Structure-Activity Relationships in Immunochemistry. 4.[1] Inhibition of Complement by Benzylpyridinium Ions. On the Predictive Value of Correlation Equations

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A quantitative structure-activity relationship formulated for 69 benzylpyridinium ions inhibiting complement is shown to predict the activity of 63 new benzylpyridinium derivatives. The utility of correlation equations in predicting the activity of new congeners is discussed.

The formulation of quantitative structure-activity relationships (QSAR) has developed rapidly in recent years by feeding on the vast accumulation of results from biomedicinal chemical studies made over the past three-quarters of a century.[3] There are relatively few examples in the literature where the formulation of a QSAR has been followed up by the synthesis of new derivatives to check up on the predictive value of correlation equations. Notable exceptions have been published.[4] In a different vein, QSAR studies led to the prediction that more hydrophilic nitrosoureas should make more potent, less toxic antileukemia drugs.[5] The prediction has been tested and found to hold.[6]

Another kind of illustration of the predictive ability of correlation equations can be made using binding studies with bovine serum albumin (BSA).

Equation 1 was formulated for the 1:1 binding of miscellaneous neutral compounds by BSA[7] at 0°. C is the

$$\log 1/C = 0.75\ (\pm 0.07) \log P + 2.30\ (\pm 0.15) \quad (1)$$

n	r	s
42	0.960	0.159

molar concentration of ligand necessary to produce the 1:1 complex.

Equation 2 was formulated 4 years later[8] from unpublished data which had been obtained in 1954 and

$$\log 1/C = 0.67\ (\pm 0.10) \log P + 2.60\ (\pm 0.22) \quad (2)$$

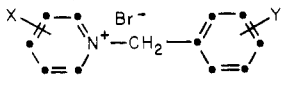
n	r	s
25	0.945	0.242

correlates a quite different set of compounds binding to BSA at 37°.

The two equations differ slightly (but not by more than the confidence limits). One would expect a lower slope at the higher temperature analogous to the behavior of ρ in the Hammett equation.[9]

There are many examples of this type of predictability where correlations with different sets of data from different laboratories yield identical equations.[10] Other examples are known where many additional points can be correlated by means of similar equations formulated with limited data.[11]

The present paper deals with an extension of our earlier study[1] of derivatives of I studied in the laboratory of the late B. R. Baker. Our earlier study of 69 derivatives of



I

I yielded correlation eq 3. In a further study of derivatives of I (unknown to us at the time eq 3 was formulated), Doll and Baker[12] tested more variations of I. We have found from these new data that the activity of 63 new derivatives is successfully predicted by eq 3 with the same variables used in the first QSAR. Compounds **50**, **52**, **55-57**, **65-77**, **80**, **81**, and **83** (see preceding paper, ref 12) were not included because of a lack of activity, unique structural features, or solubility problems. Specifically, compounds **50**, **57-77**, **80**, **81**, and **83** were of very low activity and so insoluble that reasonable results could not be obtained. The primary cause for this is lack of lipophilic substituents on the benzyl ring. The very large lipophilic groups on these derivatives on the X ring contribute *very* little to activity (0.16π) and, at the same time, greatly reduce solubility. Compound **52** is the only zwitterion in the set and compounds **55** and **56** do not contain the usual benzyl moiety.

Method. In Table I, C in $\log 1/C$ refers to the molar concentration of derivative I producing 50% inhibition of complement. These values were obtained by linear extrapolation from plots of activity vs. concentration from data in ref 1 and 11. The structural parameters of Table I were calculated as previously described.[1] The parameters π-1 and σ^+-1 refer to X substituents while π-2 and σ-2 refer to Y substituents. π is the hydrophobic parameter of the substituent.[13] The indicator variable D-1 is assigned the value of 1.00 for cases where Y = 2-SO_2F; otherwise it assumes the value of zero. The unusual activity of this group indicated by the positive coefficient with D-1 has been discussed.[1]

Table II contains the squared correlation matrix showing the degree of collinearity between the variables for the 132 data points.

