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Potential Antitumor Agents. 32. Role of Agent Base Strength in the Quantitative Structure–Antitumor Relationships for 4'-(9-Acridinylamino)methanesulfonanilide Analogues

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Several homologous series of 9-anilinoacridines, each bearing a different pK_a modulating acridine substituent, have been synthesized and screened in the L1210 leukemia system, to examine if measures of agent lipophilic–hydrophilic balance utilized in regression analysis should be corrected for the effects of changing base strength. The measure of tumor selectivity modeled was the maximum increase in life span in L1210 tests (ILS_{max}), and dose potency was gauged as D_{40}, the molar drug dose necessary to provide 40% extension in life span. Agent lipophilic–hydrophilic balance was measured as chromatographic R_m values, and the pK_a modulating factors examined were log $(1 - \alpha)$ and log α, where α is the fraction of drug ionized at physiological pH. Regression analyses of data from 78 L1210-active compounds show that the measured R_m values, unmodified by pK_a correction factors, furnish superior correlation equations. An equation in R_m^2, with indicator variables denoting the presence of acridine 3-NO_2 or 4-CONRR' substituents, successfully models ILS_{max}. To develop successful regression equations for D_{40} it was necessary to restrict attention to close structural congeners which are likely to be metabolized by similar routes. Results for a series of 3-nitroacridine derivatives which may be reduced in vivo to more dose-potent and/or more hydrophilic compounds could not be incorporated. Acceptable equations developed for D_{40} contain terms in R_m, R_m^2, and pK_a or $t_{1/2}$. The latter provides a measure of the rate of agent thiolytic cleavage, a prominent contributor to drug decay in vivo.

The high, broad spectrum antitumor activity of previously examined members[1-8] of the 4'-(9-acridinylamino)-methanesulfonanilide series has lead to the clinical trial of one congener (**22**, Table I, *m*-AMSA, NSC249992).[9] To aid the discovery of more effective second-generation analogues, it was hoped to discern those drug features associated with tumor selectivity by development of quantitative structure–activity relationships (QSAR) for this series. With 12 apparently nonequivalent drug positions available for substitution and varying dependence of biologic activity on the steric and electronic contributions of substituents at each of these positions, further compounded by the less than desirable accuracy of antitumor screening data, we have been unable to develop satisfactory QSAR by conventional approaches. A possible contributor to this lack of success is the varying pK_a values of the drugs. The magnitudes of the ionization constants (see Table I for examples) are such that each substituted agent will likely provide a different percentage of cationic species at physiologic pH values. It has been shown that virtually any drug substituent, appended to either the acridine or 9-anilino ring system, will alter agent base strength.[8] Certain qualitative SAR in this drug series are difficult to rationalize without ascribing a critical role to agent base strength.[6] Additionally, in an earlier QSAR study of unrelated series of antitumor drugs we had successfully quantified the contribution of agent pK_a values to antitumor activity.[10] With the failure of conventional methods of developing QSAR, in the present series it became necessary to design an alternate method of gauging the role of base strength in antitumor activity, and such a study forms the basis of this article.

Chemistry. Agent generation involved the general procedures evolved earlier.[1-3] Thus, Jourdan–Ullmann condensation of a substituted 2-chlorobenzoic acid and the requisite aniline afforded a *N*-arylanthranilic acid.[2] Ring closure then provided the substituted 9(10*H*)-acridones, which with $SOCl_2$/DMF[2] furnished the corresponding 9-chloroacridines. Acid-catalyzed coupling of the latter with the appropriate 3'-methoxy-4'-aminoalkanesulfonanilide[3] provided the bulk of the cogeners required.

4-Hydroxy-9(10*H*)-acridone could be conveniently prepared by pyridine hydrochloride dealkylation of 4-methoxy-9(10*H*)-acridone. The 4-*O*-alkylacridones necessary for preparation of **41–43** were then prepared by alkylation (RBr/Me_2SO) of the sodium salt of the 4-hydroxy-9-(10*H*)-acridone. Reaction of the latter under similar conditions with 4-bromobutyronitrile gave a cyano ether which readily hydrolyzed to the corresponding acid. The latter was elaborated, as in earlier work,[5] to the amide variant **47**.

Selective reaction of the acid chloride function of 9-chloroacridine-4-carbonyl chloride[5] with *n*-butylamine in alkaline media at low temperatures afforded the corresponding *n*-butylamide. Acid-catalyzed coupling with the appropriate aromatic amine component then furnished **71–73**. For other 4-carboxamide variants, the previously[5] prepared 4'-[9-[4-[(4-nitrophenoxy)carbonyl]acridinyl]-amino]methanesulfon-*m*-anisidide was reacted with glycine methylamide to afford **77** or with 6-aminohexanol. In the latter case, further reaction of the resultant alcohol with limited quantities of methanesulfonyl chloride in pyridine

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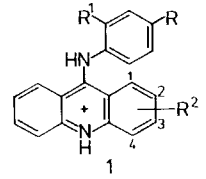
Table I. Structural Details and Physicochemical and Biologic Parameters for the 9-Anilinoacridines



