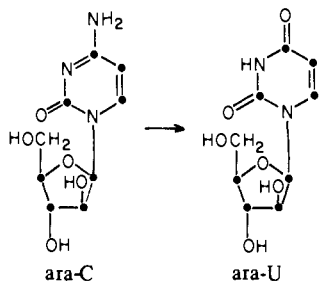
Table XIV. Development of QSAR of Eq 7 for Uridine Phosphorylase (Walker 256)

Intercept	π-L	I-1	I-4	I-2	I-3	r	s	$F_{1,X}$[a]
−0.39	0.41					0.676	0.687	73.4
−0.45	0.35	1.68				0.747	0.472	98.7
−0.65	0.42	1.72	0.61			0.889	0.432	11.4
−0.65	0.35	1.82	0.60	0.43		0.904	0.406	12.3
−0.95	0.41	1.73	0.56	0.56	0.34	0.912	0.392	7.36

[a] $F_{1,60;\alpha\,0.001} = 11.97$; $F_{1,60;\alpha\,0.01} = 7.08$.

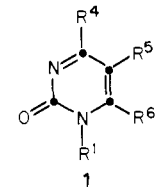
information is the potency of the SH function. Increasing activity by increasing MR-Y would probably be of very little value for in vivo systems. A slight improvement over eq 8 can be obtained (see Table XVII) by adding the variable I-3, which takes the value of 1 for X = OH. The collinearity between I-3 and I-1 makes for ambivalence in the use of I-3. If more 4-X functions (other than SH and OH) had been studied, I-3 might be a more important term.

Cytosine Nucleoside Deaminase (*E. coli* **B**). This enzyme catalyzes the deamination of nucleosides such as ara-C to ara-U.



ara-C ara-U

Ara-C is a rather effective antitumor agent for certain types of cancers; however, ara-U is not very cytotoxic. Baker hoped eventually to find an inhibitor of cytosine nucleoside deaminase which would be selective against tumor enzyme but inactive against human enzyme and in this way increase the effectiveness of ara-C. This initial study was done with enzyme from *E. coli*. The QSAR for uracils causing 50% inhibition of the cytosine nucleoside deaminase has been formulated from the data in Table XVIII. Equation 9, using π-5 and π-1,6, gives a somewhat



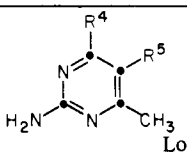
1

$$\log 1/C = 0.283\ (\pm 0.06)\ (\pi\text{-}5) + 0.188\ (\pm 0.07)\ (\pi\text{-}1,6) + 0.265\ (\pm 0.16)\ (I\text{-}1) + 2.257\ (\pm 0.24) \quad (9)$$

$n = 71$ $r = 0.927$ $s = 0.227$

better correlation than the corresponding equation using MR-5 and MR-1,6 (r = 0.897 for the MR equation). As in most of Baker's studies, the high collinearity between π and MR (see Table XIX) precludes one's making a clear decision about the nature of 1,5,6-space. Our inclination

Table XV. Constants Used for Deriving Eq 8 for Thymidylate Synthetase



No.	R^4	R^5	Log S/I Obsd[a]	Log S/I Calcd[b]	$\lvert\Delta$ log $S/I\rvert$	MR-5	*I*-1	*I*-2	Ref
1	OH	$(CH_2)_3NHCOCH_3$	−2.70	−2.83	0.13	2.89	0.0	1.0	12g
2	OH	$(CH_2)_3N(COCH_3)CH_2$-(2-C_5H_4N)	−2.69	−2.16	0.53	5.55	0.0	1.0	12c
3	OH	$(CH_2)_3NHC_4H_9$	−2.54	−1.93	0.61	3.82	0.0	0.0	12c
4	OH	$(CH_2)_3N(COCH_3)CH_2$-(4-C_5H_4N)	−2.30	−2.16	0.14	5.55	0.0	1.0	12b
5	OH	$(CH_2)_3N(COCH_3)CH_2$-(3-C_5H_4N)	−2.28	−2.16	0.12	5.55	0.0	1.0	12c
6	OH	$(CH_2)_3NHSO_2C_4H_9$	−2.26	−1.76	0.49	4.48	0.0	0.0	12g
7	OH	$(CH_2)_3N(COCH_3)CH_2$-(2-C_4H_3O)	−2.23	−2.31	0.08	4.96	0.0	1.0	12c
8	OH	$(CH_2)_3C_6H_5$	−2.04	−1.90	0.13	3.93	0.0	0.0	12i
9	H	$(CH_2)_3NHC_6H_5$	−2.00	−1.78	0.21	4.40	0.0	0.0	12a
10	$N(CH_3)_2$	$(CH_2)_3NHC_6H_5$	−2.00	−1.78	0.21	4.40	0.0	0.0	12f
11	OH	$NHCH_2CH{=}CHC_6H_5$	−1.90	−1.77	0.13	4.46	0.0	0.0	12i
12	OH	$(CH_2)_3NHCOC_6H_4$-4-$CH_2OC_2H_5$	−1.82	−1.92	0.10	6.46	0.0	1.0	12g
13	NH_2	$(CH_2)_3NHC_6H_5$	−1.80	−1.78	0.02	4.40	0.0	0.0	12a
14	OH	$NH(CH_2)_3C_6H_5$	−1.76	−1.78	0.02	4.40	0.0	0.0	12i
15	OH	$(CH_2)_3NHC_6H_5$	−1.70	−1.78	0.08	4.40	0.0	0.0	12a
16	OH	$(CH_2)_3NH$-(3-C_5H_4N)	−1.67	−1.85	0.18	4.14	0.0	0.0	12c
17	OH	$(CH_2)_3N(COCH_3)CH_2C_6H_5$	−1.59	−2.10	0.51	5.78	0.0	1.0	12c
18	OH	$(CH_2)_4C_6H_5$	−1.54	−1.79	0.25	4.39	0.0	0.0	12b
19	OH	$(CH_2)_3NH$-(2-$C_{10}H_7$)	−1.48	−1.39	0.09	5.94	0.0	0.0	12c
20	OH	$(CH_2)_3NHSO_2C_6H_5$	−1.43	−1.59	0.16	5.15	0.0	0.0	12d
21	OH	$(CH_2)_3NHSO_2C_6H_4$-4-CN	−1.43	−1.46	0.03	5.68	0.0	0.0	12d
22	OH	$(CH_2)_3NHC_6H_4$-4-F	−1.28	−1.79	0.51	4.39	0.0	0.0	12c
23	OH	$(CH_2)_3NHSO_2C_6H_4$-4-$COCH_2Br$	−1.23	−1.16	0.07	6.85	0.0	0.0	12d
24	OH	$(CH_2)_3N(C_4H_9)Ts$	−1.23	−1.00	0.23	7.47	0.0	0.0	12e
25	OH	$(CH_2)_3NHSO_2C_6H_4$-4-NO_2	−1.20	−1.46	0.26	5.69	0.0	0.0	12d
26	OH	$(CH_2)_3NHSO_2C_6F_5$	−1.08	−1.65	0.57	4.92	0.0	0.0	12d
27	OH	$(CH_2)_3N(C_6H_5)SO_2C_6H_4$-4-$NO_2$	−1.08	−0.84	0.24	8.12	0.0	0.0	12d
28	SH	$(CH_2)_3NHC_6H_5$	−1.04	−0.88	0.16	4.40	1.0	0.0	12a
29	OH	$(CH_2)_3NHSO_2C_6H_4$-4-$CH_2NHCOCH_2Br$	−1.04	−0.95	0.09	7.69	0.0	0.0	12d
30	SH	$(CH_2)_3NHC_6H_4$-4-$N(CH_3)_2$	−0.93	−0.51	0.42	5.85	1.0	0.0	12b
31	SH	$(CH_2)_3N(C_6H_5)COC_6H_5$	−0.85	−0.80	0.05	7.33	1.0	1.0	12h
32	OH	$(CH_2)_3N(Ts)CH_2C_6H_4$-3-NH_2	−0.85	−0.65	0.20	8.85	0.0	0.0	12e
33	OH	$(CH_2)_3N(Ts)CH_2C_6H_4$-4-NH_2	−0.79	−0.65	0.14	8.85	0.0	0.0	12e
34[c]	OH	$(CH_2)_3NHTs$	−0.76	−1.48	0.72	5.61	0.0	0.0	12g
35	SH	$(CH_2)_3N(C_6H_5)COOC_6H_5$	−0.71	−0.74	0.03	7.55	1.0	1.0	12h
36[c]	SH	$(CH_2)_3N(COCH_3)C_6H_5$	−0.59	−1.29	0.70	5.41	1.0	1.0	12b
37	OH	$(CH_2)_3N(Ts)CH_2C_6H_4$-3-NO_2	−0.59	−0.60	0.01	9.05	0.0	0.0	12e
38	OH	$(CH_2)_3N(Ts)(CH_2)_3NHCOCH_2Br$	−0.59	−0.59	0.00	9.08	0.0	0.0	12e
39	OH	$(CH_2)_3N(C_6H_5)SO_2C_6H_4$-4-$NH_2$	−0.45	−0.89	0.44	7.92	0.0	0.0	12d
40	OH	$(CH_2)_3N(Ts)CH_2C_6H_4$-4-$NHCOCH_2Br$	−0.45	−0.21	0.24	10.59	0.0	0.0	12e
41	OH	$(CH_2)_3N(Ts)CH_2C_6H_4$-4-NO_2	−0.28	−0.60	0.32	9.05	0.0	0.0	12e
42	SH	$(CH_2)_3NHC_6H_5$-4-Cl	−0.15	−0.75	0.60	4.90	1.0	0.0	12b
43	OH	$(CH_2)_3N(Ts)CH_2C_6H_4$-3-$NHCOCH_2Br$	0.05	−0.21	0.26	10.59	0.0	0.0	12e

[a] Calculated from results of Baker et al.[12] [b] Calculated using eq 8. [c] These molecules not used in deriving equations.

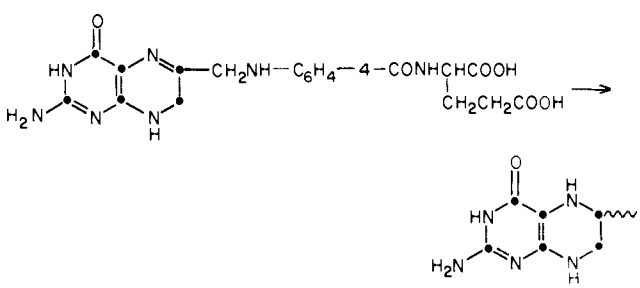
Table XVI. Squared Correlation Matrix for Variables Pertaining to Eq 8 for Thymidylate Synthetase

	π-Y	MR-Y	*I*-3	*I*-1	*I*-2
π-Y	1.00	0.33	0.04	0.09	0.03
MR-Y		1.00	0.05	0.00	0.01
I-3			1.00	0.49	0.00
I-1				1.00	0.03
I-2					1.00

is, until better data are in hand, to regard it as not typically hydrophobic because of the low coefficients with π and MR terms.

In eq 9, *I*-1 takes the value of 1 for 4-NH_2, 4-SH, and 4-NHOH functions. These functions increase inhibitory activity, on the average, by about 1.8-fold over the 4-OH group. Studying π-1 and π-6 independently indicated that these two variables could be combined into π-1,6; however, relatively few 6-substituents were studied. The one unique case, compound **43**, in which large substituents are present in both the 1 and 6 positions, is rather poorly fit. This suggests that 1,6-space may have rather limited bulk tolerance. Compound **42** is unique in that it is a 2-thiopyridone; it is well fit without a correction for the replacement of O by S. This study was not very encouraging since only 250-fold variation in activity was found and no typical hydrophobic sites were uncovered in the 1, 5, or 6 position.

Dihydrofolate Reductase (Pigeon Liver). This enzyme reduces dihydrofolate to tetrahydrofolate.



The crucial role of tetrahydrofolate in the transfer of 1-carbon fragments in the synthesis of the DNA bases

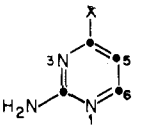
Table XVII. Development of QSAR of Eq 8 for Thymidylate Synthetase

Intercept	MR-Y	I-1	I-2	I-3	r	s	$F_{1,X}$[a]
−3.01	0.27				0.745	0.478	48.6
−3.12	0.27	0.77			0.828	0.407	15.7
−2.91	0.26	0.91	−0.66		0.914	0.299	33.4
−3.10	0.24	1.22	−0.71	0.34	0.923	0.287	4.37

[a] $F_{1,30;\alpha\,0.001} = 13.3$; $F_{1,30;\alpha\,0.05} = 4.17$.

makes it most interesting for control studies. The unusual degree of variation of its structure from system to system provides the possibility for selective toxicity.[18]

Baker's group achieved a variation in concentration in the inhibitors correlated by eq 10 of 1000000. The most



X = OH, SH, or NH_2
(causing 50% inhibition)

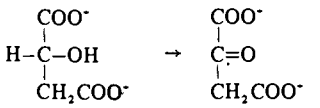
$$\log [S]/[I]\,0.5 = 1.116\ (\pm 0.23)\ (I\text{-}6) + 2.168\ (\pm 0.27)\ (I\text{-}2) + 0.895\ (\pm 0.13)\ (\pi\text{-}6) - 1.227\ (\pm 0.49)\ (I\text{-}4) + 1.184\ (\pm 0.42)\ (I\text{-}1) - 1.606\ (\pm 0.50)\ (I\text{-}5) + 1.634\ (\pm 0.47)\ (I\text{-}3) + 0.255\ (\pm 0.09)\ (\pi\text{-}5) - 3.116\ (\pm 0.29) \quad (10)$$

n = 108, r = 0.932, s = 0.520

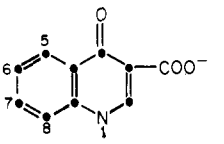
pronounced effect, that by 5-$(CH_2)_nC_6H_5$ or 5-CH_2R (n = 0–4 and R = 4 or 5 carbon atoms), is accounted for by assigning the variable I-6 a value of 1. These bulky groups appear to reach hydrophobic space located somewhat off of the 5 position (see Discussion) and possibly cause a conformational change since small groups or groups with other geometries are accounted for by π-5. The variable I-1 is assigned the value of 1 for 4-SH and I-2 assumes this value for 4-NH_2. These latter two groups can be interchanged by rotation of the pyrimidine ring about its 2–5 axis; such a rotation transposes 1- and 3-, and 4- and 6-substituents. We have assumed that 2,4-diamino binding is preferred since this makes no difference with respect to other substituents (no substituents are present on the 1 or 3 position; 2 and 5 positions are invariant). These variables indicate that, on the average, 4-SH is about 15 times more potent than 4-OH and 4-NH_2 is about 150 times as potent. The coefficient with π-6 is typical of that seen for hydrophobic interactions but that with π-5 is not; this reveals that enzymic space near the 5 position is not hydrophobic. In addition, π-5 is seen to be the least important variable and of marginal importance. Although the COO^- group is so hydrophilic that it lowers activity, the large coefficient with the indicator variable I-3 shows that it is 40 times more active than π alone would predict. This is not surprising since the natural substrate, folic acid, contains two carboxyl groups which would fall far out in 5- and 6-space. Thus the carboxyl group shows some specificity as might be expected. The variable I-4 is assigned the value of 1 when no substituent is present in the 5 position. The negative coefficient with this term brings out the importance, as does I-6, of a bulky group in the 5 position. Since I-5 takes the value of 1 for 6-$(CH_2)_nC_6H_5$ (n = 0, 1, 2) and the coefficient with this term is negative, large groups in the 6 position run into the problem of steric hindrance. Moderate size groups (up to $CH_3CH_2CH_2$–) are well fit and these characterize a small hydrophobic pocket at the 6 position.