Results and Discussion

Equation 3 was derived[1] for 69 variations of I causing 50% inhibition of complement and eq 4 was formulated from the original 69 plus the 63 new derivatives of Table I. The agreement of the corresponding coefficients in these

$$\log 1/C = 0.18\ (\pm 0.04)\ (\pi\text{-}1) + 0.46\ (\pm 0.14)\ (\pi\text{-}2) + 1.01\ (\pm 0.28)\ (\sigma^+\text{-}1) + 0.72\ (\pm 0.12)\ (D\text{-}1) + 2.50\ (\pm 0.13) \quad (3)$$

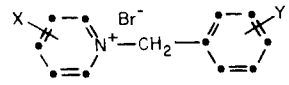
n	r	s
69	0.939	0.198

$$\log 1/C = 0.16\ (\pm 0.03)\ (\pi\text{-}1) + 0.38\ (\pm 0.11)\ (\pi\text{-}2) + 0.91\ (\pm 0.25)\ (\sigma^+\text{-}1) + 0.71\ (\pm 0.10)\ (D\text{-}1) + 2.58\ (\pm 0.10) \quad (4)$$

n	r	s
132	0.945	0.213

equations is well within the 95% confidence limits. Equation 4 gives a slightly better correlation with respect to correlation coefficients (r) but is slightly poorer than eq 3 with respect to standard deviation (s). Considering the diversity in the 63 new derivatives added to eq 3, the