1

									log (ILS_{max})[f]			log ($1/D_{40}$)[g]		
no.	R	R^1	R^2	anion[a]	R_m[b]	pK_a[c]	LD_{10}[d]	D_{40}[e]	obsd	calcd	diff	obsd	calcd	diff
2	CH_2CONH_2	H	H	MsO^-	−0.33	7.43	55	21	1.81	1.97	−0.16			
3	$(CH_2)_2CONH_2$	H	H	MsO^-	−0.17	7.63	75	73	1.92	2.02	−0.10			
4	$(CH_2)_3CONH_2$	H	H	MsO^-	0.09	7.67	85	32	2.09	2.04	0.05			
5	$(CH_2)_4CONH_2$	H	H	MsO^-	0.25	(7.7)[h]	110	20	1.91	2.01	−0.10			
6	$(CH_2)_5CONH_2$	H	H	MsO^-	0.41	(7.7)	125	85	1.99	1.96	0.03			
7	$(CH_2)_6CONH_2$	H	H	MsO^-	0.58	(7.7)	110	66	1.85	1.86	−0.01			
8	$(CH_2)_7CONH_2$	H	H	MsO^-	0.68	(7.7)	120	105	1.72	1.79	−0.07			
9	$(CH_2)_8CONH_2$	H	H	MsO^-	0.77	(7.7)	60		1.40	1.71	−0.31			
10	$NHSO_2CH_3$	H	H	Cl^-	0.00	7.19	66	15	2.12	2.06	0.06			
11	$NHSO_2CH_2CH_3$	H	H	Cl^-	0.25	7.19	330	30	1.99	2.01	−0.02			
12	$NHSO_2(CH_2)_2CH_3$	H	H	Cl^-	0.43	7.20	350	70	1.91	1.95	−0.04			
13	$NHSO_2(CH_2)_3CH_3$	H	H	Cl^-	0.56	7.18	350	90	1.82	1.87	−0.05			
14	$NHSO_2(CH_2)_4CH_3$	H	H	Cl^-	0.66	7.19	70	50	1.74	1.80	−0.06			
15	$NHSO_2(CH_2)_5CH_3$	H	H	Cl^-	0.75	7.17	120		1.54	1.73	−0.19			
16	$NHSO_2CH_3$	H	3-$NHCOCH_3$	MsO^-	−0.12	7.34	19	0.5	2.16	2.03	0.13			
17	$NHSO_2CH_2CH_3$	H	3-$NHCOCH_3$	MsO^-	0.10	7.35	28	1.2	2.06	2.04	0.02			
18	$NHSO_2(CH_2)_2CH_3$	H	3-$NHCOCH_3$	MsO^-	0.30	7.33	33	1.7	2.06	2.00	0.06			
19	$NHSO_2(CH_2)_3CH_3$	H	3-$NHCOCH_3$	MsO^-	0.46	7.32	39	2.3	1.92	1.93	−0.01			
20	$NHSO_2(CH_2)_4CH_3$	H	3-$NHCOCH_3$	MsO^-	0.59	7.35	40	11.4	1.78	1.85	−0.07			
21	$NHSO_2(CH_2)_5CH_3$	H	3-$NHCOCH_3$	MsO^-	0.70	7.34	21	18	1.63	1.77	−0.14			
22	$NHSO_2CH_3$	OCH_3	H	MsO^-	0.18	7.34	9.0	2.5	2.05	2.03	0.02	5.29	5.37	−0.08
23	$NHSO_2CH_2CH_3$	OCH_3	H	MsO^-	0.38	7.40	10.5	2.7	1.95	1.97	−0.02	5.27	5.13	0.13
24	$NHSO_2(CH_2)_2CH_3$	OCH_3	H	MsO^-	0.53	7.41	28	7.8	1.91	1.89	0.02	4.82	4.89	−0.07
25	$NHSO_2(CH_2)_3CH_3$	OCH_3	H	MsO^-	0.62	7.41	71	17.1	1.89	1.84	0.05	4.49	4.70	−0.21
26	$NHSO_2(CH_2)_4CH_3$	OCH_3	H	MsO^-	0.68	7.39	37	18.0	1.81	1.79	0.02	4.48	4.57	−0.09
27	$NHSO_2(CH_2)_5CH_3$	OCH_3	H	MsO^-	0.75	7.42	56	17.4	1.83	1.73	0.10	4.51	4.40	0.11
28	$NHSO_2(CH_2)_6CH_3$	OCH_3	H	MsO^-	0.80	7.42	85	33.4	1.76	1.69	0.07	4.24	4.27	−0.03
29	$NHSO_2(CH_2)_7CH_3$	OCH_3	H	MsO^-	0.83	7.44	45	45	1.60	1.66	−0.06	4.12	4.19	−0.07
30	$NHSO_2CH_3$	OCH_3	3-$NHCOCH_3$	Cl^-	0.07	7.56	22.5	0.5	2.08	2.04	0.04	5.98	5.68	0.30
31	$NHSO_2CH_2CH_3$	OCH_3	3-$NHCOCH_3$	Cl^-	0.30	7.54	14.5	1.0	2.00	2.00	0.00	5.70	5.48	0.22
32	$NHSO_2(CH_2)_2CH_3$	OCH_3	3-$NHCOCH_3$	Cl^-	0.48	7.57	14	2.2	1.93	1.92	0.01	5.37	5.21	0.16
33	$NHSO_2(CH_2)_3CH_3$	OCH_3	3-$NHCOCH_3$	Cl^-	0.56	7.56	22	6.2	1.97	1.88	0.09	4.93	5.06	−0.13
34	$NHSO_2(CH_2)_4CH_3$	OCH_3	3-$NHCOCH_3$	Cl^-	0.62	7.54	85	12.8	1.87	1.84	0.03	4.63	4.93	−0.30
35	$NHSO_2(CH_2)_5CH_3$	OCH_3	3-$NHCOCH_3$	Cl^-	0.70	7.54	35	15	1.84	1.77	0.07	4.57	4.75	−0.18
36	$NHSO_2(CH_2)_6CH_3$	OCH_3	3-$NHCOCH_3$	Cl^-	0.75	7.55	28	15	1.83	1.73	0.10	4.58	4.63	−0.05
37	$NHSO_2CH_3$	OCH_3	4-OCH_3	Cl^-	0.19	7.39	10	2.1	2.04	2.03	0.01	5.34	5.37	−0.03