Malate Dehydrogenase. With the exception of chymotrypsin and trypsin, the enzymes considered up to this point are involved with DNA synthesis. These inhibitors might be effective in the growth and division phase of cells where division is very fast. Many tumors are slow in dividing and, hence, are resistant to inhibitors of DNA synthesis. Baker decided to search for inhibitors of the enzymes involved in glucose metabolism and in this way limit the source of energy. He hoped to find selective inhibitors of the tumor enzyme.

Malate dehydrogenase plays a role in the Krebs cycle by the conversion of malate to oxalacetate.



The inhibition of this reaction by 1,4-dihydro-4-quinolone-3-carboxylates yielded the data in Table XXIV from which the following QSAR was formulated.



$$\log 1/C = 0.699\ (\pm 0.06)\ (\pi\text{-}5) + 0.290\ (\pm 0.08)\ (\text{MR-}6,7,8) - 1.121\ (\pm 0.37)\ (I\text{-}1) + 3.156\ (\pm 0.18) \quad (11)$$

n = 75, r = 0.943, s = 0.385

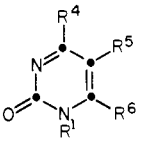
A slightly better correlation can be obtained if MR-6,7,8 is factored into MR-6, π-7, and MR-8 (r = 0.959, s = 0.337). The coefficients with the factored terms are close and there is very high collinearity between π-7 and MR-7; hence, until better data are in hand, it seems best to designate 6-, 7-, and 8-substituent space as primarily polar rather than hydrophobic. The coefficient with the π-5 term is in the range one normally expects for hydrophobic interaction.

I-1 takes the value of 1 for cases where 5-$O(CH_2)_nOC_6H_5$ (n = 3 or 4) is present. The negative coefficient and the fact that cases where n = 2 are well fit suggest that the longer chains position the phenyl moiety outside of 5-hydrophobic space. The value for π of C_6H_5 is 2.13 which, multiplied by 0.7 (the coefficient with π-5), gives 1.5. This is close to the missing increment in log $1/C$ accounted for by the coefficient of I-1. Attempts to find an electronic role for substituents by means of σ were unsuccessful.

Baker achieved an activity of 20000-fold with the quinolonecarboxylates with the best inhibitors being active at 10^{-7} M. The best inhibitors, however, are much too lipophilic to be useful for in vivo work. Malate dehydrogenase, like dihydrofolate reductase,[4b] contains both hydrophobic areas (5-space) and polar areas (6-, 7-, 8-space) with good bulk tolerance. The superoptimal lipophilicity of inhibitors with large hydrophobic 5-substituents can be counterbalanced with hydrophilic substituents in the 6, 7, or 8 position. A careful study of malate dehydrogenase from bacterial and mammalian sources might uncover a route to effective antibacterials.

Glutamate Dehydrogenase. This is one of the enzymes which connects the glucose energy pathway with amino acid metabolism.

Table XVIII. Constants Used for Deriving Eq 9 for Cytosine Nucleoside Deaminase

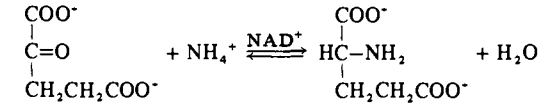


No.	Substituents	Log 1/C Obsd[a]	Log 1/C Calcd[b]	|Δ log 1/C|	π-5	π-1,6	I-1	Ref
1	1-$CH_2C_6H_5$-4-OH	2.10	2.63	0.53	0.0	2.01	0.0	13a
2	4-OH-6-C_5H_{11}	2.52	2.73	0.21	0.0	2.50	0.0	13a
3	1-c-C_5H_9-4-OH	2.57	2.66	0.09	0.0	2.14	0.0	13a
4	1-$CH_2C_6H_4$-2′-$NHCOCH_2Br$-4-OH	2.64	2.56	0.08	0.0	1.64	0.0	13a
5	1-$CH_2C_6H_4$-3′-$NHCOCH_2Br$-4-OH	2.64	2.56	0.08	0.0	1.64	0.0	13a
6	1-$(CH_2)_3C_6H_5$-4-OH	2.64	2.85	0.21	0.0	3.16	0.0	13a
7	4-OH-6-$NHCH_2C_6H_5$	2.66	2.44	0.22	0.0	1.00	0.0	13a
8	1-$(CH_2)_3OC_6H_5$-4-OH	2.70	2.84	0.14	0.0	3.11	0.0	13a
9	4-OH-6-$NH(CH_2)_3C_6H_5$	2.70	2.76	0.06	0.0	2.66	0.0	13a
10	1-$(CH_2)_4C_6H_5$-4-OH	2.72	2.95	0.23	0.0	3.66	0.0	13a
11	4-OH-6-$CH_2C_6H_5$	2.74	2.63	0.11	0.0	2.01	0.0	13a
12	1-$(CH_2)_3C_6H_4$-4′-$COOC_2H_5$-4-OH	2.77	2.95	0.18	0.0	3.67	0.0	13a
13	4-OH-6-$(CH_2)_3C_6H_5$	2.82	2.85	0.03	0.0	3.16	0.0	13a
14	1-$(CH_2)_5C_6H_5$-4-OH	2.82	3.04	0.22	0.0	4.16	0.0	13a
15	1-$(CH_2)_3C_6H_5$-4-OH-5-$CH_2OC_2H_5$	3.00	3.00	0.00	0.53	3.16	0.0	13b
16	1-$(CH_2)_3C_6H_5$-4-OH-6-C_3H_7	3.03	3.13	0.10	0.0	4.66	0.0	13b
17	1-$(CH_2)_3OC_6H_5$-4-NH_2-5-C_6H_5	3.36	3.66	0.30	1.96	3.11	1.0	13c
18	1-$(CH_2)_3OC_6H_4$-2′-Cl-4-NH_2-5-C_6H_5	3.40	3.79	0.39	1.96	3.82	1.0	13c
19	1-$(CH_2)_2OC_6H_5$-4-OH-5-C_6H_5	3.42	3.30	0.12	1.96	2.61	0.0	13b
20	1-$(CH_2)_4OC_6H_5$-4-OH-5-C_6H_5	3.43	3.49	0.06	1.96	3.61	0.0	13b
21	1-$(CH_2)_2C_6H_5$-4-NH_2-5-C_6H_3-3′,4′-Cl_2	3.43	3.98	0.55	3.38	2.66	1.0	13c
22	1-$(CH_2)_3OC_6H_5$-4-NH_2-5-C_6H_4-2′-Cl	3.46	3.86	0.40	2.67	3.11	1.0	13c
23	1-$(CH_2)_3OC_6H_5$-4-OH-5-$CH_2C_6H_5$	3.47	3.41	0.06	2.01	3.11	0.0	13b
24	1-$(CH_2)_3OC_6H_4$-4′-NO_2-4-NH_2-5-C_6H_5	3.52	3.65	0.13	1.96	3.03	1.0	13c
25	1-$(CH_2)_3OC_6H_4$-3′-NO_2-4-NH_2-5-C_6H_5	3.55	3.65	0.10	1.96	3.03	1.0	13c
26	1-$(CH_2)_3OC_6H_4$-2′-NO_2-4-NH_2-5-C_6H_5	3.55	3.65	0.10	1.96	3.03	1.0	13c
27	1-$(CH_2)_3C_6H_5$-4-NH_2-5-C_6H_3-3′,4′-Cl_2	3.62	4.07	0.45	3.38	3.16	1.0	13c
28	1-$(CH_2)_3OC_6H_5$-4-OH-5-C_6H_5	3.64	3.40	0.24	1.96	3.11	0.0	13b
29	1-$(CH_2)_3OC_6H_4$-3′-CH_3-4-NH_2-5-C_6H_4-4′-NH_2	3.70	3.41	0.29	0.73	3.61	1.0	13c
30	1-$(CH_2)_3C_6H_5$-4-OH-5-C_6H_5	3.70	3.41	0.29	1.96	3.16	0.0	13b
31	1-$(CH_2)_3OC_6H_5$-4-NH_2-5-C_6H_4-3′-Cl	3.72	3.86	0.14	2.67	3.11	1.0	13c
32	1-$(CH_2)_3OC_6H_5$-4-NH_2-5-C_6H_4-4′-CH_3	3.72	3.80	0.08	2.46	3.11	1.0	13c
33	1-$(CH_2)_3OC_6H_5$-4-NHOH-5-C_6H_5	3.74	3.66	0.08	1.96	3.11	1.0	13c
34	1-$(CH_2)_3OC_6H_5$-4-OH-5-$(CH_2)_2C_6H_5$	3.74	3.59	0.15	2.66	3.11	0.0	13b
35	1-$(CH_2)_3OC_6H_5$-4-NH_2-5-C_6H_4-4′-NO_2	3.80	3.58	0.22	1.68	3.11	1.0	13c
36	1-$(CH_2)_3OC_6H_5$-4′-Cl-4-NH_2-5-C_6H_5	3.80	3.79	0.01	1.96	3.82	1.0	13c
37	1-$(CH_2)_3OC_6H_5$-4-NH_2-5-C_6H_4-4′-NH_2	3.80	3.31	0.49	0.73	3.11	1.0	13c
38	1-$(CH_2)_3OC_6H_5$-4-NH_2-5-C_6H_4-4′-NHAc	3.80	3.39	0.41	0.99	3.11	1.0	13c
39	1-$(CH_2)_3OC_6H_5$-4-NH_2-5-C_6H_4-4′-Cl	3.80	3.86	0.06	2.67	3.11	1.0	13c
40	1-$(CH_2)_3OC_6H_5$-4-OH-5-$(CH_2)_3C_6H_5$	3.82	3.74	0.08	3.16	3.11	0.0	13b
41	1-$(CH_2)_3OC_6H_4$-3′-Cl-4-NH_2-5-C_6H_5	3.82	3.79	0.03	1.96	3.82	1.0	13c
42	1-$(CH_2)_3OC_6H_5$-2-S-4-NH_2-5-C_6H_5	3.82	3.66	0.16	1.96	3.11	1.0	13c
43	1-$(CH_2)_3C_6H_5$-4-OH-6-C_5H_{11}	3.85	3.32	0.53	0.0	5.66	0.0	13b
44	1-$(CH_2)_3OC_6H_5$-4-NH_2-5-C_6H_4-4′-OCH_3	3.92	3.65	0.27	1.94	3.11	1.0	13c
45	1-$(CH_2)_3OC_6H_5$-4-OH-5-C_6H_3-3′,4′-Cl_2	3.92	3.80	0.12	3.38	3.11	0.0	13c
46	1-$(CH_2)_3OC_6H_4$-2′-Cl-4-NH_2-5-C_6H_3-3′,4′-Cl_2	3.96	4.20	0.24	3.38	3.82	1.0	13c
47	1-$(CH_2)_3OC_6H_4$-3′-NO_2-4-NH_2-5-C_6H_3-3′,4′-Cl_2	3.96	4.05	0.09	3.38	3.03	1.0	13c
48	1-$(CH_2)_3OC_6H_5$-4-NH_2-5-C_6H_4-4′-$NHCOC_6H_4$-4″-SO_2F	4.00	3.81	0.19	2.50	3.11	1.0	13d
49	1-$(CH_2)_3OC_6H_4$-4′-$NHSO_2C_6H_4$-4″-SO_2F-4-NH_2-5-C_6H_3-3′,4′-Cl_2	4.00	4.16	0.16	3.38	3.61	1.0	13d
50	1-$(CH_2)_3OC_6H_4$-4′-$NHCOC_6H_4$-4″-SO_2F-4-NH_2-5-C_6H_3-3′,4′-Cl_2	4.00	4.16	0.16	3.38	3.65	1.0	13d
51	1-$(CH_2)_3OC_6H_4$-4′-$NHCOC_6H_4$-3″-SO_2F-4-NH_2-5-C_6H_3-3′,4′-Cl_2	4.01	4.16	0.15	3.38	3.65	1.0	13d
52	1-$(CH_2)_3OC_6H_4$-4′-OCH_3-4-NH_2-5-C_6H_3-3′,4′-Cl_2	4.10	4.06	0.04	3.38	3.09	1.0	13c
53	1-$(CH_2)_3OC_6H_4$-4′-NO_2-4-NH_2-5-C_6H_3-3′,4′-Cl_2	4.12	4.05	0.07	3.38	3.03	1.0	13c
54	1-$(CH_2)_3OC_6H_4$-2′-$NHCONHC_6H_4$-3″-SO_2F-4-NH_2-5-C_6H_3-3′,4′-Cl_2	4.12	4.43	0.31	3.38	5.05	1.0	13d
55	1-$(CH_2)_3SC_6H_4$-4′-NO_2-4-NH_2-5-C_6H_3-3′,4′-Cl_2	4.13	4.17	0.04	3.38	3.66	1.0	13c
56	1-$(CH_2)_3OC_6H_2$-2′-NO_2-4′,6′-Cl_2-4-NH_2-5-C_6H_3-3′,4′-Cl_2	4.14	4.31	0.17	3.38	4.45	1.0	13c
57[c]	1-$(CH_2)_3OC_6H_5$-4-SH-5-C_6H_5	4.15	3.66	0.49	1.96	3.11	1.0	13c
58	1-$(CH_2)_3OC_6H_4$-2′-NO_2-4-NH_2-5-C_6H_3-3′,4′-Cl_2	4.17	4.05	0.12	3.38	3.03	1.0	13c
59	1-$(CH_2)_3OC_6H_3$-3′-Cl-4′-NO_2-4-NH_2-5-C_6H_3-3′,4′-Cl_2	4.21	4.18	0.03	3.38	3.74	1.0	13c
60	1-$(CH_2)_6C_6H_5$-4-NH_2-5-C_6H_3-3′,4′-Cl_2	4.21	4.35	0.14	3.38	4.66	1.0	13c
61	1-$(CH_2)_3OC_6H_5$-4-NH_2-5-C_6H_3-3′,4′-Cl_2	4.21	4.06	0.15	3.38	3.11	1.0	13c
62	1-$(CH_2)_3OC_6H_5$-4-NH_2-5-C_6H_4-4′-$NHCONHC_6H_4$-3″-SO_2F	4.22	4.18	0.04	3.80	3.11	1.0	13d
63	1-$(CH_2)_2OC_6H_5$-4-NH_2-5-C_6H_3-3′,4′-Cl_2	4.24	3.97	0.27	3.38	2.61	1.0	13c
64	1-$(CH_2)_4OC_6H_5$-4-NH_2-5-C_6H_3-3′,4′-Cl_2	4.25	4.16	0.09	3.38	3.61	1.0	13c
65	1-$(CH_2)_3OC_6H_4$-2′-$NHCOC_6H_4$-4″-SO_2F-4-NH_2-5-C_6H_3-3′,4′-Cl_2	4.25	4.16	0.09	3.38	3.65	1.0	13d
66	1-$(CH_2)_3OC_6H_4$-2′-$NHCOC_6H_5$-4-NH_2-5-C_6H_3-3′,4′-Cl_2	4.28	4.15	0.13	3.38	3.60	1.0	13c
67	1-$(CH_2)_3OC_6H_5$-4-NH_2-5-C_6H_4-4′-$NHCONHC_6H_4$-4″-SO_2F	4.28	4.18	0.10	3.80	3.11	1.0	13d
68	1-$(CH_2)_3OC_6H_3$-3′,4′-Cl_2-4-NH_2-5-C_6H_3-3′,4′-Cl_2	4.36	4.33	0.03	3.38	4.53	1.0	13c
69	1-$(CH_2)_3OC_6H_4$-3′-Cl-4-NH_2-5-C_6H_3-3′,4′-Cl_2	4.38	4.20	0.18	3.38	3.82	1.0	13c

Table XVIII (*Continued*)

No.	Substituents	Log 1/C Obsd[a]	Log 1/C Calcd[b]	|Δ log 1/C|	π-5	π-1,6	I-1	Ref
70	1-$(CH_2)_3OC_6H_4$-4′-NHCONHC$_6$H$_4$-4″-SO_2F-4-NH_2-5-C_6H_3-3′,4′-Cl_2	4.46	4.41	0.05	3.38	4.95	1.0	13d
71	1-$(CH_2)_3OC_6H_4$-4′-Cl-4-NH_2-5-C_6H_3-3′,4′-Cl_2	4.48	4.20	0.28	3.38	3.82	1.0	13c
72	1-$(CH_2)_3OC_6H_4$-3′-NHCOC$_6$H$_5$-4-NH_2-5-C_6H_3-3′,4′-Cl_2	4.51	4.15	0.36	3.38	3.60	1.0	13c

[a] Calculated from results of Baker et al.[13] [b] Calculated using eq 9. [c] This compound not used in deriving equations because of only one compound bearing 4-SH.