Table I. Constants Used for Deriving Eq 3-5



No.	X	Y	Log 1/C				π-1	π-2	D-1	σ⁺-1	D-2
			Obsd[a]	Calcd[b]	Calcd[c]	Calcd[d]					
1	3-(3,4-$Cl_2C_6H_3OCH_2CONHCH_2$)	H	2.46	2.80	2.85	2.85	2.08	0.00	0.0	−0.07	0.0
2	4-CH_3	4-SO_2F	2.48	2.46	2.53	2.55	0.56	0.37	0.0	−0.31	0.0
3	H	4-SO_2F	2.55	2.67	2.72	2.73	0.00	0.37	0.0	0.00	0.0
4[e]	2,3-(CH=CH)$_2$	4-SO_2F	2.55	2.66	2.72	2.72	1.32	0.13	0.0	−0.14	0.0
5	3-CH_3CONH	4-SO_2F	2.64	2.71	2.75	2.76	−0.97	0.37	0.0	0.21	0.0
6	3-$C_6H_5OCH_2CONH$	4-SO_2F	2.69	3.00	3.02	3.01	0.66	0.37	0.0	0.21	0.0
7	3-$C_6H_5CH_2CONH$	4-SO_2F	2.71	2.97	2.99	2.99	0.49	0.37	0.0	0.21	0.0
8	3-C_6H_5CONH	4-SO_2F	2.72	2.78	2.82	2.82	0.49	0.37	0.0	0.02	0.0
9[e]	3-(3,4-$Cl_2C_6H_3OCH_2CONHCH_2$)	4-MeO	2.81	2.79	2.85	2.85	2.08	−0.02	0.0	−0.07	0.0
10[e]	4-$C_6H_5CH_2$	4-SO_2F	2.89	2.72	2.76	2.78	2.01	0.37	0.0	−0.31	0.0
11	4-C_6H_5	4-SO_2F	2.89	2.84	2.87	2.88	1.96	0.37	0.0	−0.18	0.0
12	3-(2-$ClC_6H_4OCH_2CONH$)	4-SO_2F	2.90	3.13	3.13	3.13	1.37	0.37	0.0	0.21	0.0
13	3-[L-4-Ts-NH($CH_2C_6H_5$)$CHCONHCH_2$]	4-SO_2F	2.92	2.95	2.97	2.97	1.92	0.37	0.0	−0.07	0.0
14	4-$C_6H_5(CH_2)_2$	4-SO_2F	2.96	2.84	2.87	2.88	2.66	0.37	0.0	−0.31	0.0
15[e]	4-$C_6H_5(CH_2)_4$	4-SO_2F	3.00	3.02	3.03	3.03	3.66	0.37	0.0	−0.31	0.0
16[e]	3-(3,4-$Cl_2C_6H_3OCH_2CONH$)	4-NO_2	3.00	2.88	2.95	2.93	2.08	−0.43	0.0	0.21	0.0
17	4-$C_6H_5(CH_2)_3$	4-SO_2F	3.02	2.93	2.95	2.96	3.16	0.37	0.0	−0.31	0.0
18	3-(3,4-$Cl_2C_6H_3OCH_2CONHCH_2$)	4-SO_2F	3.04	2.97	2.99	2.99	2.08	0.37	0.0	−0.07	0.0
19[e]	3-(3,4-$Cl_2C_6H_3OCH_2CONH$)	H	3.05	3.08	3.11	3.10	2.08	0.00	0.0	0.21	0.0
20[e]	3-(3,4-$Cl_2C_6H_3OCH_2CONH$)	4-CH_3O	3.05	3.08	3.10	3.09	2.08	−0.02	0.0	0.21	0.0
21	3-$C_6H_5(CH_2)_4$	4-SO_2F	3.05	3.26	3.25	3.24	3.66	0.37	0.0	−0.07	0.0
22	3-(3,4-$Cl_2C_6H_3OCH_2CONH$)	3-NO_2	3.06	2.88	2.95	2.93	2.08	−0.43	0.0	0.21	0.0
23	3-(3-$ClC_6H_4OCH_2CONH$)	4-SO_2F	3.06	3.13	3.13	3.13	1.37	0.37	0.0	0.21	0.0
24	3-(4-$ClC_6H_4OCH_2CONH$)	4-SO_2F	3.08	3.13	3.13	3.13	1.37	0.37	0.0	0.21	0.0