38	$NHSO_2CH_2CH_3$	OCH_3	4-OCH_3	Cl^-	0.43	7.36	14	5.0	1.94	1.95	−0.01	4.98	5.07	−0.09
39	$NHSO_2(CH_2)_2CH_3$	OCH_3	4-OCH_3	Cl^-	0.63	7.38	24	5.0	1.96	1.83	0.13	4.99	4.69	0.30
40	$NHSO_2(CH_2)_3CH_3$	OCH_3	4-OCH_3	Cl^-	0.80	7.35	36	8.6	1.80	1.69	0.11	4.77	4.28	0.49
41	$NHSO_2CH_3$	OCH_3	4-OCH_2CH_3	Cl^-	0.43	7.37	27	7.5	2.01	1.95	0.06	4.79	5.07	−0.28
42	$NHSO_2CH_3$	OCH_3	4-$O(CH_2)_2CH_3$	Cl^-	0.58	7.36	22	8.0	1.97	1.86	0.11	4.79	4.80	−0.01
43	$NHSO_2CH_3$	OCH_3	4-$O(CH_2)_3CH_3$	Cl^-	0.68	7.34	36	11.4	1.90	1.79	0.11	4.64	4.58	0.06
44	$NHSO_2CH_3$	OCH_3	4-$O(CH_2)_2OH$	Cl^-	0.10	7.36	12	1.9	2.02	2.04	−0.02	5.41	5.44	−0.03
45	$NHSO_2CH_3$	OCH_3	4-$OCH_2CHOHCH_2OH$	Cl^-	−0.09	7.00	23	1.3	2.11	2.04	−0.07	5.60	5.51	0.09
46	$NHSO_2CH_3$	OCH_3	4-$OCH_2CONHCH_3$	Cl^-	−0.02	7.35	500	1.6	2.04	2.04	0.00	5.51	5.49	0.02
47	$NHSO_2CH_3$	OCH_3	4-$O(CH_2)_3CONH_2$	Cl^-	−0.15	7.36	25	2.9	2.05	2.03	0.02	5.26	5.50	−0.24
48	$NHSO_2CH_3$	OCH_3	4-aza[i]	Cl^-	−0.07	6.09	70	16.6	1.97	2.04	−0.07	4.41	4.52	−0.11
49	$NHSO_2CH_2CH_3$	OCH_3	4-aza	Cl^-	0.17	6.07	71	24.3	2.00	2.03	−0.03	4.26	4.41	−0.15
50	$NHSO_2(CH_2)_2CH_3$	OCH_3	4-aza	Cl^-	0.37	6.04	130	47.7	1.99	1.97	0.02	3.98	4.18	−0.20
51	$NHSO_2(CH_2)_3CH_3$	OCH_3	4-aza	Cl^-	0.54	6.06	125	41.8	1.93	1.89	0.04	4.05	3.90	0.15
52	$NHSO_2(CH_2)_4CH_3$	OCH_3	4-aza	Cl^-	0.64	6.05	88	43.6	1.89	1.82	0.07	4.04	3.69	0.35
53	$NHSO_2(CH_2)_5CH_3$	OCH_3	4-aza	Cl^-	0.74	6.03	400	197	1.75	1.74	0.01	3.40	3.45	−0.05
54	$NHSO_2(CH_2)_6CH_3$	OCH_3	4-aza	Cl^-	0.81	6.04	400		1.54	1.68	−0.14		3.27	
55	$NHSO_2CH_3$	OCH_3	3-NO_2	Cl^-	0.10	5.72	3.2	0.3	1.83	2.11	−0.23	6.20[j]	4.69	1.51
56	$NHSO_2CH_2CH_3$	OCH_3	3-NO_2	Cl^-	0.34	5.70	9.1	0.8	1.98	2.06	−0.08	5.75[j]	4.46	1.29
57	$NHSO_2(CH_2)_2CH_3$	OCH_3	3-NO_2	Cl^-	0.55	5.69	56	3.1	1.97	1.96	0.01	5.18[j]	4.11	1.07
58	$NHSO_2(CH_2)_3CH_3$	OCH_3	3-NO_2	Cl^-	0.70	5.71	50	5.0	1.93	1.85	0.08	4.98[j]	3.78	1.20
59	$NHSO_2(CH_2)_4CH_3$	OCH_3	3-NO_2	Cl^-	0.78	5.69	50	19.4	1.86	1.79	0.07	4.44[j]	3.58	0.86
60	$NHSO_2(CH_2)_5CH_3$	OCH_3	3-NO_2	Cl^-	0.83	5.70	130	105	1.87	1.74	0.13	3.72[j]	3.45	0.27
61	$NHSO_2(CH_2)_6CH_3$	OCH_3	3-NO_2	Cl^-	0.89	5.69	200	150	1.74	1.69	0.05	3.57[j]	3.26	0.31
62	$NHSO_2CH_3$	OCH_3	4-$CONH_2$	Cl^-	−0.27	6.37	42	10.8	2.05	2.08	−0.03	4.65	4.81	−0.16
63	$NHSO_2CH_2CH_3$	OCH_3	4-$CONH_2$	Cl^-	0.00	6.35	22	4.5	2.22	2.13	0.09	5.04	4.83	0.21
64	$NHSO_2(CH_2)_2CH_3$	OCH_3	4-$CONH_2$	Cl^-	0.22	6.35	35	7.8	2.08	2.10	−0.02	4.81	4.68	0.13
65	$NHSO_2(CH_2)_3CH_3$	OCH_3	4-$CONH_2$	Cl^-	0.39	6.34	130	17.8	2.04	2.05	−0.01	4.47	4.47	0.00
66	$NHSO_2(CH_2)_4CH_3$	OCH_3	4-$CONH_2$	Cl^-	0.49	6.36	110	37.5	1.97	1.99	−0.02	4.15	4.31	−0.16
67	$NHSO_2(CH_2)_5CH_3$	OCH_3	4-$CONH_2$	Cl^-	0.58	6.33	170	51.9	1.94	1.94	0.00	4.02	4.13	−0.11
68	$NHSO_2(CH_2)_6CH_3$	OCH_3	4-$CONH_2$	Cl^-	0.65	6.33	350	100	1.89	1.89	0.00	3.75	3.98	−0.23
69	$NHSO_2CH_3$	OCH_3	4-CONHZ[k]	Cl^-	−0.55	6.35	200	18.5	1.95	1.94	0.01	4.55	4.57	−0.02
70	$NHSO_2(CH_2)_2CH_3$	OCH_3	4-CONHZ[k]	Cl^-	−0.10	6.35	500	34.5	2.21	2.18	0.03	4.29	4.84	−0.55
71	$NHSO_2CH_3$	OCH_3	4-$CONH(CH_2)_3CH_3$	Cl^-	0.47	6.36	58	22.4	1.98	2.01	−0.03	4.38	4.34	0.04
72	$NHSO_2(CH_2)_2CH_3$	OCH_3	4-$CONH(CH_2)_3CH_3$	Cl^-	0.70	6.35	150	57	1.84	1.93	−0.09	3.99	3.87	0.12
73	$NHSO_2(CH_2)_4CH_3$	OCH_3	4-$CONH(CH_2)_3CH_3$	Cl^-	0.76	6.36	300	275	1.65	1.81	−0.16	3.33	3.72	−0.39
74	$NHSO_2CH_3$	OCH_3	4-$CONHCH_3$	Cl^-	0.06	6.36	9.5	2.9	2.13	2.12	0.01	5.23	4.80	0.43
75	$NHSO_2CH_3$	OCH_3	4-$CON(CH_3)_2$	Cl^-	0.09	6.16	24	9.1	2.09	2.12	0.03	4.75	4.78	−0.03
76	$NHSO_2CH_3$	OCH_3	4-$CONHCH_2CONH_2$	Cl^-	−0.50	6.18	95	11.7	1.99	1.97	0.02	4.66	4.63	0.03
77	$NHSO_2CH_3$	OCH_3	4-$CONHCH_2CONHCH_3$	Cl^-	−0.29	6.20	120	2.1	2.25	2.07	0.18	5.41	4.80	0.61
78	$NHSO_2CH_3$	OCH_3	4-$CONHCH_2CHOHCH_2OH$	Cl^-	−0.36	6.34	115	16.5	1.92	2.04	−0.12	4.52	4.76	−0.24
79	$NHSO_2CH_3$	OCH_3	4-$CONH(CH_2)_6OSO_2CH_3$	Cl^-	0.68	6.35	230	30	1.84	1.87	−0.03	4.25	3.92	0.33