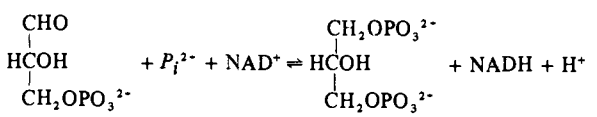
The quinolones studied with malate dehydrogenase are also very effective against glutamate dehydrogenase. The QSAR of eq 12 comes from the data in Table XXVII.

$$\log 1/C = 0.491\ (\pm 0.04)\ (\pi\text{-}5) + 0.233\ (\pm 0.05)\ (\text{MR-}6) - 0.553\ (\pm 0.17)\ (I\text{-}1) + 3.355\ (\pm 0.08) \quad (12)$$

$$n = 87 \quad r = 0.948 \quad s = 0.253$$

Equation 12 is a very good correlation with, on the average, 28 data points/variable. The QSAR for glutamate dehydrogenase is remarkably similar to that for malate dehydrogenase. In each case, 5-space appears to be hydrophobic. While this statement must be qualified because of extremely high collinearity between π-5 and MR-5 (Table XXVIII), the relatively large coefficient with π-5 suggests normal hydrophobic interaction. No parameterization of 7-substituents proved to be of value and, although adding a term in π-8 made a very slight improvement in the correlation (r = 0.949, s = 0.247; $F_{1,80}$ = 4.0), this term is of dubious value. The message is that 7 and 8 positions appear to be open to solvent, even for groups as large as C_6H_5 or $CH_2C_6H_5$. I-1 takes the value of 1 for 5- or 6-$O(CH_2)_nC_6H_5$ (n = 2–5). The negative coefficient with this term suggests a disturbance of the hydrophobic area. Again, no role could be found for an electronic effect of substituents. This enzyme also seems to be a good candidate for further chemotherapeutic work. While the best inhibitors are about ten times less effective than with the malate enzyme, they are active at concentrations approaching 10^{-6} M.

Glyceraldehyde-3-phosphate Dehydrogenase. This dehydrogenase was also found to be inhibited by the 4-quinolone-3-carboxylates. It is an enzyme which is important in the glycolytic pathway where its function is to convert glyceraldehyde 3-phosphate to 1,3-diphosphoglycerate.



The QSAR of eq 13 has been formulated from the data of

$$\log 1/C = 0.0906\ (\pm 0.02)\ (\text{MR-}1,5,6,8) + 0.498\ (\pm 0.18)\ (I\text{-}1) - 0.149\ (\pm 0.10)\ (I\text{-}2) + 3.127\ (\pm 0.10) \quad (13)$$

$$n = 72 \quad r = 0.849 \quad s = 0.172$$

Table XXX. In eq 13, MR refers to all positions on the quinolone ring except the 7 position; this suggests that the 7 position is open to solvent. The variable I-1 takes the value of 1 for 5-CH_2CH_2-C_6H_4-3′- or 4′-X. This is not a well-documented parameter since only four data points support it. It is a point worthy of further study. I-2 takes the value of 1 for congeners having H in both the 1 and 5 positions. It does not contribute greatly to the reduction in the variance but does suggest a small negative steric effect which may be relieved by omitting substituents in the 1 and 5 positions.

Table XIX. Squared Correlation Matrix for Variables Pertaining to Eq 9 for Cytosine Nucleoside Deaminase

	π-5	MR-5	I-1	π-1,6	MR-1,6
π-5	1.00	0.74	0.51	0.10	0.14
MR-5		1.00	0.50	0.05	0.05
I-1			1.00	0.09	0.11
π-1,6				1.00	0.33
MR-1,6					1.00

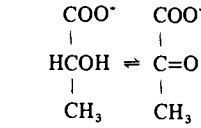
Table XX. Development of QSAR of Eq 9 for Cytosine Nucleoside Deaminase

Intercept	π-5	I-1	π-1,6	r	s	$F_{1,X}$[a]
2.79	0.40			0.905	0.255	308
2.75	0.32	0.32		0.925	0.232	15.4
2.38	0.30	0.29	0.13	0.935	0.216	11.1

[a] $F_{1,60;\,\alpha\,0.001} = 12$; $F_{1,60;\,\alpha\,0.005} = 8.5$.

An equation slightly better than eq 13 can be obtained by factoring the MR term into π-5 + MR-1,6,8 (r = 0.863). So little is gained by the additional term and there is such high collinearity between π-5 and MR-5 (Table XXXI) that more work would have to be done before such factoring could be justified.

Lactate Dehydrogenase. This enzyme consists of four subunits. It is known to exist in a variety of isoenzymic forms so that it is an interesting subject for chemotherapy. Its function is the conversion of lactate to pyruvate in the glycolytic process. This also makes it of interest to cancer chemotherapy since many tumors show high rates of glycolysis.[19] The QSAR of eq 14 for the inhibitory activity



$$\log 1/C = 0.0803\ (\pm 0.02)\ (\text{MR-}1,5,6,8) + 0.487\ (\pm 0.16)\ (I\text{-}1) - 0.114\ (\pm 0.09)\ (I\text{-}2) + 3.853\ (\pm 0.11) \quad (14)$$

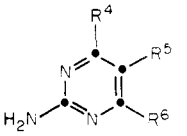
$$n = 79 \quad r = 0.836 \quad s = 0.173$$

of 4-quinolone-3-carboxylates has been developed from the data in Table XXXIII. The correlation of eq 14 for lactate dehydrogenase is remarkably similar to that of eq 13 for the glyceraldehyde dehydrogenase. Similar variables have been employed and the quality of the two correlations is about the same. I-1 in eq 14 takes the value of 1 for 5-$(CH_2)_nC_6H_5$ where n = 2–6. This is assumed to be due to hydrophobic interaction of the phenyl rings. I-2 accounts for 1-H which has a small negative effect on activity. One could consider that substrates require some bulky 1-substituents to fix themselves in the binding pocket of the enzyme.

Discussion

The overview of Baker's enzyme studies presented in the

Table XXI. Constants Used for Deriving Eq 10 for Dihydrofolate Reductase



No.	R^4	R^5	R^6	Log S/I Obsd[a]	Log S/I Calcd[b]	Δ log S/I	π-5	π-6	I-1	I-2	I-3	I-4	I-5	I-6	Ref
1	OH	H	CH_3	−3.51	−3.90	0.39	0.0	0.50	0.0	0.0	0.0	1.0	0.0	0.0	14f
2	NH_2	C_2H_5	OH	−3.45	−1.79	1.66	1.0	−1.23	0.0	1.0	0.0	0.0	0.0	0.0	14r
3	NH_2	H	OH	−3.34	−3.28	0.06	0.0	−1.23	0.0	1.0	0.0	1.0	0.0	0.0	14f
4	OH	$(CH_2)_3NHSO_2C_4H_9$	CH_3	−3.11	−2.24	0.87	1.68	0.50	0.0	0.0	0.0	0.0	0.0	0.0	14d
5	OH	CH_3	CH_3	−3.10	−2.54	0.56	0.50	0.50	0.0	0.0	0.0	0.0	0.0	0.0	14r
6	OH	$(CH_2)_4C_6H_5$	COO^-	−2.79	−3.33	0.54	3.66	−4.36	0.0	0.0	1.0	0.0	0.0	1.0	14m
7	OH	$(CH_2)_3N(COCH_3)CH_2$-(4-Py)	CH_3	−2.78	−2.22	0.56	1.75	0.50	0.0	0.0	0.0	0.0	0.0	0.0	14p
8	OH	$(CH_2)_3N(COCH_3)CH_2$-(3-Py)	CH_3	−2.78	−2.23	0.55	1.73	0.50	0.0	0.0	0.0	0.0	0.0	0.0	14p
9	OH	$(CH_2)_3NHSO_2C_6H_4$-4-COO^-	CH_3	−2.67	−1.68	0.99	−2.55	0.50	0.0	0.0	1.0	0.0	0.0	0.0	14h
10	OH	$(CH_2)_3NHTs$	CH_3	−2.60	−2.08	0.52	2.31	0.50	0.0	0.0	0.0	0.0	0.0	0.0	14d
11	OH	C_2H_5	CH_3	−2.56	−2.41	0.15	1.00	0.50	0.0	0.0	0.0	0.0	0.0	0.0	14r
12	OH	$CH_2CH=CH_2$	CH_3	−2.52	−2.39	0.13	1.10	0.50	0.0	0.0	0.0	0.0	0.0	0.0	14r
13	OH	$(CH_2)_3N(COCH_3)CH_2$-(2-Py)	CH_3	−2.48	−2.25	0.23	1.64	0.50	0.0	0.0	0.0	0.0	0.0	0.0	14p
14	OH	$(CH_2)_3NHCOCH_3$	CH_3	−2.34	−2.53	0.19	0.53	0.50	0.0	0.0	0.0	0.0	0.0	0.0	14d
15	NH_2	H	NH_2	−2.30	−2.32	0.02	0.0	−0.16	0.0	1.0	0.0	1.0	0.0	0.0	14f
16	NH_2	H	CH_3	−2.26	−1.73	0.53	0.0	0.50	0.0	1.0	0.0	1.0	0.0	0.0	14f
17	OH	C_3H_7	CH_3	−2.26	−2.29	0.03	1.50	0.50	0.0	0.0	0.0	0.0	0.0	0.0	14r
18	OH	$(CH_2)_3NHCOCH_2C_6H_5$	CH_3	−2.20	−2.12	0.08	2.14	0.50	0.0	0.0	0.0	0.0	0.0	0.0	14d
19[c]	OH	$(CH_2)_4C_6H_5$	C_3H_7	−2.18	0.27	2.45	3.66	1.50	0.0	0.0	0.0	0.0	0.0	1.0	14i
20	NH_2	C_6H_4-4-Cl	COO^-	−2.18	−1.42	0.76	2.67	−4.36	0.0	1.0	1.0	0.0	0.0	1.0	14m
21	OH	$(CH_2)_3OC_6H_5$	CH_3	−2.15	−1.88	0.27	3.11	0.50	0.0	0.0	0.0	0.0	0.0	0.0	14k
22	OH	$(CH_2)_3NHCOC_6H_4$-4-NH_2	CH_3	−2.11	−2.18	0.07	1.91	0.50	0.0	0.0	0.0	0.0	0.0	0.0	14d
23	OH	$(CH_2)_3NHC_6H_5$	CH_3	−2.11	−1.98	0.13	2.71	0.50	0.0	0.0	0.0	0.0	0.0	0.0	14j
24	OH	$NH(CH_2)_3C_6H_5$	CH_3	−2.08	−1.99	0.09	2.66	0.50	0.0	0.0	0.0	0.0	0.0	0.0	14f
25	OH	$(CH_2)_3NH$-(3-Py)	CH_3	−2.04	−2.52	0.48	0.59	0.50	0.0	0.0	0.0	0.0	0.0	0.0	14p
26	OH	$(CH_2)_3NHC_6H_4$-4-F	CH_3	−2.04	−1.94	0.10	2.85	0.50	0.0	0.0	0.0	0.0	0.0	0.0	14p
27	NH_2	*sec*-C_4H_9	OH	−2.01	−1.59	0.42	1.80	−1.23	0.0	1.0	0.0	0.0	0.0	0.0	14o
28	OH	$(CH_2)_3NHCOC_6H_4$-4-$CH_2OC_2H_5$	CH_3	−2.00	−1.99	0.01	2.67	0.50	0.0	0.0	0.0	0.0	0.0	0.0	14d
29	OH	$(CH_2)_3N(COCH_3)CH_2C_6H_5$	CH_3	−2.00	−2.02	0.02	2.54	0.50	0.0	0.0	0.0	0.0	0.0	0.0	14p
30	OH	$(CH_2)_4C_6H_5$	CHO	−1.94	−1.65	0.29	3.66	−0.65	0.0	0.0	0.0	0.0	0.0	1.0	14m
31	OH	$(CH_2)_3NHCOC_6H_4$-4-COO^-	CH_3	−1.90	−1.60	0.30	−2.22	0.50	0.0	0.0	1.0	0.0	0.0	0.0	14h
32	OH	$(CH_2)_3NHCOC_6H_5$	CH_3	−1.90	−2.12	0.22	2.14	0.50	0.0	0.0	0.0	0.0	0.0	0.0	14d
33	NH_2	C_3H_7	OH	−1.88	−1.67	0.21	1.50	−1.23	0.0	1.0	0.0	0.0	0.0	0.0	14r
34	NH_2	c-C_5H_9	OH	−1.88	−1.50	0.38	2.14	−1.23	0.0	1.0	0.0	0.0	0.0	0.0	14o
35	OH	$(CH_2)_3NHC_6H_4$-3-CF_3	CH_3	−1.78	−1.75	0.03	3.59	0.50	0.0	0.0	0.0	0.0	0.0	0.0	14p
36	OH	$(CH_2)_3NHCOC_6H_4$-4-NO_2	CH_3	−1.76	−2.19	0.43	1.86	0.50	0.0	0.0	0.0	0.0	0.0	0.0	14d
37[c]	SH	$(CH_2)_4C_6H_5$	C_6H_5	−1.73	0.26	1.99	3.66	1.96	1.0	0.0	0.0	0.0	1.0	1.0	14i
38	OH	$(CH_2)_3NHC_6H_4$-4-NO_2	CH_3	−1.72	−1.85	0.13	3.20	0.50	0.0	0.0	0.0	0.0	0.0	0.0	14p
39	NH_2	C_3H_7	NH_2	−1.70	−0.71	0.99	1.50	−0.16	0.0	1.0	0.0	0.0	0.0	0.0	14r
40	OH	$(CH_2)_3NH$-(2-$C_{10}H_7$)	CH_3	−1.67	−1.65	0.02	3.98	0.50	0.0	0.0	0.0	0.0	0.0	0.0	14p
41	OH	C_4H_9	CH_3	−1.64	−2.16	0.52	2.00	0.50	0.0	0.0	0.0	0.0	0.0	0.0	14r
42	OH	C_8H_{17}	CH_3	−1.58	−1.65	0.07	4.00	0.50	0.0	0.0	0.0	0.0	0.0	0.0	14r
43	OH	$(CH_2)_3N(COCH_3)CH_2$-(2-C_4H_3O)	CH_3	−1.54	−2.15	0.61	2.04	0.50	0.0	0.0	0.0	0.0	0.0	0.0	14p
44	OH	$(CH_2)_3N(C_4H_9)Ts$	CH_3	−1.51	−1.57	0.06	4.31	0.50	0.0	0.0	0.0	0.0	0.0	0.0	14d
45	OH	$(CH_2)_3N(C_4H_9)COC_6H_5$	CH_3	−1.51	−1.61	0.10	4.14	0.50	0.0	0.0	0.0	0.0	0.0	0.0	14d
46	OH	$(CH_2)_3NHC_6H_4$-4-$(CH_2)_6COCH_2Cl$	CH_3	−1.51	−0.93	0.58	6.81	0.50	0.0	0.0	0.0	0.0	0.0	0.0	14a
47	OH	$(CH_2)_3NHC_6H_4$-4-$COCH_2Cl$	CH_3	−1.48	−2.02	0.54	2.55	0.50	0.0	0.0	0.0	0.0	0.0	0.0	14a
48	OH	$(CH_2)_4C_6H_5$	$(CH_2)_2C_6H_4$-4-NH-$COCH_2Br$	−1.48	−0.62	0.86	3.66	2.29	0.0	0.0	0.0	0.0	1.0	1.0	14q
49	OH	$(CH_2)_3NHC_6H_4$-4-CO-Gly	CH_3	−1.43	−1.57	0.14	−2.12	0.50	0.0	0.0	1.0	0.0	0.0	0.0	14a
50	OH	$(CH_2)_3C_6H_5$	CH_3	−1.43	−0.75	0.68	3.16	0.50	0.0	0.0	0.0	0.0	0.0	1.0	14f
51	NH_2	H	C_6H_5	−1.43	−2.03	0.60	0.0	1.96	0.0	1.0	0.0	1.0	1.0	0.0	14j
52[c]	NH_2	C_6H_4-4-Cl	$COOC_2H_5$	−1.36	1.30	2.66	2.67	0.51	0.0	1.0	0.0	0.0	0.0	1.0	14m
53	OH	$(CH_2)_3NHC_6H_4$-4-$(CH_2)_2COCH_2Cl$	CH_3	−1.30	−1.44	0.14	4.81	0.50	0.0	0.0	0.0	0.0	0.0	0.0	14a
54	OH	$(CH_2)_3NHC_6H_4$-4-CO-Glu	CH_3	−1.20	−1.52	0.32	−1.92	0.50	0.0	0.0	1.0	0.0	0.0	0.0	14a
55	NH_2	$(CH_2)_2CH=CH_2$	OH	−1.17	−1.64	0.47	1.60	−1.23	0.0	1.0	0.0	0.0	0.0	0.0	14o
56	NH_2	$CH(CH_3)C_3H_7$	OH	−1.14	−1.46	0.32	2.30	−1.23	0.0	1.0	0.0	0.0	0.0	0.0	14o
57	OH	$(CH_2)_3NHC_6H_4$-4-COO^-	CH_3	−1.11	−1.45	0.34	−1.65	0.50	0.0	0.0	1.0	0.0	0.0	0.0	14a
58[c]	NH_2	*i*-C_5H_{11}	Cl	−1.09	1.39	2.48	2.30	0.71	0.0	1.0	0.0	0.0	0.0	1.0	14s
59	NH_2	$(CH_2)_3C_6H_5$	OH	−1.00	−0.13	0.87	3.16	−1.23	0.0	1.0	0.0	0.0	0.0	1.0	14f
60	SH	$(CH_2)_3NHC_6H_4$-4-$N(CH_3)_2$	CH_3	−1.00	−0.75	0.25	2.89	0.50	1.0	0.0	0.0	0.0	0.0	0.0	14k
61	OH	$(CH_2)_3N(COCH_3)C_6H_4$-4-COO^-	CH_3	−0.95	−1.47	0.52	−1.70	0.50	0.0	0.0	1.0	0.0	0.0	0.0	14h
62[c]	NH_2	C_6H_4-4-Cl	CF_3	−0.92	1.64	2.56	2.67	0.88	0.0	1.0	0.0	0.0	0.0	1.0	14n
63	SH	$(CH_2)_3N(C_6H_5)COC_6H_5$	CH_3	−0.92	−0.40	0.52	4.27	0.50	1.0	0.0	0.0	0.0	0.0	0.0	14e
64	NH_2	C_8H_{17}	OH	−0.90	−1.03	0.13	4.00	−1.23	0.0	1.0	0.0	0.0	0.0	0.0	14r
65	SH	$(CH_2)_3NHC_6H_5$	CH_3	−0.86	−0.79	0.07	2.71	0.50	1.0	0.0	0.0	0.0	0.0	0.0	14j
66	NH_2	C_4H_9	OH	−0.82	−1.54	0.72	2.00	−1.23	0.0	1.0	0.0	0.0	0.0	0.0	14r
67	OH	C_6H_{13}	CH_3	−0.77	−0.79	0.02	3.00	0.50	0.0	0.0	0.0	0.0	0.0	1.0	14r