25	3-(3,4-$Cl_2C_6H_3OCH_2CONHCH_2$)	3-SO_2F	3.10	2.97	2.99	2.99	2.08	0.37	0.0	−0.07	0.0
26	H	2-SO_2F	3.15	3.39	3.43	3.42	0.00	0.37	1.0	0.00	0.0
27	2-(3,4-$Cl_2C_6H_3CH_2CH_2$)	4-SO_2F	3.17	3.09	3.10	3.10	4.08	0.37	0.0	−0.31	0.0
28	2-[3,4-$Cl_2C_6H_3(CH_2)_4$]	4-SO_2F	3.22	3.27	3.27	3.26	5.08	0.37	0.0	−0.31	0.0
29	3-(3,4-$Cl_2C_6H_3OCH_2CONHCH_2$)	3-Cl-4-SO_2F	3.25	3.30	3.26	3.26	2.08	1.08	0.0	−0.07	0.0
30	3-(3,4-$Cl_2C_6H_3OCH_2CONH$)	4-SO_2F	3.27	3.26	3.25	3.24	2.08	0.37	0.0	0.21	0.0
31	3-[L-4-Ts-NHCH($C_6H_5CH_2$)CONH]	4-SO_2F	3.28	3.23	3.22	3.21	1.92	0.37	0.0	0.21	0.0
32[e]	3-(2,4-$Cl_2C_6H_3OCH_2CONH$)	4-SO_2F	3.30	3.26	3.25	3.24	2.08	0.37	0.0	0.21	0.0
33[e]	4-[3,4-$Cl_2C_6H_3O(CH_2)_3$]	4-SO_2F	3.30	3.17	3.18	3.17	4.53	0.37	0.0	−0.31	0.0
34[e]	3-(3,4-$Cl_2C_6H_3OCH_2CONH$)	4-CH_3	3.31	3.34	3.32	3.31	2.08	0.56	0.0	0.21	0.0
35	3-(2,3-$Cl_2C_6H_3OCH_2CONH$)	4-SO_2F	3.31	3.26	3.25	3.24	2.08	0.37	0.0	0.21	0.0
36	3-(3,4-$Cl_2C_6H_3OCH_2CONHCH_2$)	4-Cl-3-SO_2F	3.31	3.30	3.26	3.26	2.08	1.08	0.0	−0.07	0.0
37[e]	3-[3,4-$Cl_2C_6H_3(CH_2)_4$]	4-SO_2F	3.31	3.51	3.48	3.46	5.08	0.37	0.0	−0.07	0.0
38	3-(3,4-$Cl_2C_6H_3CH_2CH_2$)	4-SO_2F	3.32	3.33	3.32	3.31	4.08	0.37	0.0	−0.07	0.0
39	4-(3,4-$Cl_2C_6H_3CH_2CH_2$)	4-SO_2F	3.34	3.09	3.10	3.10	4.08	0.37	0.0	−0.31	0.0
40[e]	3-(3,4-$Cl_2C_6H_3OCH_2CONH$)	3-SO_2F	3.36	3.26	3.25	3.24	2.08	0.37	0.0	0.21	0.0
41[e]	4-[3,4-$Cl_2C_6H_3(CH_2)_4$]	4-SO_2F	3.38	3.27	3.27	3.26	5.08	0.37	0.0	−0.31	0.0
42	3-(3,4-$Cl_2C_6H_3OCH_2CONHCH_2$)	2-Cl-4-SO_2F	3.43	3.30	3.26	3.26	2.08	1.08	0.0	−0.07	0.0
43	H	6-Cl-2-SO_2F	3.43	3.72	3.70	3.69	0.00	1.08	1.0	0.00	0.0
44	2-[3,4-$Cl_2C_6H_3(CH_2)_4$]	2-SO_2F	3.64	3.99	3.98	3.95	5.08	0.37	1.0	−0.31	0.0
45	3-(3,4-$Cl_2C_6H_5OCH_2CONH$)	3-Cl-4-SO_2F	3.66	3.59	3.52	3.51	2.08	1.08	0.0	0.21	0.0
46	3-(3,4-$Cl_2C_6H_3OCH_2CONH$)	4-Cl-3-SO_2F	3.72	3.59	3.52	3.51	2.08	1.08	0.0	0.21	0.0
47	2-(3,4-$Cl_2C_6H_3CH_2CH_2$)	2-SO_2F	3.72	3.81	3.81	3.79	4.08	0.37	1.0	−0.31	0.0