[a] Counterion in the salt form employed in screening. [b] R_m; measure of agent lipophilic–hydrophilic balance from reverse-phase chromatography; see ref 11. [c] pK_a; acridine ionization constant determined UV spectrophotometrically in 20% DMF–H_2O; see ref 6. [d] LD_{10}; drug dose in (mg/kg)/day proving lethal to 10% of animals, determined by the methods of ref 11. [e] D_{40}; dose in (mg/kg)/day providing 40% extension of life in L1210 assays; see ref 11. [f] ILS_{max}; maximum increase in life span in L1210 tests. Observed values (obsd) determined as discussed in the text and ref 11. Calculated figures (calcd) are derived from eq 13. [g] D_{40} for these values are quoted in molar quantities. Calculated values are derived from eq 16. [h] pK_a values in parentheses are assumed on the basis of preceding examples. [i] 4-aza; carbon-4 of the acridine ring replaced by -N=. [j] Values for these nitro compounds not employed in deriving eq 16. [k] -CONHZ; amide derived from α-methyl-D-glucosaminide; see ref 5.

afforded the methanesulfonic ester **79**.

Approach Plan. When the desired end point of a QSAR study is the development of more tumor-selective agents, the input measure of biologic activity employed should reflect this aim. As before,[11] we have employed as a measure of such selectivity the percentage increase in life span of leukemic (L1210) mice at a constant level of toxicity (LD_{10}) to the animals. From a full dose profile of activity, ILS_{max}, the increase in life span seen at the measured LD_{10} dose has been obtained from the linear correlation between significant life extensions observed and the logarithms of the corresponding doses.[11] Also available from such correlations are the dose necessary to provide a standard response of 40% ILS (D_{40}) and the derived chemotherapeutic index ($CI = LD_{10}/D_{40}$). Earlier,[12] an examination of a cross-correlation matrix between these variables, for a series of antileukemic bisquaternary ammonium heterocycles, showed that both ILS_{max} and CI can be considered as measures of antitumor selectivity effectively divorced from drug toxicity, as modeled by the LD_{10} values. In contrast, D_{40} is a composite measure highly inversely correlated with toxicity (LD_{10}) and directly with ILS_{max}.[12] A correlation matrix for these various measures for the 78 agents considered in this paper shows an extremely similar situation (Table III), even though the two classes of compound are structurally dissimilar.