Table XXI (Continued)

No.	R^4	R^5	R^6	Log S/I Obsd[a]	Log S/I Calcd[b]	$\lvert\Delta$ log S/I$\rvert$	π-5	π-6	I-1	I-2	I-3	I-4	I-5	I-6	Ref
68	NH_2	$CH_2CH=CHCH_3$	OH	−0.77	−1.64	0.87	1.60	−1.23	0.0	1.0	0.0	0.0	0.0	0.0	14o
69	NH_2	c-C_6H_{11}	OH	−0.77	−1.41	0.64	2.51	−1.23	0.0	1.0	0.0	0.0	0.0	0.0	14o
70	OH	$(CH_2)_4C_6H_5$	CH_3	−0.70	−0.62	0.08	3.66	0.50	0.0	0.0	0.0	0.0	0.0	1.0	14k
71	NH_2	C_6H_{13}	OH	−0.70	−0.17	0.53	3.00	−1.23	0.0	1.0	0.0	0.0	0.0	1.0	14r
72	OH	C_5H_{11}	CH_3	−0.70	−0.92	0.22	2.50	0.50	0.0	0.0	0.0	0.0	0.0	1.0	14r
73	OH	C_6H_4-4-Cl	CH_3	−0.68	−0.87	0.19	2.67	0.50	0.0	0.0	0.0	0.0	0.0	1.0	14s
74	NH_2	C_4H_9	C_6H_5	−0.68	−0.29	0.39	2.00	1.96	0.0	1.0	0.0	0.0	1.0	0.0	14i
75	NH_2	H	C_6H_4-4-C_6H_5	−0.68	−0.27	0.41	0.0	3.92	0.0	1.0	0.0	1.0	1.0	0.0	14i
76	NH_2	OC_6H_4-4-Cl	CH_3	−0.65	0.21	0.86	2.79	0.50	0.0	1.0	0.0	0.0	0.0	0.0	14b
77	NH_2	C_4H_9	NH_2	−0.58	−0.58	0.00	2.00	−0.16	0.0	1.0	0.0	0.0	0.0	0.0	14r
78	OH	$(CH_2)_3NHC_6H_4$-4-$(CH_2)_4COCH_2Cl$	CH_3	−0.58	−1.19	0.61	5.81	0.50	0.0	0.0	0.0	0.0	0.0	0.0	14a
79	SH	$(CH_2)_3N(COCH_3)C_6H_5$	CH_3	−0.52	−0.73	0.21	2.97	0.50	1.0	0.0	0.0	0.0	0.0	0.0	14k
80	OH	$(CH_2)_3NHC_6H_4$-4-CH=CHCOCl	CH_3	−0.48	−0.18	0.30	3.37	0.50	0.0	0.0	1.0	0.0	0.0	0.0	14a
81	NH_2	$CH_2CH=C(CH_3)_2$	OH	−0.45	−0.40	0.05	2.10	−1.23	0.0	1.0	0.0	0.0	0.0	1.0	14r
82	NH_2	$CH_2CH(CH_3)C_2H_5$	OH	−0.37	−0.35	0.02	2.30	−1.23	0.0	1.0	0.0	0.0	0.0	1.0	14o
83	SH	$(CH_2)_3NHC_6H_5$-4-Cl	CH_3	−0.36	−0.61	0.25	3.42	0.50	1.0	0.0	0.0	0.0	0.0	0.0	14k
84	OH	$(CH_2)_4C_6H_4$-4-$COOC_2H_5$	CH_3	−0.34	−0.49	0.15	4.17	0.50	0.0	0.0	0.0	0.0	0.0	1.0	14h
85	NH_2	$(CH_2)_4C_6H_5$	OH	−0.15	0.00	0.15	3.66	−1.23	0.0	1.0	0.0	0.0	0.0	1.0	14f
86	OH	i-C_5H_{11}	CH_3	−0.15	−0.97	0.82	2.30	0.50	0.0	0.0	0.0	0.0	0.0	1.0	14r
87	NH_2	$CH(CH_3)CH_2CH(CH_3)_2$	OH	−0.13	−1.39	1.26	2.60	−1.23	0.0	1.0	0.0	0.0	0.0	0.0	14o
88	NH_2	$(CH_2)_3C_6H_5$	NH_2	−0.08	0.83	0.91	3.16	−0.16	0.0	1.0	0.0	0.0	0.0	1.0	14f
89	NH_2	i-C_5H_{11}	OH	0.18	−0.35	0.53	2.30	−1.23	0.0	1.0	0.0	0.0	0.0	1.0	14r
90	NH_2	$(CH_2)_3NHC_6H_5$	$CH_2C_6H_5$	0.20	−0.06	0.26	2.71	2.01	0.0	1.0	0.0	0.0	1.0	0.0	14i
91	NH_2	$(CH_2)_4C_6H_5$	NH_2	0.23	0.96	0.73	3.66	−0.16	0.0	1.0	0.0	0.0	0.0	1.0	14f
92	SH	i-C_5H_{11}	CH_3	0.36	0.22	0.14	2.30	0.50	1.0	0.0	0.0	0.0	0.0	1.0	14s
93	OH	$(CH_2)_4C_6H_4$-4-COO^-	CH_3	0.38	−0.10	0.48	−0.70	0.50	0.0	0.0	1.0	0.0	0.0	1.0	14h
94	NH_2	$(CH_2)_3NHC_6H_5$	CH_3	0.43	0.19	0.24	2.71	0.50	0.0	1.0	0.0	0.0	0.0	0.0	14j
95	NH_2	C_6H_5	OH	0.46	−0.43	0.89	1.96	−1.23	0.0	1.0	0.0	0.0	0.0	1.0	14r
96	NH_2	i-C_5H_{11}	NH_2	0.46	0.61	0.15	2.30	−0.16	0.0	1.0	0.0	0.0	0.0	1.0	14r
97	NH_2	C_4H_9	CH_3	0.48	0.01	0.47	2.00	0.50	0.0	1.0	0.0	0.0	0.0	0.0	14i
98	NH_2	$(CH_2)_3N(C_6H_5)Ts$	CH_3	0.49	0.63	0.14	4.44	0.50	0.0	1.0	0.0	0.0	0.0	0.0	14e
99	SH	C_6H_4-4-Cl	CH_3	0.55	0.31	0.24	2.67	0.50	1.0	0.0	0.0	0.0	0.0	1.0	14s
100	NH_2	$(CH_2)_4C_6H_5$	C_6H_5	0.74	1.25	0.51	3.66	1.96	0.0	1.0	0.0	0.0	1.0	1.0	14i
101	NH_2	C_5H_{11}	CH_3	0.78	1.25	0.47	2.50	0.50	0.0	1.0	0.0	0.0	0.0	1.0	14r
102	NH_2	$(CH_2)_3NHC_6H_5$	C_6H_5	0.83	−0.11	0.94	2.71	1.96	0.0	1.0	0.0	0.0	1.0	0.0	14i
103	NH_2	C_6H_4-4-Cl	$(CH_2)_2C_6H_4$-4-$NHCOCH_2Br$	1.05	1.29	0.24	2.67	2.29	0.0	1.0	0.0	0.0	1.0	1.0	14q
104	NH_2	$(CH_2)_4C_6H_5$	$CH_2C_6H_5$	1.25	1.29	0.04	3.66	2.01	0.0	1.0	0.0	0.0	1.0	1.0	14i
105	NH_2	C_6H_4-4-Cl	CH_2Br	1.36	1.55	0.19	2.67	0.79	0.0	1.0	0.0	0.0	0.0	1.0	14l
106	NH_2	i-C_5H_{11}	CH_3	1.40	1.20	0.20	2.30	0.50	0.0	1.0	0.0	0.0	0.0	1.0	14r
107	NH_2	C_6H_4-4-Cl	CH_3	1.48	1.30	0.18	2.67	0.50	0.0	1.0	0.0	0.0	0.0	1.0	14m
108	NH_2	$(CH_2)_3C_6H_5$	CH_3	1.52	1.42	0.10	3.16	0.50	0.0	1.0	0.0	0.0	0.0	1.0	14r
109	NH_2	$(CH_2)_4C_6H_5$	$(CH_2)_2C_6H_4$-4-$NHCOCH_2Br$	2.18	1.54	0.64	3.66	2.29	0.0	1.0	0.0	0.0	1.0	1.0	14q
110	NH_2	C_6H_3-3,4-Cl_2	CH_3	2.27	1.48	0.79	3.38	0.50	0.0	1.0	0.0	0.0	0.0	1.0	14b
111	NH_2	$(CH_2)_4C_6H_5$	CH_3	2.35	1.55	0.80	3.66	0.50	0.0	1.0	0.0	0.0	0.0	1.0	14f
112	NH_2	$(CH_2)_4C_6H_5$	C_3H_7	2.46	2.44	0.02	3.66	1.50	0.0	1.0	0.0	0.0	0.0	1.0	14i
113	NH_2	C_6H_3-3,4-Cl_2	C_2H_5	2.52	1.92	0.60	3.38	1.00	0.0	1.0	0.0	0.0	0.0	1.0	14b

[a] Calculated from results of Baker et al.[14] [b] Calculated using eq 10. [c] These molecules not used in deriving equations.

Table XXII. Squared Correlation Matrix for Variables Pertaining to Eq 10 for Dihydrofolate Reductase

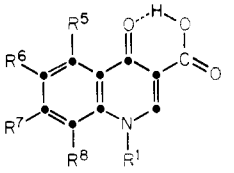
	I-6	I-2	π-6	MR-6	I-4	I-1	I-5	I-3	π-5	MR-5
I-6	1.00	0.07	0.01	0.03	0.03	0.00	0.01	0.00	0.08	0.02
I-2		1.00	0.03	0.04	0.03	0.06	0.08	0.05	0.00	0.24
π-6			1.00	0.38	0.02	0.00	0.33	0.04	0.00	0.03
MR-6				1.00	0.03	0.00	0.81	0.01	0.00	0.00
I-4					1.00	0.00	0.04	0.01	0.12	0.22
I-1						1.00	0.01	0.01	0.01	0.01
I-5							1.00	0.01	0.00	0.01
I-3								1.00	0.27	0.07
π-5									1.00	0.12
MR-5										1.00

Table XXIII. Development of QSAR of Eq 10 for Dihydrofolate Reductase

Intercept	I-6	I-2	π-6	I-4	I-1	I-5	I-3	π-5	r	s	$F_{1,X}$[a]
−1.55	1.76								0.609	1.100	62.5
−1.90	1.46	1.02							0.704	0.990	26.0
−2.12	1.51	1.21	0.48						0.802	0.837	42.7
−2.07	1.29	1.46	0.55	1.90					0.855	0.730	33.6
−2.20	1.27	1.60	0.54	1.88	1.18				0.879	0.675	18.7
−2.27	1.31	1.84	0.73	1.81	1.14	−1.14			0.895	0.633	14.8
−2.43	1.30	2.03	0.81	1.81	1.26	−1.32	0.79		0.908	0.598	13.3
−3.12	1.12	2.17	0.89	1.23	1.18	−1.60	1.63	0.25	0.932	0.520	33.4

[a] $F_{1,60;\alpha\,0.001} = 12.0$.