48	4-(3,4-$Cl_2C_6H_3CH_2CH_2$)	2-SO_2F	3.72	3.81	3.81	3.79	4.08	0.37	1.0	−0.31	0.0
49	3-[3,4-$Cl_2C_6H_3(CH_2)_2$]	2-SO_2F	3.72	4.06	4.03	4.00	4.08	0.37	1.0	−0.07	0.0
50	3,4-$(CH=CH)_2$	6-Cl-2-SO_2F	3.74	3.71	3.70	3.68	1.32	0.84	1.0	−0.14	0.0
51	3-(3,4-$Cl_2C_6H_3OCH_2CONH$)	2-Cl-4-SO_2F	3.77	3.59	3.52	3.51	2.08	1.08	0.0	0.21	0.0
52	4-$C_6H_5(CH_2)_4$	6-Cl-2-SO_2F	3.80	4.07	4.01	3.99	3.66	1.08	1.0	−0.31	0.0
53	3-$C_6H_5(CH_2)_2$	6-Cl-2-SO_2F	3.80	4.13	4.07	4.04	2.66	1.08	1.0	−0.07	0.0
54	4-$C_6H_5(CH_2)_3$	6-Cl-2-SO_2F	3.80	3.98	3.93	3.91	3.16	1.08	1.0	−0.31	0.0
55	4-[3,4-$Cl_2C_6H_3(CH_2)_4$]	2-SO_2F	4.00	3.99	3.98	3.95	5.08	0.37	1.0	−0.31	0.0
56	3-(3,4-$Cl_2C_6H_3OCH_2CONHCH_2$)	3-Cl-2-SO_2F	4.07	4.03	3.97	3.95	2.08	1.08	1.0	−0.07	0.0
57	2,3-$(CH=CH)_2$	6-Cl-2-SO_2F	4.15	3.71	3.70	3.68	1.32	0.84	1.0	−0.14	0.0
58	3-(3,4-$Cl_2C_6H_3OCH_2CONHCH_2$)	4-Cl-2-SO_2F	4.17	4.03	3.97	3.95	2.08	1.08	1.0	−0.07	0.0
59	3-(3,4-$Cl_2C_6H_3OCH_2CONH$)	3-Cl-2-SO_2F	4.18	4.31	4.23	4.19	2.08	1.08	1.0	0.21	0.0
60	3-$C_6H_5(CH_2)_4$	6-Cl-2-SO_2F	4.22	4.31	4.23	4.20	3.66	1.08	1.0	−0.07	0.0
61	3-(3,4-$Cl_2C_6H_3OCH_2CONHCH_2$)	6-Cl-2-SO_2F	4.24	4.03	3.97	3.95	2.08	1.08	1.0	−0.07	0.0
62	3-(3,4-$Cl_2C_6H_3OCH_2CONH$)	2-SO_2F	4.29	3.98	3.96	3.93	2.08	0.37	1.0	0.21	0.0
63	3-(3,4-$Cl_2C_6H_3OCH_2CONHCH_2$)	5-Cl-2-SO_2F	4.31	4.03	3.97	3.95	2.08	1.08	1.0	−0.07	0.0
64	3-(3,4-$Cl_2C_6H_3OCH_2CONH$)	4-Cl-2-SO_2F	4.32	4.31	4.23	4.19	2.08	1.08	1.0	0.21	0.0
65	3-[3,4-$Cl_2C_6H_3(CH_2)_4$]	6-Cl-2-SO_2F	4.32	4.56	4.46	4.42	5.08	1.08	1.0	−0.07	0.0
66	3-(3,4-$Cl_2C_6H_3OCH_2CONH$)	5-Cl-2-SO_2F	4.33	4.31	4.23	4.19	2.08	1.08	1.0	0.21	0.0
67	3-(3,4-$Cl_2C_6H_3OCH_2CONHCH_2$)	2-SO_2F	4.38	3.70	3.71	3.68	2.08	0.37	1.0	−0.07	0.0
68	3-(3,4-$Cl_2C_6H_3OCH_2CONH$)	6-Cl-2-SO_2F	4.46	4.31	4.23	4.19	2.08	1.08	1.0	0.21	0.0
69	3-[3,4-$Cl_2C_6H_3(CH_2)_4$]	2-SO_2F	4.57	4.24	4.20	4.15	5.08	0.37	1.0	−0.07	0.0
1[a,e]	3-[4-(4-SO_2F-C_6H_4CONH)$C_6H_4OCH_2CONHCH_2$]	H	2.77	2.77	2.82	2.82	1.20	0.00	0.0	0.05	0.0
2[a]	3-[4-(4-SO_2F-C_6H_4CONH)$C_6H_4CH_2CH_2CONHCH_2$]	H	2.83	2.69	2.75	2.76	1.45	0.00	0.0	−0.07	0.0
3[a]	3-[4-(C_6H_5CONH)$C_6H_4(CH_2)_4$]	H	2.86	3.17	3.19	3.18	4.15	0.00	0.0	−0.07	0.0
4[a]	4-[4-(4-SO_2F-C_6H_4CONH)$C_6H_4(CH_2)_2$]	H	2.92	2.76	2.82	2.82	3.20	0.00	0.0	−0.31	0.0
5[a]	3-[4-(4-SO_2F-C_6H_4CONH)$C_6H_4(CH_2)_2$]	H	2.92	3.00	3.04	3.03	3.20	0.00	0.0	−0.07	0.0
6[a,e]	3-[4-(4-SO_2F-$C_6H_4CH_2CONH$)$C_6H_4(CH_2)_4$]	H	3.13	3.18	3.20	3.19	4.20	0.00	0.0	−0.07	0.0
7[a]	4-[4-(4-SO_2F-C_6H_4CONH)$C_6H_4(CH_2)_4$]	H	3.20	2.94	2.98	2.98	4.20	0.00	0.0	−0.31	0.0