While second-generation agents should clearly be as tumor-selective as possible, it is also necessary that they be dose potent, so that it is practical to administer optimum effective doses and these can be satisfactorily formulated. Development of the most desirable agent, in contrast to the most active, then requires that measures of both dose potency (D_{40}) and selectivity (ILS_{max}) be optimized. Both these measures have been modeled in the studies that follow.

Agent lipophilic–hydrophilic balance has been measured as R_m values of agent cations in a reverse-phase partition chromatographic system.[11] For a standard series of chemicals of known log P (1-octanol/H_2O) values (range −2.92–1.64), there was a linear relationship with R_m values measured in this system (eq 1).[11] A consequence of ad-

$$\log P = 2.00(\pm 0.15)R_m + 0.51(\pm 0.10) \quad (1)$$

$$n = 21,\ r = 0.99,\ s = 0.21,\ F_{1,19} = 678$$

ditivity of measures of log P is that the partition properties of neutral and cationic drug species, within a series of closely related agents, will be simply related (eq 2). R_m

$$R_m \text{ (neutral drug)} = R_m \text{ (cation)} + \text{a constant} \quad (2)$$

values measured for cationic species then provide a relative measure of those for the neutral form of the agents.

In considering partition-dependent movement of drugs to sites providing antitumor action and dose-limiting toxicity, three major effects of ionization can be envisaged: (1) Movement is responsive to measures of log P for the neutral species alone. In this case, biologic activity should then correlate directly with R_m values. (2) Drug migration is a function of log P for the neutral species, but allowance must be made for the varying levels of neutral species as a result of drug ionization. Scherrer and Howard[13] have examined the consequences of such effects and show many experimental results are better fitted by regression equations employing a modified partition parameter (log D) such that:

$$\log D = \log P + C_D \quad (3)$$

Scrutiny of the "correction for dissociation" factor C_D shows that this is, in fact, log $(1 - \alpha)$, where α is the fraction of drug ionized at the biologically pertinent pH. Equation 3 can thus be rewritten as eq 4. Taking account of the

$$\log D = \log P + \log (1 - \alpha) \quad (4)$$

nature of the correlation equations, employing linear combinations of logarithmic terms, acceptable measures of such ionization corrected values in the present study would then be eq 5. (3) Access of agent cation to a membrane carrier,

$$R_n = R_m + \log (1 - \alpha) \quad (5)$$

or a particular site, is rate limiting. As in our earlier study[10] with tumor-active dialkanolamine dialkanesulfonate esters, it can be shown that measured R_m values should then be modified by a log α term. Denoting such corrected R_m values as R_c values, as before,[10] gives eq 6. To examine

$$R_c = R_m + \log \alpha \quad (6)$$

the possible importance of effects 1–3, trial regression analyses should then employ R_m, R_n, and R_c values. In such studies the various R values are examined as independent variables. Importantly, if it could be unequivocally demonstrated that only one of these measures was acceptable then, in future studies, these values would be measurable quantities and examination of the role of a greater number of independent variables thereby permitted.

Scrutiny of these various R measures suggests that they probably afford very crude approximations to those applicable in vivo. Agent dissociation constants are usually measured in aqueous media, and changes in ionization constants within in vivo lipoidal regions, of markedly different dielectric constant, are ignored. It is also generally assumed, as in this work, that the operative physiological pH by which α values are calculated is close to 7 and that this remains the same intra- and extracellularly. Additionally, there may be some combination of effects 1–3 operative in the biologic test system. Despite these shortcomings, a necessary first step is to examine whether one of R_m, R_n, or R_c is better able to accommodate variance of the biologic data. Because of the failure of usual retrospective methods of QSAR, it was planned to limit the variables influencing biologic activity by screening homologous series of alkanesulfonanilide cogeners with each such series bearing a different pK_a-modulating acridine substituent. From existing examples, a close to parabolic relationship between R_m, R_n, or R_c would be expected for members of any single homologous series, if these vary only in lipophilic–hydrophilic balance. However, successful merging of screening results from two homologous series, when these have different base strengths of the core-substituted acridine, might demonstrate if a particular measure of R was preferable.

It would also have been desirable to examine if the alternative biphasic equations in log P proposed by Kubinyi[14] were preferable to the usually considered parabolic relationships. However, the difficulties in fitting data by iterative nonlinear regression require that the upwards and downwards slopes of the curves be fitted separately,[15] and this demands adequate numbers of data points on both sides of the optimum R_m value. In the present series, it proved impossible to generate sufficient numbers of hydrophilic compounds to satisfy this requirement.

Modeling Drug–Tumor Selectivity (ILS_{max}). The first group of compounds examined, **2**–**47**, comprise six different homologous series (Table I). Preliminary calculations showed the expected parabolic-type relationship between log (ILS_{max}) and lipophilic/hydrophilic balance within each series, although with so few examples in each the relationship was seldom highly significant. Most of