Table XXIV. Constants Used for Deriving Eq 11 for Malate Dehydrogenase



No.	Substituents	Log 1/C Obsd[a]	Log 1/C Calcd[b]	|Δ log 1/C|	π-5	MR-6,7,8	I-1	Ref
1	8-CH_3	2.68	3.38	0.70	0.0	0.77	0.0	15a
2	8-CF_3	2.85	3.36	0.51	0.0	0.70	0.0	15a
3	1-$(CH_2)_4OC_6H_4$-4′-NH_2-6-OCH_3	3.05	3.44	0.39	0.0	0.99	0.0	15b
4	1-$CH_2C_6H_5$	3.06	3.24	0.18	0.0	0.30	0.0	15b
5	6-CH_3	3.15	3.38	0.23	0.0	0.77	0.0	15a
6	8-OCH_3	3.19	3.44	0.25	0.0	0.99	0.0	15a
7	1-C_4H_9	3.19	3.24	0.05	0.0	0.30	0.0	15b
8	H	3.28	3.24	0.04	0.0	0.30	0.0	15a
9	1-CH_3	3.28	3.24	0.04	0.0	0.30	0.0	15a
10	7,8-(N-CH=CHCH=)	3.28	3.60	0.32	0.0	1.53	0.0	15c
11	1-$CH_2C_6H_4$-3′-NH_2-6-OCH_3	3.30	3.44	0.14	0.0	0.99	0.0	15b
12	8-Cl	3.39	3.39	0.00	0.0	0.80	0.0	15a
13	6-NO_2	3.40	3.43	0.03	0.0	0.94	0.0	15a
14	8-Br	3.40	3.47	0.07	0.0	1.09	0.0	15a
15[c]	7-$O(CH_2)_3OC_6H_5$	3.40	4.48	1.08	0.0	4.57	0.0	15c
16	1-CH_3-7-$CH_2C_6H_5$	3.40	4.08	0.68	0.0	3.20	0.0	15c
17	1-CH_3-8-OCH_3	3.47	3.44	0.03	0.0	0.99	0.0	15b
18	7-Cl	3.48	3.39	0.09	0.0	0.80	0.0	15a
19	1-CH_3-8-$CH_2C_6H_5$	3.49	4.08	0.59	0.0	3.20	0.0	15c
20	1-CH_3-8-Cl	3.52	3.39	0.13	0.0	0.80	0.0	15b
21	1-$CH_2C_6H_4$-4′-COOH-6-OCH_3	3.52	3.44	0.08	0.0	0.99	0.0	15b
22	6-C_6H_5	3.54	3.95	0.41	0.0	2.74	0.0	15c
23	8-C_6H_5	3.59	3.95	0.36	0.0	2.74	0.0	15c
24	6-C_4H_9	3.60	3.78	0.18	0.0	2.16	0.0	15c
25	1-CH_3-5-$O(CH_2)_3OC_6H_5$-8-Cl	3.62	4.08	0.46	2.59	0.80	1.0	15d
26	1-$(CH_2)_3C_6H_5$-6-OCH_3	3.64	3.44	0.20	0.0	0.99	0.0	15b
27	1-C_4H_9-6-OCH_3	3.66	3.44	0.22	0.0	0.99	0.0	15b
28	1-$(CH_2)_4OC_6H_5$-6-OCH_3	3.66	3.44	0.22	0.0	0.99	0.0	15b
29	1-CH_3-6-OCH_3	3.70	3.44	0.26	0.0	0.99	0.0	15b
30	1-C_6H_{13}-6-OCH_3	3.70	3.44	0.26	0.0	0.99	0.0	15b
31	1-$CH_2C_6H_4$-3′-NO_2-6-OCH_3	3.70	3.44	0.26	0.0	0.99	0.0	15b
32	1-$CH_2C_6H_5$-6-OCH_3	3.72	3.44	0.28	0.0	0.99	0.0	15b
33	6-$CH_2C_6H_5$	3.72	4.08	0.36	0.0	3.20	0.0	15c
34	1-$(CH_2)_3OC_6H_5$-6-OCH_3	3.74	3.44	0.30	0.0	0.99	0.0	15b
35	5,8-Cl_2	3.77	3.88	0.11	0.71	0.80	0.0	15a
36	6-OC_6H_5	3.77	4.02	0.25	0.0	2.97	0.0	15c
37	8-$CH_2C_6H_5$	3.85	4.08	0.23	0.0	3.20	0.0	15c
38	7,8-$(CH=CH)_2$	3.89	3.72	0.17	0.0	1.94	0.0	15c
39	5-CH_3-8-Cl	3.92	3.74	0.18	0.50	0.80	0.0	15a
40	5-$O(CH_2)_3OC_6H_5$	3.92	3.93	0.01	2.59	0.30	1.0	15d
41	6-Cl	3.96	3.39	0.57	0.0	0.80	0.0	15a
42	6-$OCH_2C_6H_5$	3.96	4.15	0.19	0.0	3.42	0.0	15c
43	5-C_6H_5-8-Cl	4.03	4.76	0.73	1.96	0.80	0.0	15d
44	1-$(CH_2)_4OC_6H_4$-4′-NO_2-6-OCH_3	4.05	3.44	0.61	0.0	0.99	0.0	15b
45	6-$O(CH_2)_2C_6H_5$	4.14	4.28	0.14	0.0	3.88	0.0	15c
46	7-C_6H_5	4.17	3.95	0.22	0.0	2.74	0.0	15c
47	6,8-Cl_2	4.20	3.53	0.67	0.0	1.30	0.0	15a
48	5-$O(CH_2)_3OC_6H_5$-8-Cl	4.20	4.08	0.12	2.59	0.80	1.0	15d
49	6-$O(CH_2)_2OC_6H_5$	4.37	4.35	0.02	0.0	4.10	0.0	15c
50	5-$O(CH_2)_4OC_6H_5$-8-CH_3	4.42	4.42	0.00	3.09	0.77	1.0	15d
51	7-$CH_2C_6H_5$	4.48	4.08	0.40	0.0	3.20	0.0	15c
52	8-$O(CH_2)_3OC_6H_5$	4.48	4.48	0.00	0.0	4.57	0.0	15c
53	5-$CH_2CH_2C_6H_5$-8-Cl	4.66	5.25	0.59	2.66	0.80	0.0	15d
54	5-$O(CH_2)_4OC_6H_5$-8-Cl	4.77	4.43	0.34	3.09	0.80	1.0	15d
55	6-$O(CH_2)_3OC_6H_5$	5.02	4.48	0.54	0.0	4.57	0.0	15c
56	5-$CH_2C_6H_5$-8-Cl	5.23	4.79	0.44	2.01	0.80	0.0	15d
57	5-$CH=CHC_6H_5$-8-Cl	5.33	5.32	0.01	2.77	0.80	0.0	15d
58	6-$O(CH_2)_5OC_6H_5$	5.34	4.75	0.59	0.0	5.49	0.0	15c
59	5-$CH_2CH_2C_6H_3$-3′-F-8-Cl	5.37	5.34	0.03	2.80	0.80	0.0	15e
60	5-$CH_2CH_2C_6H_4$-4′-CH_3-8-Cl	5.40	5.60	0.20	3.16	0.80	0.0	15e
61	6-$O(CH_2)_4OC_6H_5$	5.41	4.62	0.79	0.0	5.03	0.0	15c
62	5-$CH=CHC_6H_3$-3′,4′-(OCH_2O)-8-Cl	5.51	5.29	0.22	2.72	0.80	0.0	15e
63	5-CH_2CH_2-(1-$C_{10}H_7$)-8-Cl	5.52	6.17	0.65	3.98	0.80	0.0	15e
64[c]	6-$O(CH_2)_3C_6H_5$	5.57	4.42	1.15	0.0	4.34	0.0	15c
65	5-$CH_2CH_2C_6H_3$-4′-Cl-8-Cl	5.66	5.74	0.08	3.37	0.80	0.0	15e
66[c]	5-$CH_2CH_2C_6H_4$-2′-C_6H_5-8-Cl	5.77	6.62	0.85	4.62	0.80	0.0	15e
67	5-CH_2CH_2-(2-$C_{10}H_7$)-8-Cl	5.92	6.17	0.25	3.98	0.80	0.0	15e
68	5-CH=CH-(1-$C_{10}H_7$)-8-Cl	5.96	6.25	0.29	4.09	0.80	0.0	15e

Table XXIV (*Continued*)

No.	Substituents	Log 1/C Obsd[a]	Log 1/C Calcd[b]	|Δ log 1/C|	π-5	MR-6,7,8	I-1	Ref
69	5-$(CH_2)_4C_6H_5$-8-Cl	6.00	5.95	0.05	3.66	0.80	0.0	15d
70[c]	5-$CH_2CH_2C_6H_3$-3',4'-(OCH_2O)-8-Cl	6.10	5.21	0.89	2.61	0.80	0.0	15e
71	5-CH=CHC_6H_3-2',6'-Cl_2-8-Cl	6.12	6.32	0.20	4.19	0.80	0.0	15e
72	5-$CH_2CH_2C_6H_3$-3'-Cl-8-Cl	6.26	5.74	0.52	3.37	0.80	0.0	15e
73	5-$CH_2CH_2C_6H_3$-3',4'-Cl_2-8-Cl	6.32	6.24	0.08	4.08	0.80	0.0	15e
74	5-$(CH_2)_6C_6H_5$-8-Cl	6.34	6.64	0.30	4.66	0.80	0.0	15d
75	5-$CH_2CH_2C_6H_4$-3'-C_6H_5-8-Cl	6.39	6.62	0.23	4.62	0.80	0.0	15e
76	5-$CH_2CH_2C_6H_4$-4'-C_6H_5-8-Cl	6.60	6.62	0.02	4.62	0.80	0.0	15e
77	5-$CH_2CH_2C_6H_3$-2',5'-Cl_2-8-Cl	6.72	6.24	0.48	4.08	0.80	0.0	15e
78	5-$CH_2CH_2C_6H_3$-2',4'-Cl_2-8-Cl	6.96	6.24	0.72	4.08	0.80	0.0	15e
79	5-$CH_2CH_2C_6H_3$-2',6'-Cl_2-8-Cl	7.00	6.24	0.76	4.08	0.80	0.0	15e

[a] Calculated from results of Baker et al.[15] [b] Calculated using eq 11. [c] These molecules not used in deriving equations.

Table XXV. Squared Correlation Matrix for Variables Pertaining to Eq 11 for Malate Dehydrogenase

	π-5	MR-6,7,8	I-1	MR-5
π-5	1.00	0.15	0.06	0.97
MR-6,7,8		1.00	0.03	0.16
I-1			1.00	0.06
MR-5				1.00

Table XXVI. Development of QSAR of Eq 11 for Malate Dehydrogenase

Intercept	π-5	MR-6,7,8	I-1	r	s	$F_{1,X}$[a]
3.66	0.57			0.855	0.592	198
3.10	0.66	0.31		0.912	0.471	43.3
3.16	0.70	0.29	−1.12	0.943	0.385	36.8

[a] $F_{1,60;\alpha\ 0.001} = 12$.

two papers in this series, when taken with other enzymic studies,[20] constitutes convincing evidence that one can, in general, expect to be able to formulate enzyme–inhibitor structure–activity studies in numerical terms. The advantages of this approach are that large masses of data can be structured objectively. When dealing with thousands or even hundreds of molecules, the human mind must have such assistance if we are ever going to make a serious attempt to organize the incredible number of structure–activity studies which are being published at an ever-increasing rate. A numerical structuring of the data is the first important step. Hopefully, a relatively few general parameters can be developed so that equations developed in one system can be precisely compared with a system which might at first glance seem quite remote. Correlation equations will eventually be employed in developing our understanding of a host of interactions between micro- and macromolecules which constitute the driving forces for biochemical and molecular biological processes. Final understanding of cellular processes will have to be obtained on intact cells. We shall have to deduce the inner processes of the cells by means of information obtained via molecular probes.

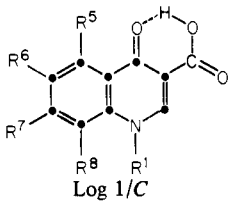
Structuring data via correlation equations is of course of great help in planning research. Even someone completely unfamiliar with a developing research project can quickly comprehend from correlation equations what sections of substituent space have been explored, what areas need exploration, and in what areas the best prospects for development lie.

It is very difficult to isolate those data points which are "strange" in large masses of data. These points are the congeners which may need retesting because of experimental error, or these molecules may be acting by a different mechanism from that of the main body of compounds, or it may be that improper parameters are being employed because new and different substituent effects are involved.

The problem of recognizing the significant patterns in structure–activity studies is one of the most complex confronting the scientific mind. The first step in this problem is to define a set of congeners (a set of molecules, all members of which are acting mechanistically in the same way). This is by *no means* simple and calls for the highest quality biochemistry or pharmacology. Correlation analysis can be of importance in maintaining the integrity of a growing set of congeners as a study develops. Defining a set of congeners means recognizing first-order specifity of the intermolecular interactions. Second-order intermolecular interactions of the members of the set can then be factored into two classes: nonspecific and specific. Our general approach to the formulation of QSAR has been hierarchical, that is, to sort out interactions in the following order: (1) nonspecific hydrophobic and dispersion; (2) electronic; (3) steric parameterizable by continuous variables; (4) steric parameterizable by discrete variables; (5) discrete interactions by special molecular constellations, the basic character of which is not apparent.

Nonspecific Hydrophobic and Dispersion Interaction. From our current view of the structure of biomacromolecules it has become clear that pools of apolar side chains often clump together in micellular fashion to form hydrophobic pockets. Correlative to this, there must be large areas of polar space; hence, for ligand interaction with biomacromolecules one would a priori expect to need two types of parameters for two limiting types of space. Handling the problem of ligand interaction with mixed space is of course much more difficult. We have operationally defined the hydrophobic parameters log P and π using octanol–water partition coefficients. There is now sufficient evidence in hand to convince us that these constants permit a useful start to be made on defining hydrophobic interactions. There is considerable evidence that when ligand interaction depends linearly on hydrophobic interaction, one can expect a slope with π or log P in the range of 0.4–1.2. When such terms are encountered in correlation equations, one can assume as a *working hypothesis* that interaction in substituent space depends on desolvation. This is not always the case; we have found examples with MR (scaled by 0.1) with coefficients approaching 1. It is possible that conformational changes amplify the simple MR effect reflected by low MR coefficients. Very few examples are known with slopes (with tight confidence limits) much higher than 1.2. Slopes in the range of 0.1–0.3 appear to be the result of weaker interactions and *suggest* that they are the result of dispersion forces without significant desolvation; such interactions might occur on a polar "surface" or in a polar cavity of a macromolecule. It would seem that molar refractivity (MR) might be a better parameter to model such interactions than π or log P. Unfortunately, little proper data are available to rigorously test this hypothesis.