8[a,e]	3-[4-(4-SO_2F-$C_6H_4CH_2CH_2CONH$)$C_6H_4(CH_2)_4$]	H	3.28	3.26	3.27	3.25	4.62	0.00	0.0	−0.07	0.0
9[a]	2,3-$(CH=CH)_2$-4-$C_6H_5(CH_2)_2$	2-SO_2F	3.38	3.66	3.67	3.65	3.98	0.37	1.0	−0.45	0.0
10[a]	2,3-$(CH=CH)_2$	2-SO_2F	3.38	3.49	3.52	3.50	1.32	0.37	1.0	−0.14	0.0
11[a]	3-[4-(4-SO_2F-C_6H_4CONH)$C_6H_4(CH_2)_4$]	H	3.54	3.18	3.20	3.19	4.20	0.00	0.0	−0.07	0.0
12[a]	2,3-1′,2′-Naphtho	2-SO_2F	3.60	3.73	3.73	3.71	2.64	0.37	1.0	−0.14	0.0
13[a,e]	3-[4-$C_6H_5C_6H_4(CH_2)_4$]	H	3.67	3.44	3.43	3.74	5.62	0.00	0.0	−0.07	1.0
14[a,e]	3-[4-(4-SO_2F-C_6H_4CONH)$C_6H_4(CH_2)_4$]	4-C_6H_5	3.82	4.09	3.94	3.93	4.20	1.96	0.0	−0.07	0.0
15[a,e]	3-[4-(4-SO_2F-C_6H_4CONH)$C_6H_4(CH_2)_4$]	2,3-$(CH=CH)_2$	3.82	3.80	3.70	3.69	4.20	1.32	0.0	−0.07	0.0
16[a]	3-[4-(4-SO_2F-C_6H_4CONH)$C_6H_4(CH_2)_4$]	2-SO_2F	3.90	4.08	4.05	4.02	4.20	0.37	1.0	−0.07	0.0
17[a,e]	3-[3-$C_6H_5C_6H_4(CH_2)_4$]	2-SO_2F	3.98	4.33	4.28	4.24	5.62	0.37	1.0	−0.07	0.0
18[a]	4-[$(C_6H_5)_2CHCH_2CH_2$]	6-Cl-2-SO_2F	4.01	4.33	4.25	4.22	5.09	1.08	1.0	−0.31	0.0
19[a]	3-(4-$C_6H_5C_6H_4OCH_2CONH$)	6-Cl-2-SO_2F	4.05	4.29	4.21	4.51	2.87	1.08	1.0	0.05	1.0
20[a]	3-(2-$C_{10}H_7CH_2CH_2$)	6-Cl-2-SO_2F	4.05	4.37	4.28	4.25	3.98	1.08	1.0	−0.07	0.0
21[a]	3-[$(C_6H_5)_2CH$]	6-Cl-2-SO_2F	4.07	4.35	4.27	4.23	3.94	1.08	1.0	−0.08	0.0
22[a]	3-(4-$C_6H_5C_6H_4CH_2CH_2CONHCH_2$)	6-Cl-2-SO_2F	4.10	4.17	4.10	4.40	2.87	1.08	1.0	−0.07	1.0
23[a]	3-[3-$ClC_6H_4(CH_2)_4$]	6-Cl-2-SO_2F	4.11	4.44	4.35	4.31	4.37	1.08	1.0	−0.07	0.0
24[a]	3-[4-$FC_6H_4(CH_2)_4$]	6-Cl-2-SO_2F	4.13	4.34	4.26	4.22	3.80	1.08	1.0	−0.07	0.0
25[a]	3-[2-$CH_3C_6H_4(CH_2)_4$]	6-Cl-2-SO_2F	4.15	4.41	4.32	4.29	4.22	1.08	1.0	−0.07	0.0
26[a]	3-[4-$CH_3CONHC_6H_4(CH_2)_4$]	6-Cl-2-SO_2F	4.15	4.14	4.07	4.05	2.69	1.08	1.0	−0.07	0.0
27[a]	3-[3-$CH_3C_6H_4(CH_2)_4$]	6-Cl-2-SO_2F	4.16	4.41	4.32	4.29	4.22	1.08	1.0	−0.07	0.0
28[a]	3-[4-$NO_2C_6H_4(CH=CH)_2$]	6-Cl-2-SO_2F	4.17	4.35	4.27	4.23	3.20	1.08	1.0	0.05	0.0
29[a]	4-(3-$C_6H_5C_6H_4CH_2CH_2$)	6-Cl-2-SO_2F	4.21	4.24	4.17	4.14	4.62	1.08	1.0	−0.31	0.0
30[a]	3-[4-($C_6H_5CH_2CH_2CONH$)$C_6H_4(CH_2)_4$]	6-Cl-2-SO_2F	4.24	4.47	4.38	4.34	4.57	1.08	1.0	−0.07	0.0
31[a]	3-[4-($C_6H_5OCH_2CONH$]$C_6H_4(CH_2)_4$]	6-Cl-2-SO_2F	4.24	4.43	4.34	4.30	4.32	1.08	1.0	−0.07	0.0
32[a]	3-[4-$CH_3C_6H_4(CH_2)_4$]	6-Cl-2-SO_2F	4.24	4.41	4.32	4.29	4.22	1.08	1.0	−0.07	0.0
33[a]	3-[3,4-$(CH_3)_2C_6H_3(CH_2)_4$]	6-Cl-2-SO_2F	4.26	4.56	4.46	4.42	5.05	1.08	1.0	−0.07	0.0
34[a]	3-[$C_6H_5CH_2CH(C_6H_5)CH_2CH_2$]	6-Cl-2-SO_2F	4.27	4.66	4.55	4.50	5.59	1.08	1.0	−0.07	0.0