Table II. Analytical Details for Previously Unreported Compounds

no.	mp, °C	formula	anal.[a]
34	212–214	$C_{27}H_{30}N_4O_4S\cdot HCl$	C, H, N, S
35	195 dec	$C_{28}H_{32}N_4O_4S\cdot HCl\cdot 2H_2O$	C, H, N, S
36	182–184	$C_{29}H_{34}N_4O_4S\cdot HCl\cdot 2H_2O$	C, H, N, S
37	234–235	$C_{22}H_{21}N_3O_4S\cdot HCl\cdot H_2O$	C, H, N
38	190–192	$C_{23}H_{23}N_3O_4S\cdot HCl\cdot H_2O$	C, H, N, Cl
39	270–271	$C_{24}H_{25}N_3O_4S\cdot HCl$	C, H, N, Cl
40	269–270	$C_{25}H_{27}N_3O_4S\cdot HCl$	C, H, N, Cl
41	254–256	$C_{23}H_{23}N_3O_4S\cdot HCl$	C, H, N, Cl
42	172–175	$C_{24}H_{25}N_3O_4S\cdot HCl$	C, H, N
43	196–197	$C_{25}H_{26}N_3O_4S\cdot HCl\cdot 0.5H_2O$	C, H, N
46	277 dec	$C_{24}H_{24}N_4O_5S\cdot HCl$	C, H, N, Cl
47	252–254	$C_{25}H_{26}N_4O_5S\cdot HCl$	C, H, N
49	257–258	$C_{21}H_{20}N_4O_3S\cdot HCl$	C, H, N, Cl
50	222–224	$C_{22}H_{22}N_4O_3S\cdot HCl$	C, H, N, Cl
51	192–194	$C_{23}H_{24}N_4O_3S\cdot HCl\cdot 2H_2O$	C, H, N, Cl
52	255–257	$C_{24}H_{26}N_4O_3S\cdot HCl$	C, H, N, Cl
53	230–233	$C_{25}H_{28}N_4O_3S\cdot HCl\cdot 0.5H_2O$	C, H, N, Cl
54	114–115	$C_{26}H_{30}N_4O_3S\cdot HCl$	C, H, N, Cl
59	276–277	$C_{25}H_{26}N_4O_5S\cdot HCl$	C, H, N, Cl
60	271–272	$C_{26}H_{28}N_4O_5S\cdot HCl$	C, H, N, Cl
61	245–247	$C_{27}H_{30}N_4O_5S\cdot HCl$	C, H, N, Cl
63	252–253	$C_{23}H_{22}N_4O_4S\cdot HCl\cdot H_2O$	C, H, N, Cl
64	289–290	$C_{24}H_{24}N_4O_4S\cdot HCl$	C, H, N, Cl
65	276–278	$C_{25}H_{26}N_4O_4S\cdot HCl$	C, H, N, Cl
66	267–268	$C_{26}H_{28}N_4O_4S\cdot HCl$	C, H, N, Cl
67	174–178	$C_{27}H_{30}N_4O_4S\cdot HCl$	C, H, N, Cl
68	153–155	$C_{27}H_{30}N_4O_4S\cdot HCl$	C, H, N, Cl
69	253–254	$C_{28}H_{32}N_4O_4S\cdot HCl$	C, H, N, Cl
72	158–159	$C_{28}H_{32}N_4O_4S\cdot HCl$	C, H, N, Cl
73	261–262	$C_{30}H_{36}N_4O_4S\cdot HCl\cdot H_2O$	C, H, N, Cl
77	278 dec	$C_{25}H_{25}N_5O_5S\cdot HCl$	C, H, N, Cl
79	66–67	$C_{29}H_{34}N_4O_7S_2\cdot HCl\cdot 0.5H_2O$	C, H, N, S

[a] Analyses for the indicated elements were within ±0.4% of the theoretical figures for the formula provided.

the compounds proved too lipophilic for optimum activity, so advantage was taken of the previously noted[5] bulk tolerance about the 4 position in this class of compound to prepare a small number of sterically demanding but more hydrophilic 4-*O*-alkyl congeners, **44–47**. The activities of these compounds fitted well into the preliminary equation derived for the 4-*O*-alkyl homologous series, **37–43**, confirming the bulk tolerance in this position. All of these compounds possess similar pK_a values (7.2–7.6), and thus little difference in utility between the three alternative measures of agent lipophilic/hydrophilic balance was seen (eq 7–9). It is interesting to note that ILS_{max} is virtually

$$\log (ILS_{max}) = -0.75(\pm 0.25)R_m^2 + 0.13(\pm 0.11)R_m + 2.05 \quad (7)$$

$n = 46$, $r = 0.83$, $s = 0.09$, $F_{2,43} = 48.4$, $R_m(\text{optimum}) = 0.19$

$$\log (ILS_{max}) = 0.73(\pm 0.27)R_c^2 + 2.07 \quad (8)$$

$n = 46$, $r = 0.80$, $s = 0.09$, $F_{1,44} = 49.0$, $R_c(\text{optimum}) = 0.0$

$$\log (ILS_{max}) = 1.21(\pm 0.34)R_n^2 - 0.62(\pm 0.23)R_n + 1.46 \quad (9)$$

$n = 46$, $r = 0.80$, $s = 0.09$, $F_{2,43} = 40.7$, $R_n(\text{optimum}) = -0.26$

invariant with compound structure and is dependent almost totally on lipophilic/hydrophilic balance. Calculations were carried out using indicator variables for the different acridine substituents to gauge their effects on tumor selectivity, but the coefficients of these terms were never significant.

To enable a decision to be made between the three alternate measures of lipophilic/hydrophilic balance, three

Table III. Cross-correlation Matrix (r Matrix) for the Biologic Parameters Examined

	log ($1/D_{40}$)	log (CI)	log (LD_{10})
log (ILS_{max})	0.52	0.59	−0.19
log ($1/D_{40}$)		0.69	−0.74
log (CI)			−0.04

further homologous series were examined whose members possessed pK_a values appreciably different from those of compounds **2–47**. The average pK_a for the 4-aza analogues **48–54** was approximately 6.05.

The 3-nitro analogues **55–61** similarly have low pK_a values. Further, the apparently divergent screening results obtained with certain nitro-containing examples[6] provided one reason for initiating this study. Earlier,[7] a series of isomeric aza analogues (cf. **48–54**) were prepared to ascertain if low pK_a materials would retain antitumor activity. The activity of the aza series,[7] of comparable pK_a values to the nitro examples, shows that it is not necessary to postulate obligatory reduction of the weakly basic nitro compounds to higher pK_a materials in order that antileukemic activity be observed.