Table XXVII. Constants Used for Deriving Eq 12 for Glutamate Dehydrogenase



No.	Substituents	Log 1/C Obsd[a]	Log 1/C Calcd[b]	|Δ log 1/C|	π-5	MR-6	I-1	Ref
1	8-CH_3	2.68	3.38	0.70	0.0	0.10	0.0	15a
2	7-Cl	2.77	3.38	0.61	0.0	0.10	0.0	15a
3	8-NO_2	2.89	3.38	0.49	0.0	0.10	0.0	15a
4	6-CH_3	3.10	3.49	0.39	0.0	0.57	0.0	15a
5	1-$CH_2C_6H_4$-4′-NO_2-6-OCH_3	3.12	3.54	0.42	0.0	0.79	0.0	15b
6	H	3.22	3.38	0.16	0.0	0.10	0.0	15a
7	8-C_6H_5	3.24	3.38	0.14	0.0	0.10	0.0	15c
8	6-Cl	3.26	3.49	0.23	0.0	0.60	0.0	15a
9	8-OCH_3	3.27	3.38	0.11	0.0	0.10	0.0	15a
10	8-CF_3	3.29	3.38	0.09	0.0	0.10	0.0	15a
11	1-CH_3	3.30	3.38	0.08	0.0	0.10	0.0	15a
12	7-$CH_2C_6H_5$	3.33	3.38	0.05	0.0	0.10	0.0	15c
13	1-CH_3-7-$CH_2C_6H_5$	3.34	3.38	0.04	0.0	0.10	0.0	15c
14	1-$CH_2C_6H_4$-3′-NO_2-6-OCH_3	3.35	3.54	0.19	0.0	0.79	0.0	15b
15	1-$(CH_2)_4OC_6H_4$-4′-NH_2-6-OCH_3	3.35	3.54	0.19	0.0	0.79	0.0	15b
16	6-OCH_3	3.37	3.54	0.17	0.0	0.79	0.0	15a
17	7,8-(N-CH=CHCH=)	3.39	3.38	0.01	0.0	0.10	0.0	15c
18	1-$CH_2C_6H_4$-3′-NH_2-6-OCH_3	3.40	3.54	0.14	0.0	0.79	0.0	15b
19	1-C_4H_9	3.42	3.38	0.04	0.0	0.10	0.0	15b
20	8-$CH_2C_6H_5$	3.47	3.38	0.09	0.0	0.10	0.0	15c
21	8-Cl	3.48	3.38	0.10	0.0	0.10	0.0	15a
22	8-Br	3.48	3.38	0.10	0.0	0.10	0.0	15a
23	1-CH_3-6-$O(CH_2)_3OC_6H_5$	3.48	3.82	0.34	0.0	4.37	1.0	15c
24	1-CH_3-8-$CH_2C_6H_5$	3.48	3.38	0.10	0.0	0.10	0.0	15c
25	1-CH_3-8-OCH_3	3.49	3.38	0.11	0.0	0.10	0.0	15b
26	5,8-Cl_2	3.51	3.73	0.22	0.71	0.10	0.0	15a
27	6,8-Cl_2	3.52	3.49	0.03	0.0	0.60	0.0	15a
28	6-$NHCOCH_3$	3.54	3.70	0.16	0.0	1.49	0.0	15a
29	1-CH_3-8-Cl	3.54	3.38	0.16	0.0	0.10	0.0	15b
30	1-$(CH_2)_3C_6H_5$-6-OCH_3	3.54	3.54	0.00	0.0	0.79	0.0	15b
31	1-$(CH_2)_2OC_6H_5$-6-OCH_3	3.54	3.54	0.00	0.0	0.79	0.0	15b
32	1-$CH_2C_6H_5$	3.55	3.38	0.17	0.0	0.10	0.0	15b
33	1-CH_3-8-C_6H_5	3.57	3.38	0.19	0.0	0.10	0.0	15c
34	7-C_6H_5	3.59	3.38	0.21	0.0	0.10	0.0	15c
35	1-CH_3-6-OCH_3	3.57	3.54	0.03	0.0	0.79	0.0	15b
36	1-C_4H_9-6-OCH_3	3.60	3.54	0.06	0.0	0.79	0.0	15b
37	1-$CH_2C_6H_4$-4′-COOH-6-OCH_3	3.60	3.54	0.06	0.0	0.79	0.0	15b
38	1-$(CH_2)_3OC_6H_5$-6-OCH_3	3.62	3.54	0.08	0.0	0.79	0.0	15b
39	1-$CH_2C_6H_5$-6-OCH_3	3.64	3.54	0.10	0.0	0.79	0.0	15b
40[c]	1-CH_3-5-C_6H_5-8-Cl	3.64	4.34	0.70	1.96	0.10	0.0	15d
41	6-$O(CH_2)_3OC_6H_5$	3.68	3.82	0.14	0.0	4.37	1.0	15c
42	6-NO_2	3.70	3.53	0.17	0.0	0.74	0.0	15a
43	1-$(CH_2)_4OC_6H_5$-6-OCH_3	3.70	3.54	0.16	0.0	0.79	0.0	15b
44	1-C_6H_{13}-6-OCH_3	3.72	3.54	0.18	0.0	0.79	0.0	15b
45	5-$O(CH_2)_2OC_6H_5$-8-CH_3	3.82	3.85	0.03	2.09	0.10	1.0	15d
46	6-C_4H_9	3.85	3.81	0.04	0.0	1.96	0.0	15c
47	1-CH_3-6-$OCH_2C_6H_5$	3.85	4.11	0.26	0.0	3.22	0.0	15c
48	1-CH_3-5-$O(CH_2)_3OC_6H_5$	3.89	4.10	0.21	2.59	0.10	1.0	15d
49	6-$O(CH_2)_4OC_6H_5$	3.92	3.93	0.01	0.0	4.83	1.0	15c
50	5-CH_3-8-Cl	3.96	3.62	0.34	0.50	0.10	0.0	15a
51	7,8-$(CH=CH)_2$	4.00	3.38	0.62	0.0	0.10	0.0	15c
52	5-$O(CH_2)_3OC_6H_5$	4.00	4.10	0.10	2.59	0.10	1.0	15d
53	1-$(CH_2)_4OC_6H_4$-4′-NO_2-6-OCH_3	4.01	3.54	0.47	0.0	0.79	0.0	15b
54	6-$OCH_2C_6H_5$	4.01	4.11	0.10	0.0	3.22	0.0	15c
55	6-C_6H_5	4.03	3.95	0.08	0.0	2.54	0.0	15c
56	5-$O(CH_2)_4OC_6H_5$-8-CH_3	4.11	4.34	0.23	3.09	0.10	1.0	15d
57	6-OC_6H_5	4.12	4.05	0.07	0.0	3.00	0.0	15c
58	6-$O(CH_2)_5OC_6H_5$	4.12	4.04	0.08	0.0	5.29	1.0	15c
59	1-CH_3-5-$O(CH_2)_3OC_6H_5$-8-Cl	4.15	4.10	0.05	2.59	0.10	1.0	15d
60	6-$CH_2C_6H_5$	4.25	4.05	0.20	0.0	3.00	0.0	15c
61	6-$O(CH_2)_2C_6H_5$	4.26	4.21	0.05	0.0	3.68	0.0	15c
62	6-$O(CH_2)_3C_6H_5$	4.26	4.32	0.06	0.0	4.14	0.0	15c
63	5-$O(CH_2)_4OC_6H_5$-8-Cl	4.27	4.10	0.17	2.59	0.10	1.0	15d
64	6-$O(CH_2)_2OC_6H_5$	4.30	3.71	0.59	0.0	3.90	1.0	15c
65	5-C_6H_5-8-Cl	4.43	4.34	0.09	1.96	0.10	0.0	15d
66	5-$O(CH_2)_4OC_6H_5$-8-Cl	4.52	4.34	0.18	3.09	0.10	1.0	15d
67	5-$CH_2CH_2C_6H_4$-3′-F-8-Cl	4.55	4.75	0.20	2.80	0.10	0.0	15e
68	5-$CH_2C_6H_5$-8-Cl	4.89	4.37	0.52	2.01	0.10	0.0	15d

Table XXVII (*Continued*)

No.	Substituents	Log 1/C Obsd[a]	Log 1/C Calcd[b]	|Δ log 1/C|	π-5	MR-6	I-1	Ref
69	5-$CH_2CH_2C_6H_4$-4'-Cl-8-Cl	4.89	5.03	0.14	3.37	0.10	0.0	15e
70[c]	5-$CH_2CH_2C_6H_4$-4'-C_6H_5-8-Cl	4.92	5.65	0.73	4.62	0.10	0.0	15e
71	5-CH=CHC_6H_3-3',4'-(OCH_2O)-8-Cl	4.92	4.71	0.21	2.72	0.10	0.0	15e
72	5-$CH_2CH_2C_6H_5$-8-Cl	4.96	4.69	0.27	2.66	0.10	0.0	15d
73	1-CH_3-5-$(CH_2)_6C_6H_5$	5.00	5.67	0.67	4.66	0.10	0.0	15d
74	5-$CH_2CH_2C_6H_3$-3',4'-(OCH_2O)-8-Cl	5.00	4.66	0.34	2.61	0.10	0.0	15e
75	5-$CH_2CH_2C_6H_4$-4'-CH_3-8-Cl	5.05	4.93	0.12	3.16	0.10	0.0	15e
76	5-$CH_2CH_2C_6H_3$-2',4'-Cl_2-8-Cl	5.06	5.38	0.32	4.08	0.10	0.0	15e
77	5-$CH_2CH_2C_6H_4$-3'-Cl-8-Cl	5.10	5.03	0.07	3.37	0.10	0.0	15e
78	5-CH=CH-(1-$C_{10}H_7$)-8-Cl	5.17	5.39	0.22	4.09	0.10	0.0	15e
79	5-$CH_2CH_2C_6H_3$-3',4'-Cl_2-8-Cl	5.19	5.38	0.19	4.08	0.10	0.0	15e
80	5-$CH_2CH_2C_6H_3$-2',6'-Cl_2-8-Cl	5.26	5.38	0.12	4.08	0.10	0.0	15e
81	5-CH=CHC_6H_5-8-Cl	5.28	4.74	0.54	2.77	0.10	0.0	15d
82	5-$(CH_2)_4C_6H_5$-8-Cl	5.28	5.18	0.10	3.66	0.10	0.0	15d
83	5-CH=CHC_6H_3-2',6'-Cl_2-8-Cl	5.40	5.44	0.04	4.19	0.10	0.0	15e
84	5-CH_2CH_2-(2-$C_{10}H_7$)-8-Cl	5.47	5.33	0.14	3.98	0.10	0.0	15e
85	5-$CH_2CH_2C_6H_4$-3'-C_6H_5-8-Cl	5.55	5.65	0.10	4.62	0.10	0.0	15e
86	5-CH_2CH_2-(1-$C_{10}H_7$)-8-Cl	5.55	5.33	0.22	3.98	0.10	0.0	15e
87	5-$(CH_2)_6C_6H_5$-8-Cl	5.62	5.67	0.05	4.66	0.10	0.0	15d
88	5-$CH_2CH_2C_6H_3$-2',5'-Cl_2-8-Cl	5.70	5.38	0.32	4.08	0.10	0.0	15e
89	5-$CH_2CH_2C_6H_4$-2'-C_6H_5-8-Cl	5.74	5.65	0.09	4.62	0.10	0.0	15e

[a] Calculated from results of Baker et al.[15] [b] Calculated using eq 12. [c] These molecules not used in deriving equations.

Table XXVIII. Squared Correlation Matrix for Variables Pertaining to Eq 12 for Glutamate Dehydrogenase

	π-5	MR-5	π-6	MR-6	I-1
π-5	1.00	0.97	0.08	0.15	0.01
MR-5		1.00	0.09	0.15	0.04
π-6			1.00	0.88	0.14
MR-6				1.00	0.13
I-1					1.00

Table XXIX. Development of QSAR of Eq 12 for Glutamate Dehydrogenase

Intercept	π-5	MR-6	I-1	r	s
3.56	0.41			0.886	0.363
3.37	0.46	0.16		0.922	0.306
3.35	0.49	0.23	−0.55	0.948	0.253

Up to now, those doing QSAR studies have paid little attention to the use of MR; indeed, the importance of this parameter may be difficult to establish outside of the area of interaction of ligands with purified macromolecules. In the analysis of Baker's work we have observed that there is often such high collinearity between π or log *P* and MR that one cannot say with much confidence that MR models interactions in nonhydrophobic macromolecular space. An important exception to this is eq 2.

We have scaled MR by 0.1 in the analysis of Baker's work. This makes MR and π approximately equiscalar for apolar functions; e.g.

substituent	Cl	Br	I	Me	C_6H_5	CF_3	H
π	0.71	0.86	1.12	0.56	2.13	0.88	0.00
0.1 MR	0.60	0.89	1.39	0.56	2.54	0.50	0.10

Hence, when π and MR are highly collinear, one can compare their coefficients. This equivalence between π and MR is not present in polar substituents; e.g.

substituent	OH	CN	$N(Me)_2$	SO_2NH_2	$SO_2C_6H_5$	$NHCONH_2$
π	−0.67	−0.56	0.18	−1.82	0.27	−1.30
0.1 MR	0.28	0.63	1.55	1.23	3.32	1.37

Therefore, with a proper selection of substituents, one should be able to establish the utility of MR for characterizing nonhydrophobic space. We now have such experiments in progress.

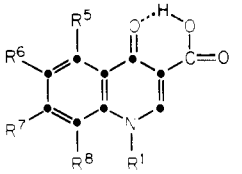
After a set of congeners has been studied using the continuous variables π, MR, σ, and E_s (when feasible), the best correlation equation may often leave a relatively large amount of variance in the data unaccounted for. At this point the study of the residuals from the "best" equation can yield new insights into the SAR which are not at all apparent from a study of the untreated data. These more specific interactions cannot be established with confidence until the large amount of relatively nonspecific variance usually present in SAR studies is greatly reduced. The use of indicator variables enormously extends the use of correlation analysis for structuring SAR studies where gross structural changes have been made.

From a comparison of the structure of inhibitors Baker chose to study with the structure of the normal enzyme substrate, Baker's modus operandi is quite evident. He normally selected a basic moiety closely resembling the normal substrate and then proceeded to make gross changes to produce what he called nonclassical antimetabolites. It is these gross changes which present such a challenge to the formulation of QSAR. It is exciting that the enormous range of structural changes can be dealt with rationally with a wide variety of enzymes.

From the point of view of medicinal chemistry, the study of purified enzymes offers the clearest opportunity to design drugs with high selective toxicity. When this can be achieved with enzyme from host and pathogen in vitro, one has at least some assurance for in vivo success even before in vivo testing is started.