Table I (*Continued*)

No.	X	Y	Log 1/C Obsd[a]	Calcd[b]	Calcd[c]	Calcd[d]	π-1	π-2	D-1	σ⁺-1	D-2
35[a]	3-$C_6H_5(CH{=}CH)_2$	6-Cl-2-SO_2F	4.28	4.40	4.31	4.27	3.48	1.08	1.0	0.05	0.0
36[a]	3-[2-$ClC_6H_4(CH_2)_4$]	6-Cl-2-SO_2F	4.29	4.44	4.35	4.31	4.37	1.08	1.0	−0.07	0.0
37[a]	3-$C_6H_5(CH{=}CH)_3$	6-Cl-2-SO_2F	4.31	4.52	4.43	4.38	4.18	1.08	1.0	0.05	0.0
38[a]	3-[3-$NO_2C_6H_4(CH{=}CH)_2$]	6-Cl-2-SO_2F	4.32	4.35	4.27	4.23	3.20	1.08	1.0	0.05	0.0
39[a]	3-[1-$C_{10}H_7(CH_2)_4$]	6-Cl-2-SO_2F	4.32	4.55	4.45	4.41	4.98	1.08	1.0	−0.07	0.0
40[a]	3-[4-(4-$NO_2C_6H_4CONH)C_6H_4(CH_2)_3$]	6-Cl-2-SO_2F	4.33	4.35	4.27	4.23	3.87	1.08	1.0	−0.07	0.0
41[a]	3-[3,4-$Cl_2C_6H_3(CH{=}CH)_2$]	6-Cl-2-SO_2F	4.33	4.65	4.54	4.50	4.90	1.08	1.0	0.05	0.0
42[a]	3-$C_6H_5(CH_2)_6$	6-Cl-2-SO_2F	4.33	4.49	4.40	4.36	4.66	1.08	1.0	−0.07	0.0
43[a]	3-[2,6-$Cl_2C_6H_3(CH_2)_4$]	6-Cl-2-SO_2F	4.36	4.57	4.46	4.42	5.08	1.08	1.0	−0.07	0.0
44[a]	3-[$(C_6H_5)_2CHCH_2CH_2$]	6-Cl-2-SO_2F	4.37	4.57	4.47	4.42	5.09	1.08	1.0	−0.07	0.0
45[a]	3-[4-$(C_6H_5CH_2CH_2)C_6H_4CH_2CH_2$]	6-Cl-2-SO_2F	4.38	4.61	4.50	4.46	5.32	1.08	1.0	−0.07	0.0
46[a]	3-[3-$C_6H_5CH_2C_6H_4(CH_2)_4$]	6-Cl-2-SO_2F	4.39	4.67	4.56	4.51	5.67	1.08	1.0	−0.07	0.0
47[a]	3-[4-$C_6H_5CONHC_6H_4(CH_2)_4$]	6-Cl-2-SO_2F	4.41	4.40	4.31	4.28	4.15	1.08	1.0	−0.07	0.0
48[a]	2,3-1',2'-Naphtho	6-Cl-2-SO_2F	4.43	4.06	4.00	3.98	2.64	1.08	1.0	−0.14	0.0
49[a]	3-[4-$ClC_6H_4(CH_2)_4$]	6-Cl-2-SO_2F	4.46	4.44	4.35	4.31	4.37	1.08	1.0	−0.07	0.0
50[a]	3-[2,4-$Cl_2C_6H_3(CH_2)_4$]	6-Cl-2-SO_2F	4.47	4.57	4.46	4.42	5.08	1.08	1.0	−0.07	0.0
51[a]	3-(4-$C_6H_5C_6H_4CH_2CH_2CONH$)	6-Cl-2-SO_2F	4.51	4.17	4.10	4.40	2.87	1.08	1.0	−0.07	1.0
52[a]	3-(4-$C_6H_5C_6H_4CONHCH_2$)	6-Cl-2-SO_2F	4.51	4.52	4.42	4.70	2.45	1.08	1.0	0.35	1.0
53[a]	3-[3-$C_6H_5CH_2CH_2C_6H_4(CH_2)_4$]	6-Cl-2-SO_2F	4.51	4.79	4.67	4.62	6.32	1.08	1.0	−0.07	0.0
54[a]	3-[4-$(CH_3)_2CHC_6H_4(CH_2)_4$]	6-Cl-2-SO_2F	4.51	4.54	4.45	4.40	4.96	1.08	1.0	−0.07	0.0
55[a]	3-[2-$C_{10}H_7(CH_2)_4$]	6-Cl-2-SO_2F	4.51	4.55	4.45	4.41	4.98	1.08	1.0	−0.07	0.0
56[a]	3-[4-$C_6H_5C_6H_4(CH{=}CH)_2$]	6-Cl-2-SO_2F	4.54	4.75	4.63	4.58	5.44	1.08	1.0	0.05	0.0
57[a]	3-[4-$C_6H_5CH_2CH_2C_6H_4(CH_2)_4$]	6-Cl-2-SO_2F	4.55	4.79	4.67	4.62	6.32	1.08	1.0	−0.07	0.0
58[a]	3-[3,4-$Cl_2C_6H_3(CH_2)_4$]	2-SO_2F	4.57	4.24	4.20	4.15	5.08	0.37	1.0	−0.07	0.0
59[a]	3-(4-$C_6H_5C_6H_4CH_2CH_2$)	6-Cl-2-SO_2F	4.57	4.48	4.39	4.68	4.62	1.08	1.0	−0.07	1.0
60[a]	3-[4-$C_6H_5CH_2C_6H_4(CH_2)_4$]	6-Cl-2-SO_2F	4.60	4.67	4.56	4.51	5.67	1.08	1.0	−0.07	0.0
61[a]	4-(4-$C_6H_5C_6H_4CH_2CH_2$)	6-Cl-2-SO_2F	4.68	4.24	4.17	4.47	4.62	1.08	1.0	−0.31	1.0
62[a]	3-[4-$C_6H_5C_6H_4(CH_2)_4$]	2-SO_2F	5.11	4.33	4.28	4.57	5.62	0.37	1.0	−0.07	1.0
63[a]	3-[4-$C_6H_5C_6H_4(CH_2)_4$]	6-Cl-2-SO_2F	5.11	4.66	4.55	4.83	5.62	1.08	1.0	−0.07	1.0