The remaining compounds examined were a series of 4-CONRR′ congeners (**62–79**) with pK_a values (average 6.35) intermediate between the nitro-substituted congeners and the 4-aza compounds. The available bulk tolerance about the acridine 4 position permitted the use of groups as bulky as glucosaminide (**69** and **70**), markedly extending the available range of R_m values. Initial calculations showed that compounds **69–79** possessed levels of activity well predicted by equations derived from the 4-$CONH_2$ homologous series **62–68** and, accordingly, all compounds (**62–79**) were considered together.

Inclusion of the more weakly basic compounds (**48–79**) into the calculations provided no useful modeling of ILS_{max} in terms of R_n. Equations 10 and 11 were developed for the other measures of lipophilic/hydrophilic balance.

$$\log (ILS_{max}) = -0.55(\pm 0.12)R_m^2 + 2.07 \quad (10)$$

$n = 78$, $r = 0.79$, $s = 0.10$, $F_{1,76} = 132.1$, $R_m(\text{optimum}) = 0.0$

$$\log (ILS_{max}) = -0.25(\pm 0.12)R_c^2 - 0.19(\pm 0.06)R_c + 2.10 \quad (11)$$

$n = 78$, $r = 0.67$, $s = 0.12$, $F_{2,75} = 30.9$, $R_c(\text{optimum}) = -0.38$

Of these two equations, that in R_m does include significantly more of the variance of the biologic data. The equation could be further improved by the use of indicator variables for the 3-NO_2 series **55–61** and the 4-CONHR compounds **62–79** but not for the 4-aza compounds **48–54**. Using $I' = 1$ for the 3-NO_2 compounds and $I'' = 1$ for the 4-CONHR series gave eq 12. The coefficients for the two

$$\log (ILS_{max}) = -0.55(\pm 0.99)R_m^2 + 0.08(\pm 0.07)I' + 0.08(\pm 0.05)I'' + 2.05 \quad (12)$$

$n = 78$, $r = 0.83$, $s = 0.09$, $F_{3,75} = 54.6$, $R_m(\text{optimum}) = 0.0$

indicator variables are identical, and a simpler equation (eq 13) results on combining these two terms. This equa-

$$\log (ILS_{max}) = -0.55(\pm 0.08)R_m^2 + 0.08(\pm 0.04)I + 2.05 \quad (13)$$

$n = 78$, $r = 0.83$, $s = 0.09$, $F_{2,75} = 82.9$, $R_m(\text{optimum}) = 0.0$

Table IV. Stepwise Development of Multivariable Equations Used for Calculation of Residuals in Table I

eq. no.	intercept	R_m^2	I	log $t_{1/2}$	R_m	r	s	$F_{1,x}$[a]
13	2.07	-0.55				0.79	0.10	132 (76)
	2.05	-0.55	0.08			0.83	0.09	12.9 (75)
16	5.08	-1.61						25.8 (48)
	4.49	-1.91		0.89				13.4 (47)
	4.46	-1.47		0.91	-0.34	0.92	0.23	5.6 (46)

[a] $F_{1,x}$ is the F statistic for introduction of each single variable, with the degrees of freedom (x) in parentheses.

tion provides a reasonable summary of the tumor selectivity of all the compounds in the data base of Table I and has been used to quote the residuals quoted therein. Equation 13, embracing as it does results from nine different homologous series of 9-anilinoacridines, emphasizes the invariance of tumor selectivity (ILS_{max}) with structure for this class of compound. If the 3-NO_2 series are considered as anomalous due to their concomitant in vivo reduction, then only the 4-CONHR groups on the acridine nucleus provide a real increase in tumor selectivity over and above their contribution to lipophilic/hydrophilic balance.

Modeling Dose Potency (D_{40}). As shown in Table III, the D_{40} dose is related to toxicity (LD_{10}), and the latter is notoriously difficult to model because of varying routes of degradation of compounds with different structures. It was found that if attention was restricted to a series of close structural relatives then effective modeling of the dose potency of these was possible. The limited group considered (**22–79**) contains only close structural homologues which are acridine-substituted *m*-AMSA derivatives. Preliminary calculations showed that, as with modeling ILS_{max}, the use of R_n as a measure of lipophilic/hydrophilic balance lead to nonsignificant correlations, and this parameter need not be further considered. It was apparent that R_m and R_c were of equal utility for the group of compounds considered in Table I. Since these essentially cover the range of pK_a values of interest with this class of antitumor agent and remembering the earlier results obtained with modeling ILS_{max}, there seems little need to consider pK_a corrections for measures of lipophilic/hydrophilic balance in future work. The use of unmodified R_m values appears adequate for QSAR studies with this class of antitumor agent.