There are several cases in the present study where we can compare inhibition of different enzymes by the same set of inhibitors or the same enzyme by different inhibitors. The QSAR for two types of pyrimidine nucleoside phosphorylase inhibited by uracils is such an example. The mammalian tumor cell enzyme (eq 7) has hydrophobic space which can be reached by substituents in either the 1 or 5 position but the evidence in hand suggests that substituents in both positions cannot simultaneously occupy hydrophobic space. Hydrophobic space does not appear to be adjacent to the 1 or 5 position in bacterial enzyme (eq 6) but is more remote and best reached from the ortho and meta positions of the 6-XC_6H_5 group. Rotation of this group through 360° would allow substituents to reach different parts of enzymic space and makes establishment of the hydrophobic pocket impossible as of the present. There is only one highly specific parameter for 6-substituents with mammalian enzyme. The

Table XXX. Constants Used for Deriving Eq 13 for Glyceraldehyde-phosphate Dehydrogenase



No.	Substituents	Log 1/C Obsd[a]	Log 1/C Calcd[b]	|Δ log 1/C|	MR-1,5,6,8	*I*-1	*I*-2	Ref
1[c]	8-CH_3	2.33	3.06	0.73	0.87	0.0	1.0	15a
2	6-CH_3	2.52	3.06	0.54	0.87	0.0	1.0	15a
3	H	2.80	3.01	0.21	0.40	0.0	1.0	15a
4[c]	6-$CH_2C_6H_5$	2.85	3.28	0.43	3.30	0.0	1.0	15c
5	8-CF_3	2.92	3.05	0.13	0.80	0.0	1.0	15a
6	6-Cl	2.96	3.06	0.10	0.90	0.0	1.0	15a
7	8-NO_2	2.96	3.08	0.12	1.09	0.0	1.0	15a
8	6-C_4H_9	2.96	3.18	0.22	2.26	0.0	1.0	15c
9	7-$O(CH_2)_3OC_6H_5$	2.96	3.16	0.20	0.40	0.0	0.0	15c
10	1-CH_3-7-$CH_2C_6H_5$	2.96	3.21	0.25	0.87	0.0	0.0	15c
11	8-$CH_2C_6H_5$	3.00	3.28	0.28	3.30	0.0	1.0	15c
12	7-Cl	3.06	3.16	0.10	0.40	0.0	0.0	15a
13	8-Br	3.07	3.09	0.02	1.19	0.0	1.0	15a
14	1-$CH_2C_6H_5$	3.11	3.43	0.32	3.30	0.0	0.0	15b
15	8-Cl	3.12	3.06	0.06	0.90	0.0	1.0	15a
16	7,8-$(CH=CH)_2$	3.17	3.23	0.06	1.17	0.0	0.0	15c
17	7,8-(NCH=CHCH=)	3.17	3.23	0.06	1.17	0.0	0.0	15c
18	7-C_6H_5	3.19	3.16	0.03	0.40	0.0	0.0	15c
19	1-CH_3	3.23	3.21	0.02	0.87	0.0	0.0	15a
20	8-OCH_3	3.26	3.08	0.18	1.09	0.0	1.0	15a
21	6-NO_2	3.26	3.07	0.19	1.04	0.0	1.0	15a
22	1-C_4H_9	3.28	3.33	0.05	2.26	0.0	0.0	15b
23	6-OC_6H_5	3.28	3.26	0.02	3.07	0.0	1.0	15c
24	6-$O(CH_2)_2C_6H_5$	3.28	3.34	0.06	3.98	0.0	1.0	15c
25	8-C_6H_5	3.28	3.23	0.04	2.84	0.0	1.0	15c
26	6,8-Cl_2	3.30	3.10	0.19	1.40	0.0	1.0	15a
27	6-$NHCOCH_3$	3.33	3.14	0.19	1.79	0.0	1.0	15a
28	6-OCH_3	3.34	3.08	0.26	1.09	0.0	1.0	15a
29	6-$O(CH_2)_2OC_6H_5$	3.36	3.36	0.00	4.20	0.0	1.0	15c
30	5-$O(CH_2)_4OC_6H_5$-8-Cl	3.37	3.64	0.27	5.63	0.0	0.0	15d
31	5-$O(CH_2)_3OC_6H_5$	3.37	3.55	0.18	4.67	0.0	0.0	15d
32	5-$CH_2C_6H_5$-8-Cl	3.39	3.47	0.08	3.80	0.0	0.0	15d
33	6-$O(CH_2)_3OC_6H_5$	3.40	3.40	0.00	4.67	0.0	1.0	15c
34	1-CH_3-8-$CH_2C_6H_5$	3.40	3.47	0.07	3.77	0.0	0.0	15c
35	5-C_6H_5-8-Cl	3.40	3.43	0.03	3.34	0.0	0.0	15d
36	6-C_6H_5	3.41	3.23	0.17	2.84	0.0	1.0	15c
37	6-$O(CH_2)_3C_6H_5$	3.44	3.38	0.06	4.44	0.0	1.0	15c
38	5-$O(CH_2)_3OC_6H_5$-8-Cl	3.47	3.60	0.13	5.17	0.0	0.0	15d
39	1-CH_3-5-$O(CH_2)_3OC_6H_5$-8-Cl	3.47	3.64	0.17	5.64	0.0	0.0	15d
40	5,8-Cl_2	3.48	3.25	0.23	1.40	0.0	0.0	15a
41	1-CH_3-6-OCH_3	3.48	3.27	0.21	1.56	0.0	0.0	15b
42	6-$O(CH_2)_4OC_6H_5$	3.48	3.44	0.04	5.13	0.0	1.0	15c
43	1-$(CH_2)_3OC_6H_5$-6-OCH_3	3.49	3.59	0.10	5.13	0.0	0.0	15b
44	1-CH_3-5-C_6H_5-8-Cl	3.49	3.47	0.02	3.81	0.0	0.0	15d
45	1-CH_3-8-Cl	3.51	3.25	0.26	1.37	0.0	0.0	15b
46	1-C_4H_9-6-OCH_3	3.51	3.39	0.12	2.95	0.0	0.0	15b
47	1-$(CH_2)_3C_6H_5$-6-OCH_3	3.51	3.57	0.06	4.92	0.0	0.0	15b
48	1-$(CH_2)_2OC_6H_5$-6-OCH_3	3.51	3.55	0.04	4.67	0.0	0.0	15b
49	1-$(CH_2)_4OC_6H_5$-6-OCH_3	3.51	3.63	0.12	5.59	0.0	0.0	15b
50	1-$CH_2C_6H_4$-4′-COOH-6-OCH_3	3.51	3.53	0.02	4.49	0.0	0.0	15b
51	5-$CH_2CH_2C_6H_5$-8-Cl	3.51	3.51	0.00	4.27	0.0	0.0	15d
52	1-CH_3-8-OCH_3	3.52	3.27	0.25	1.56	0.0	0.0	15b
53	1-C_6H_{13}-6-OCH_3	3.52	3.48	0.04	3.88	0.0	0.0	15b
54	1-$CH_2C_6H_5$-6-OCH_3	3.52	3.49	0.03	3.99	0.0	0.0	15b
55	1-$CH_2C_6H_4$-3′-NH_2-6-OCH_3	3.52	3.53	0.01	4.43	0.0	0.0	15b
56	1-CH_3-8-$O(CH_2)_3OC_6H_5$	3.52	3.59	0.07	5.14	0.0	0.0	15c
57	1-$CH_2C_6H_4$-3′-NO_2-6-OCH_3	3.54	3.55	0.01	4.62	0.0	0.0	15b
58	6-$OCH_2C_6H_5$	3.55	3.30	0.25	3.52	0.0	1.0	15c
59	1-CH_3-6-$OCH_2C_6H_5$	3.55	3.49	0.06	3.99	0.0	0.0	15c
60	1-CH_2-(1-$C_{10}H_7$)-6-OCH_3	3.59	3.85	0.26	7.97	0.0	0.0	15b
61	5-$CH_2CH_2C_6H_4$-2′-C_6H_5-8-Cl	3.59	3.73	0.14	6.70	0.0	0.0	15e
62	5-$CH_2CH_2C_6H_3$-2′,6′-Cl_2-8-Cl	3.62	3.60	0.02	5.27	0.0	0.0	15e
63	1-$CH_2C_6H_4$-4′-NO_2-6-OCH_3	3.64	3.55	0.09	4.62	0.0	0.0	15b
64[c]	5-$CH_2CH_2C_6H_4$-4′-C_6H_5-8-Cl	3.64	4.23	0.59	6.70	1.0	0.0	15e
65	1-CH_3-5-$O(CH_2)_3OC_6H_5$	3.66	3.59	0.07	5.14	0.0	0.0	15d
66	1-$(CH_2)_4OC_6H_4$-4′-NH_2-6-OCH_3	3.70	3.67	0.03	6.03	0.0	0.0	15b
67	5-CH=CHC_6H_5-8-Cl	3.77	3.51	0.26	4.22	0.0	0.0	15d
68[c]	5-CH_3-8-Cl	3.82	3.25	0.57	1.37	0.0	0.0	15a

Table XXX (*Continued*)

No.	Substituents	Log 1/C Obsd[a]	Log 1/C Calcd[b]	|Δ log 1/C|	MR-1,5,6,8	*I*-1	*I*-2	Ref
69	5-$(CH_2)_4C_6H_5$-8-Cl	3.85	3.60	0.25	5.19	0.0	0.0	15d
70	5-CH=CH-(1-$C_{10}H_7$)-8-Cl	3.89	3.65	0.24	5.76	0.0	0.0	15e
71	5-CH_2CH_2-(1-$C_{10}H_7$)-8-Cl	3.92	3.65	0.27	5.81	0.0	0.0	15e
72	5-CH_2CH_2-(2-$C_{10}H_7$)-8-Cl	4.00	4.15	0.15	5.81	1.0	0.0	15e
73	1-$(CH_2)_4OC_6H_4$-4'-NO_2-6-OCH_3	4.02	3.69	0.33	6.23	0.0	0.0	15b
74	5-$CH_2CH_2C_6H_4$-4'-CH_3-8-Cl	4.05	4.05	0.00	4.73	1.0	0.0	15e
75	5-$CH_2CH_2C_6H_3$-3',4'-Cl_2-8-Cl	4.24	4.10	0.14	5.27	1.0	0.0	15e
76	5-$CH_2CH_2C_6H_4$-3'-C_6H_5-8-Cl	4.25	4.23	0.02	6.70	1.0	0.0	15e

[a] Calculated from results of Baker et al.[15] [b] Calculated using eq 13. [c] These molecules not used in deriving equations.

Table XXXI. Squared Correlation Matrix for Variables Pertaining to Eq 13 Glyceraldehyde-3-phosphate Dehydrogenase

	MR-1,5,6,8	*I*-1	*I*-2	MR-5	π-5
MR-1,5,6,8	1.00	0.07	0.17	0.30	0.29
I-1		1.00	0.03	0.21	0.26
I-2			1.00	0.16	0.16
MR-5				1.00	0.98
π-5					1.00

Table XXXII. Development of QSAR of Eq 13 for Glyceraldehyde-3-phosphate Dehydrogenase

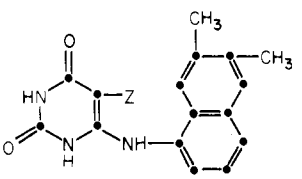
Intercept	MR-1,5,6,8	*I*-1	*I*-2	*r*	*s*	$F_{1,X}$[a]
3.00	0.12			0.743	0.215	86.3
3.03	0.10	0.52		0.825	0.182	29.2
3.12	0.09	0.50	−0.15	0.849	0.172	9.8

[a] $F_{1,60;\,\alpha\,0.001} = 12$; $F_{1,60;\,\alpha\,0.005} = 8.5$.

coefficient of 0.56 with *I*-4 indicates a small activating effect by the NH function [groups such as $(CH_2)_nC_6H_5$ are not parameterized by this variable]. Long-chain groups in this position may make some contact with the enzyme since $NH(CH_2)_5C_6H_5$ (**68** in Table XII) is underpredicted by a factor of about 5. The 6 position is an excellent spot to attach hydrophilic groups to modulate overall lipophilicity for in vivo activity. With bacterial enzyme, a large contribution to inhibitory activity is made by groups of the type $-XC_6H_5$ and an additional component is added when X = CH_2 (*I*-2). Also, a small contribution is made by groups attached to 6-XC_6H_5 (π-6). In general, the bacterial enzyme appears to be much more hydrophobic. Equation 6 has four hydrophobic terms while eq 7 has only one. Substituents on the 1 position inhibit mammalian tumor enzyme more than bacterial enzyme.

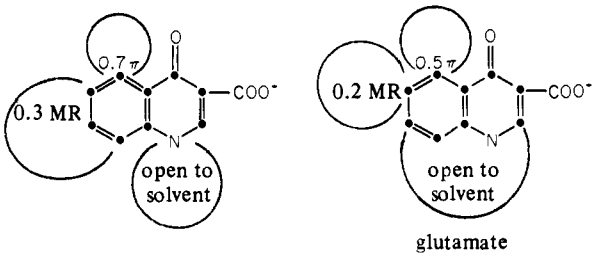
In eq 7 (mammalian enzyme), *I*-1 parameterizing 5-$CH_2C_6H_5$ and 5-$SCH_2C_6H_5$ has a coefficient of 1.74 and in eq 6 (*E. coli* enzyme), *I*-1 parameterizing 6-XC_6H_5 has a coefficient of 1.81. There is no parameterization for 6-substituents in eq 7 and there is no parameterization of 5-substituents in eq 6. This would seem to indicate that 6-space in *E. coli* has, during evolution, "moved" into the 5-space of the mammalian enzyme. While this is pure speculation, it will be interesting to compare x-ray crystallographic studies of these two enzymes. Such studies should help us decide whether *I*-1 is accounting for a hydrophobic interaction, conformational change, or both.

Assuming tumor enzyme is much like normal mammalian enzyme, one might be able to develop suitable drugs against *E. coli* by taking advantage of the differences in eq 6 and 7. The following type of compound might be interesting to study.



Z in this structure should be strongly hydrophilic to inhibit binding in 5-space of the mammalian enzyme and to place the overall log *P* for the drug in the range 0–1.0 or possibly lower.

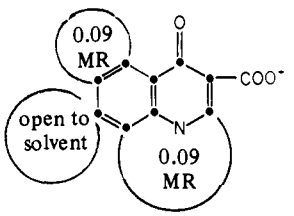
The correlation equations for the four dehydrogenases inhibited by the 4-quinolone-3-carboxylates allow interesting comparisons to be made. Malate and glutamate dehydrogenase display great similarity and sensitivity to these inhibitors. Lactate and glyceraldehyde-phosphate dehydrogenase show similar SAR and are much less sensitive to changes in inhibitor structure. The following schematic drawing can be pictured from eq 11 and 12.



glutamate

Both enzymes have hydrophobic space of about the same character at the 5 position. Slightly better binding occurs at this position with malate dehydrogenase where the substituents in the 6, 7, and 8 positions make contact with the enzyme while with glutamate dehydrogenase, the 7 and 8 positions are open to the surrounding solvent.

Glyceraldehyde-3-phosphate and lactate dehydrogenase have the same QSAR within the range of the confidence limits and the different character of the not very significant parameter *I*-1. Pictorially, they can be represented as

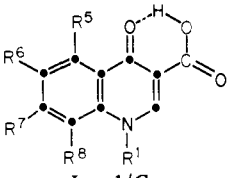


The range in inhibitory activity with both of these enzymes is only about 100-fold. The correlation equations appear to be poor in terms of *r* compared to the malate and glutamate equations but in terms of standard deviation, they are better. It is the large amount of variance in the malate and glutamate data which produce equations with such high values of *r*.

It is not too surprising that malate and glutamate dehydrogenase have such similar QSAR; both are associated with the Krebs cycle and both could have evolved from a common ancestor.

The same can be said for lactate and glyceraldehyde-3-phosphate dehydrogenase. Both of these enzymes are associated with the more primitive process of glycolysis.