[a] Calculated from results of Baker et al.[1,12] [b] Calculated using eq 3. [c] Calculated using eq 4. [d] Calculated using eq 5. [e] In the case of these log 1/C values it was necessary to use only one datum in making the extrapolation to the I_{50} concentration since only one concentration had been tested and very low activity, saturation of activity, or lysis at higher inhibition makes linear extrapolation unreliable.

Table II. Correlation Matrix for Collinearity between Variables[a]

	π-1	MR-1	π-2	MR-2	σ^+-1	D-1	D-2
π-1	1.00	0.27	0.08	0.04	0.17	0.17	0.02
MR-1		1.00	0.00	0.01	0.00	0.00	0.03
π-2			1.00	0.84	0.00	0.38	0.01
MR-2				1.00	0.00	0.33	0.01
σ^+-1					1.00	0.02	0.00
D-1						1.00	0.03
D-2							1.00

[a] Values are r^2.

correspondence between eq 3 and 4 is most impressive.

There are two types of predictions which must be considered. In the first type, one can attempt to predict the activity of new derivatives whose substituents are characterized by constants within the range of substituent space spanned by derivatives supporting the model equation. Often (but not necessarily) such derivatives will have biological activities within the range already explored. After one has a reasonable distribution of data along each vector, testing of more data points in the explored substituent space is redundant. The 63 compounds in Table I fall largely in this class. Only four have activities higher than those of the first analysis;[1] of the three continuous variables, we find the following spread in the two data sets.

compound	π-1	π-2	σ^+-1
1-69 (set 1)	−0.97–5.08	−0.43–1.08	−0.31–0.21
1a–63a (set 2)	1.2–6.32	0–1.96	−0.45–0.35

Compounds in set 2 extend the range of each of the three vectors by modest amounts and it is apparent from Table I that points with constants outside the range previously explored are well predicted in general.

None of the derivatives of set 2 have activities lower than the lowest of set 1.

The close correspondence of eq 3 and 4 shows that eq 3 is quite a robust expression and that correlation equations can be quite accurate in predicting activities of new congeners having constants within the region of explored data space as well as those having constants not too far beyond explored substituent space. This is most important to the drug designer since he must avoid redundancy in designing his molecular probes.

The second type of prediction is that for derivatives possessing activity outside the range already explored. The problem here is like making a topological map of, say, the state of New York. Even from a very carefully constructed map of New York, one could not make very accurate predictions about the topology of Ohio; however, one could make some reasonable guesses about the adjoining state of Vermont. In the present instance of the four compounds (**60a–63a**) having activities greater than those of the first set, one is accurately predicted, one is moderately well predicted, and two are poorly predicted. The most poorly fit point is off by a factor of 6.7 in a total range of activity of 450. It is noteworthy that, although each of the vectors π-1, π-2, and σ^+-1 was extended to more favorable values, these profitable changes were not all incorporated into one congener. If this had been done, eq 3 would predict an activity of 5.61 (π-1 = 6.32, π-2 = 1.96, σ^+-1 = 0.35, and D-1 = 1.0).

Study of the characteristics of the poorly fit compounds suggests the use of a new indicator variable D-2 which is assigned the value of 1.00 for X = 3- or 4-(4-C_6H_5-C_6H_4-B) where B represents flexible bridges of the type $(CH_2)_2$, $(CH_2)_4$, CH_2CONH, $(CH_2)_2CONH$, and $CONHCH_2$. All other congeners are given a value of zero for D-2. Addition of this variable to eq 4 yields eq 5. There are nine

$$\log 1/C = 0.16\ (\pm 0.03)\ (\pi\text{-}1) + 0.38\ (\pm 0.10)\ (\pi\text{-}2) + 0.86\ (\pm 0.23)\ (\sigma^+\text{-}1) + 0.69\ (\pm 0.09)\ (D\text{-}1) + 0.33\ (\pm 0.14)\ (D\text{-}2) + 2.59\ (\pm 0.09) \quad (5)$$

n	r	s
132	0.953	0.197

congeners having D-2 = 1.00 of which three are in the most active group of the new set. Equation 5 is a significant improvement over eq 4 ($F_{1,126}$ = 22.26; $F_{1,120;\ \alpha\ 0.001}$ = 11.38) and is a solid relationship based on 26 data points per variable (on the average).

Indicator variable D-2 illustrates the value of Baker's bridge principle.[14] When a large lipophilic moiety is placed further away from the ring, it encounters a binding site which is better than that region characterized by π-2 by a factor of 2.

We suggested in our previous report[1] that the role of 2-SO_2F in the benzyl moiety might be to anchor the inhibitor to complement via covalent bonding with a nucleophilic group such as a serine hydroxyl. Recently, Bing et al.[15] have shown that only the o-SO_2F derivatives show a strong *irreversible* inhibition.

We are now designing inhibitors to further extend the range of explored space. The objective of the work is not only to produce more potent inhibitors but also to systematically extend our knowledge of substituent space around the binding site of the benzylpyridinium group in the complement system.

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References and Notes

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