Table XXXIII. Constants Used for Deriving Eq 14 for Lactate Dehydrogenase



No.	Substituents	Log 1/C Obsd[a]	Log 1/C Calcd[b]	|Δ log 1/C|	MR-1,5,6,8	*I*-1	*I*-2	Ref
1[c]	8-$CH_2C_6H_5$	3.11	4.00	0.89	3.30	0.0	1.0	15c
2	H	3.36	3.77	0.41	0.40	0.0	1.0	15a
3	8-CH_3	3.47	3.81	0.34	0.87	0.0	1.0	15a
4	8-Cl	3.52	3.81	0.29	0.90	0.0	1.0	15a
5	8-NO_2	3.52	3.83	0.31	1.09	0.0	1.0	15a
6	7-Cl	3.57	3.77	0.20	0.40	0.0	1.0	15a
7	6-OCH_3	3.64	3.83	0.19	1.09	0.0	1.0	15a
8	6-CH_3	3.68	3.81	0.13	0.88	0.0	1.0	15a
9	5,8-Cl_2	3.70	3.85	0.15	1.40	0.0	1.0	15a
10	8-CF_3	3.77	3.80	0.03	0.80	0.0	1.0	15a
11	7-C_6H_5	3.77	3.77	0.00	0.40	0.0	1.0	15c
12	6-C_4H_9	3.80	3.92	0.12	2.26	0.0	1.0	15c
13	6-$CH_2C_6H_5$	3.80	4.00	0.20	3.30	0.0	1.0	15c
14	1-CH_3-6-OCH_3	3.82	3.98	0.16	1.56	0.0	0.0	15b
15	5-$CH_2C_6H_5$-8-Cl	3.82	4.04	0.22	3.80	0.0	1.0	15d
16	5-CH_3-8-Cl	3.85	3.85	0.00	1.37	0.0	1.0	15a
17[c]	1-$(CH_2)_3OC_6H_5$-6-OCH_3	3.85	4.26	0.41	5.13	0.0	0.0	15b
18	7,8-(CH=CH)$_2$	3.85	3.83	0.02	1.17	0.0	1.0	15c
19	6,8-Cl_2	3.89	3.85	0.04	1.40	0.0	1.0	15a
20	6-Cl	3.96	3.81	0.15	0.90	0.0	1.0	15a
21	6-NO_2	3.96	3.82	0.14	1.04	0.0	1.0	15a
22	6-$OCH_2C_6H_5$	3.96	4.02	0.06	3.52	0.0	1.0	15c
23	7-$CH_2C_6H_5$	3.96	3.77	0.19	0.40	0.0	1.0	15c
24	8-C_6H_5	3.96	3.97	0.01	2.84	0.0	1.0	15c
25	7,8-(NCH=CHCH=)	3.96	3.83	0.13	1.17	0.0	1.0	15c
26	1-CH_3-6-$OCH_2C_6H_5$	3.96	4.17	0.21	3.99	0.0	0.0	15c
27	1-CH_3-7-$O(CH_2)_3OC_6H_5$	3.96	3.92	0.04	0.87	0.0	0.0	15c
28	1-CH_3-8-$CH_2C_6H_5$	3.96	4.16	0.20	3.77	0.0	0.0	15c
29	8-Br	4.00	3.83	0.17	1.19	0.0	1.0	15a
30	7-$O(CH_2)_3OC_6H_5$	4.00	3.77	0.23	0.40	0.0	1.0	15c
31	1-CH_3-7-$CH_2C_6H_5$	4.00	3.92	0.08	0.87	0.0	0.0	15c
32	5-$O(CH_2)_3OC_6H_5$	4.00	4.11	0.11	4.67	0.0	1.0	15d
33	1-CH_3-5-C_6H_5-8-Cl	4.00	4.16	0.16	3.81	0.0	0.0	15d
34	8-OCH_3	4.01	3.83	0.18	1.09	0.0	1.0	15a
35	6-OC_6H_5	4.02	3.99	0.03	3.07	0.0	1.0	15c
36	1-$(CH_2)_4OC_6H_5$-6-OCH_3	4.06	4.30	0.24	5.59	0.0	0.0	15b
37	6-$NHCOCH_3$	4.07	3.88	0.19	1.79	0.0	1.0	15a
38	1-CH_3-5-$O(CH_2)_3OC_6H_5$-8-Cl	4.07	4.31	0.24	5.64	0.0	0.0	15d
39	1-C_4H_9	4.08	4.03	0.05	2.26	0.0	0.0	15b
40	1-CH_3-6-$O(CH_2)_3OC_6H_5$	4.08	4.27	0.19	5.14	0.0	0.0	15c
41	1-$(CH_2)_4OC_6H_4$-4'-NH_2-6-OCH_3	4.10	4.34	0.24	6.03	0.0	0.0	15b
42	5-$O(CH_2)_2OC_6H_5$-8-CH_3	4.10	4.11	0.01	4.67	0.0	1.0	15d
43	5-CH=CH-(1-$C_{10}H_7$)-8-Cl	4.10	4.20	0.10	5.76	0.0	1.0	15e
44	6-$O(CH_2)_2C_6H_5$	4.11	4.06	0.05	3.98	0.0	1.0	15c
45	1-CH_3	4.13	3.92	0.21	0.87	0.0	0.0	15a
46	1-$(CH_2)_2OC_6H_5$-6-OCH_3	4.14	4.23	0.09	4.66	0.0	0.0	15b
47	5-$O(CH_2)_3OC_6H_5$-8-Cl	4.14	4.15	0.01	5.17	0.0	1.0	15d
48	1-$CH_2C_6H_4$-3'-NH_2-6-OCH_3	4.16	4.21	0.05	4.43	0.0	0.0	15b
49[c]	5-$CH_2CH_2C_6H_5$-8-Cl	4.16	4.65	0.49	5.27	1.0	1.0	15d
50	5-$O(CH_2)_4OC_6H_5$-8-Cl	4.16	4.27	0.11	6.63	0.0	1.0	15d
51	1-$CH_2C_6H_5$-6-OCH_3	4.17	4.17	0.00	3.99	0.0	0.0	15b
52	6-C_6H_5	4.17	3.97	0.20	2.84	0.0	1.0	15c
53	1-$CH_2C_6H_4$-3'-NO_2-6-OCH_3	4.18	4.22	0.04	4.62	0.0	0.0	15b
54	1-$CH_2C_6H_5$	4.20	4.12	0.08	3.30	0.0	0.0	15b
55	1-CH_3-8-Cl	4.20	3.96	0.24	1.37	0.0	0.0	15b
56	1-C_6H_{13}-6-OCH_3	4.21	4.16	0.05	3.88	0.0	0.0	15b
57	6-$O(CH_2)_2OC_6H_5$	4.22	4.08	0.14	4.20	0.0	1.0	15c
58	5-C_6H_5-8-Cl	4.22	4.01	0.21	3.34	0.0	1.0	15d
59	6-$O(CH_2)_3OC_6H_5$	4.23	4.11	0.12	4.67	0.0	1.0	15c
60	6-$O(CH_2)_4OC_6H_5$	4.23	4.15	0.08	5.13	0.0	1.0	15c
61	5-$O(CH_2)_4OC_6H_5$-8-CH_3	4.23	4.19	0.05	5.60	0.0	1.0	15d
62	1-CH_3-8-OCH_3	4.24	3.98	0.26	1.56	0.0	0.0	15b
63	1-C_4H_9-6-OCH_3	4.24	4.09	0.15	2.95	0.0	0.0	15b
64	1-CH_3-8-C_6H_5	4.24	4.12	0.12	3.31	0.0	0.0	15c
65	1-CH_3-5-$O(CH_2)_3OC_6H_5$	4.26	4.27	0.01	5.14	0.0	0.0	15d
66	1-$CH_2C_6H_4$-4'-COOH-6-OCH_3	4.27	4.21	0.06	4.49	0.0	0.0	15b
67	1-CH_2-(1-$C_{10}H_7$)-6-OCH_3	4.28	4.30	0.02	5.54	0.0	0.0	15b
68	1-$CH_2C_6H_4$-4'-NO_2-6-OCH_3	4.29	4.22	0.07	4.62	0.0	0.0	15b

Table XXXIII (*Continued*)

No.	Substituents	Log 1/C Obsd[a]	Log 1/C Calcd[b]	|Δ log 1/C|	MR-1,5,6,8	*I*-1	*I*-2	Ref
69	1-$(CH_2)_3C_6H_5$-6-OCH_3	4.30	4.25	0.05	4.92	0.0	0.0	15b
70[c]	5-CH_2CH_2-(1-$C_{10}H_7$)-8-Cl	4.33	4.69	0.36	5.81	1.0	1.0	15e
71	1-CH_3-8-$O(CH_2)_5OC_6H_5$	4.34	4.27	0.07	5.14	0.0	0.0	15c
72	5-CH=CHC_6H_3-2',6'-Cl_2-8-Cl	4.36	4.16	0.20	5.27	0.0	1.0	15e
73	5-CH=CHC_6H_3-3',4'-(OCH_2O)-8-Cl	4.41	4.13	0.28	4.91	0.0	1.0	15e
74	5-$CH_2CH_2C_6H_3$-3',4'-Cl_2-8-Cl	4.42	4.65	0.23	5.27	1.0	1.0	15e
75	6-$O(CH_2)_5OC_6H_5$	4.43	4.19	0.24	5.59	0.0	1.0	15c
76	1-$(CH_2)_4OC_6H_4$-4'-NO_2-6-OCH_3	4.51	4.35	0.16	6.23	0.0	0.0	15b
77	1-CH_3-5-$(CH_2)_6C_6H_5$	4.52	4.34	0.18	6.08	0.0	0.0	15d
78	5-$CH_2CH_2C_6H_4$-3'-C_6H_5-8-Cl	4.54	4.76	0.22	6.70	1.0	1.0	15e
79[c]	5-CH=CHC_6H_5-8-Cl	4.62	4.08	0.54	4.22	0.0	1.0	15d
80	5-$CH_2CH_2C_6H_3$-2',5'-Cl_2-8-Cl	4.62	4.65	0.03	5.27	1.0	1.0	15e
81[c]	6-$O(CH_2)_3C_6H_5$	4.70	4.10	0.60	4.44	0.0	1.0	15c
82	5-$CH_2CH_2C_6H_4$-2'-C_6H_5-8-Cl	4.74	4.76	0.02	6.70	1.0	1.0	15e
83	5-CH_2CH_2-(2-$C_{10}H_7$)-8-Cl	4.74	4.69	0.05	5.81	1.0	1.0	15e
84	5-$CH_2CH_2C_6H_4$-4'-C_6H_5-8-Cl	4.77	4.76	0.01	6.70	1.0	1.0	15e
85[c]	5-$(CH_2)_4C_6H_5$-8-Cl	5.17	4.64	0.53	5.19	1.0	1.0	15d
86	5-$(CH_2)_6C_6H_5$-8-Cl	5.17	4.72	0.45	6.11	1.0	1.0	15d

[a] Calculated from results of Baker et al.[15] [b] Calculated using eq 14. [c] These molecules not used in deriving equations.

Table XXXIV. Squared Correlation Matrix for Variables Pertaining to Eq 14 for Lactate Dehydrogenase

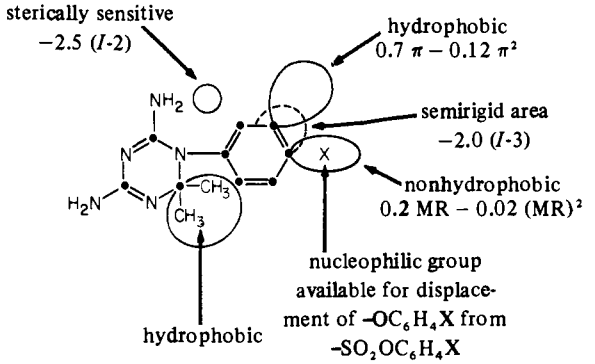
	MR-1,5,6,8	*I*-1	*I*-2
MR-1,5,6,8	1.00	0.17	0.03
I-1		1.00	0.06
I-2			1.00

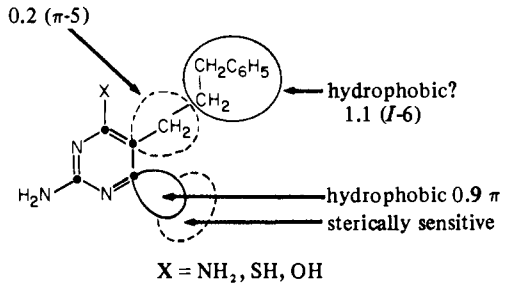
Table XXXV. Development of QSAR of Eq 14 for Lactate Dehydrogenase

Intercept	MR-1,5,6,8	*I*-1	*I*-2	*r*	*s*	$F_{1,X}$[a]
3.71	0.11			0.743	0.208	94.6
3.76	0.09	0.41		0.820	0.179	27.9
3.85	0.08	0.49	−0.11	0.836	0.173	6.9

[a] $F_{1,60;\alpha\,0.001} = 12$; $F_{1,60;\alpha\,0.025} = 5.3$.

The correlation of dihydrofolate reductase (pigeon liver) inhibitors by eq 10 can, to a certain extent, be compared with our earlier study[21] of triazines inhibiting enzyme from L1210 and Walker tumor tissue. The following diagrams illustrate similarities and differences.





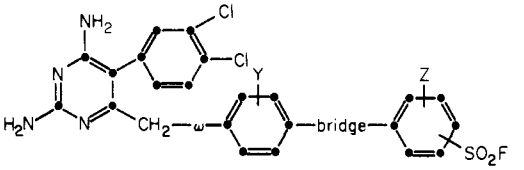
X = NH_2, SH, OH

Both enzymes and both types of inhibitors point to a large hydrophobic pocket off the 5 position. The evidence is clearer with the triazines than with the pyrimidines. With the pigeon liver enzyme, large hydrophobic groups are best parameterized by the indicator variable *I*-6. Quite a variety of large groups produce a similar effect. An attempt to use $(\pi\text{-}5)^2$ did not improve the correlation; hence, the effect may be largely dependent on a bulky apolar group causing a conformational change.

With small groups in the 5 position of the pyrimidines, typical hydrophobic interaction does not occur and almost as good correlation is obtained with MR-2. This is the least important term in eq 10 (Table XXIII) so that it is not surprising that even though π-2 and MR-2 are not collinear, they give similar results. Since groups on pyrimidine such as 5-C_6H_3-3',4'-Cl_2 are well fit by *I*-6, a good part of the 5-phenyl ring must contact hydrophobic space and/or produce a conformational change.

With the triazines, there is clearly a very sterically sensitive spot between the ortho position of the *N*-phenyl ring and the 4-NH_2 group. The type of substituents used in the pyrimidines does not allow one to draw conclusions about this space in the pigeon enzyme. Rigid groups in the 3 and 4 positions of the *N*-phenyl ring decrease inhibitory power with the triazines and mammalian enzyme. It is not possible to assess this effect with the pyrimidines.

The above two dihydrofolate reductase QSAR can be compared with a third attempt by Baker using the following basic structure.



The following QSAR has been developed for this set of congeners.[22]

$$\log 1/C = 0.36\,(I\text{-}1) - 1.01\,(I\text{-}8) - 0.78\,(I\text{-}9) + 0.42\,(I\text{-}13) - 0.22\,(I\text{-}15) + 0.51\,(I\text{-}20) + 0.67\,(I\text{-}4{\cdot}I\text{-}8) + 7.17 \quad (15)$$

n	*r*	*s*
105	0.903	0.229

All of the congeners contained the CH_2-ω-C_6H_4– moiety where ω = O or CH_2. *I*-1 takes a value of 1 for CH_2; hence, CH_2 is preferable to O for ω. The variable *I*-3 takes a value of 1 for the 4-$NHSO_2$– bridge and *I*-20 takes the value of 1 for enzyme from L1210 leukemia cells. In the cross

product term, I-4 is given the value of 1 for Y = 3-CH_3. The variable I-8 is given the value of 1 for the 4-NHCONH- bridge. The cross product indicates that the 3-CH_3 and the NHCONH- bridge have a synergistic effect on inhibitor potency. This is the most important positive contribution. The variable I-9 assumes the value of 1 for the 4-NHCO- bridge and I-15 takes the value of 1 for 4-SO_2F which indicates that 4-SO_2F is slightly less active than 3-SO_2F.

The only significant result of this rather large effort of Baker's is to show that little is to be gained with large substituents in the 6 position of the pyrimidine ring. An ethyl or propyl group in the 6 position would appear to yield maximum activity through hydrophobic interaction. Equation 15 is of interest in that it shows substituent effects to be largely additive but does not offer any positive ideas for better utilization of 6-space.

The correlation equations structuring Baker's massive enzyme inhibitor study clearly show that substituent effects, even for very large groups, are additive to a first approximation. The additivity is far more general than we had anticipated.

Correlation equations such as those discussed above are being developed at a rapid rate. Our own file is approaching 2000. As these equations become systematically organized, they will constitute a new and important way of organizing medicinal chemistry.[23]

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