Calculations employing R_m values for all the *m*-AMSA derivatives showed that while D_{40} data for each individual homologous series were related in a parabolic fashion to lipophilic/hydrophilic balance it was also very dependent on agent structure. Attempted development of an overall regression equation in R_m for the full data base for **22–79** should clearly take cognisance of the individual effects of each acridine substituent and a resulting seven-variable equation would then be expected. If such an equation could be acceptably derived, it would provide an effective summary of the data but no satisfactory explanation of the essential drug properties which modulate dose potency. A preferable approach would be to investigate the way in which the indicator variable coefficients, associated with the different acridine substituents, correlate with the physicochemical parameters of these. Attempted development of an overall equation with usually employed electronic, hydrophobic, or steric parameters, for the substituents used, were unsuccessful. However, it has been shown that a major route of drug breakdown for *m*-AMSA in vivo is a nonenzymatically mediated chemical attack by thiols which provides thiolytic removal of the essential 9-methanesulfonanilide function.[16-18] With the view that such a reaction will modify available drug levels and could therefore influence dose potency, trial regressions using measures of drug thiolytic susceptibility were attempted. The measures employed were the half-lives ($t_{1/2}$) of the agents in the presence of excess mercaptoethanol and, under such conditions, reactions were of pseudo-first-order kinetics. $t_{1/2}$ will then be proportional to rate of reaction and log $t_{1/2}$ a suitable parameter for incorporation into linear, free-energy based regression equations. For compounds **22–79**, binomial regression equations in R_m alone (eq 14) were of low standard. Further inclusion of log $t_{1/2}$,

$$\log (1/D_{40}) = -1.75(\pm 0.56)R_m^2 + 5.17 \quad (14)$$

$$n = 57,\ r = 0.63,\ s = 0.49,\ F_{1,55} = 36.3$$

as an additional variable, provided a significant improvement (eq 15). However, a considerably superior equation

$$\log (1/D_{40}) = -1.80(\pm 0.46)R_m^2 + 0.63(\pm 0.22) \log(t_{1/2}) + 4.74 \quad (15)$$

$$n = 57,\ r = 0.78,\ s = 0.40,\ F_{2,54} = 43.0$$

resulted when data for the discordant 3-nitro derivatives (**55–61**) was deleted (eq 16). Equation 16 was used to

compounds **22–54** and **62–79**

$$\log (1/D_{40}) = -1.47(\pm 0.48)R_m^2 - 0.34(\pm 0.28)R_m + 0.91(\pm 0.15) \log (t_{1/2}) + 4.46 \quad (16)$$

$$n = 50,\ r = 0.92,\ s = 0.23,\ F_{3,46} = 83.7$$

calculate the residuals for log $(1/D_{40})$ shown in Table I.

As shown in Table III, there is relatively high correlation between $1/D_{40}$ and LD_{10} prompting attempted modeling of the latter using these same variables of R_m, R_m^2, and $t_{1/2}$. In this case, a relatively poor equation resulted for the range of agents **22–79**, even with exclusion of the 3-nitro compounds (eq 17).

compounds **22–54** and **62–79**

$$\log (LD_{10}) = -0.33(\pm 0.70)R_m^2 - 0.66(\pm 0.40)R_m + 0.29(\pm 0.21) \log (t_{1/2}) + 3.75 \quad (17)$$

$$n = 50,\ r = 0.66,\ s = 0.33,\ F_{3,46} = 11.7$$

While the equation for D_{40} employing $t_{1/2}$ as a variable (eq 16) fits well to the data, it must be emphasized that only five different values of $t_{1/2}$ have been employed, each corresponding to one of the different substituted acridine nuclei used. Such meager data must clearly be viewed with caution. In fact, in this limited series there is high covariance between $t_{1/2}$ and acridine pK_a values (eq 18). Sub-

$$\log t_{1/2} = 0.66(\pm 0.20)pK_a - 3.71 \quad (18)$$

$$n = 6,\ r = 0.85,\ s = 0.18,\ F_{1,4} = 41.0$$

stitution of pK_a values for $t_{1/2}$ in eq 16 provides, as expected, a comparably well-fit equation (eq 19). As found

compounds **22–54** and **62–79**

$$\log (1/D_{40}) = -1.40(\pm 0.53)R_m^2 - 0.42(\pm 0.31)R_m + 0.71(\pm 0.12)pK_a + 0.39 \quad (19)$$

$$n = 50,\ r = 0.91,\ s = 0.25,\ F_{3,46} = 67.9$$

earlier, further inclusion of the data for the 3-nitro compounds **55–61** (cf. eq 16) into the latter equation provided a much inferior correlation.

Discussion

Within each homologous series of 9-anilinoacridines the major altering variable is presumably agent lipophilic–hydrophilic balance. Parabolic relationships between measures of the latter, and those for biologic activity, provide quite acceptable regression equations which adequately summarize such data. When computer modeling drug–tumor selectivity (ILS_{max}), employing such parabolic relationships, superior equations result if measured R_m values are employed rather than their possible pK_a-corrected counterparts. This result appears surprising, since the pK_a values of the agents chosen span the range which provides a large variation in ionization at physiological pH.

D_{40}, employed as a measure of dose–potency, is related to LD_{10} and the latter is notoriously difficult to model, possibly because of varying routes of metabolic degradation as agent structure changes. Provided consideration is restricted to those compounds which are close structural relatives, acceptable correlations for D_{40} can be obtained, even though there is a nearly 400-fold variation of this measure in the subgroup considered.

The approach method employed assists in discerning those substituents which provide clearly discordant screening results. There appears little doubt that a 3-nitro substituent should be so considered. Since the cationic character of 9-aminoacridine derivatives is normally assumed essential for various types of biologic activity, we earlier questioned[7] if the weakly basic 3-nitro analogues of this series ($pK_a = 5.72$) were active per se or whether it was the more strongly basic reduction products which were responsible for any observed tumor-inhibitory properties. Certain aza analogues are of comparable low base strengths to these compounds[7] but are highly unlikely to be reduced to more basic compounds in vivo. Since certain aza compounds proved to be tumor inhibitory (see Table I for further examples), we then concluded[7] that obligatory reduction of such nitro functions was not a prerequisite for tumor inhibition to be observed. However, 3-nitro-*m*-AMSA (**55**) does appear to suffer reduction in vivo and, in mice, a very complex mixture of derivatives is produced. While in vivo nitro-group reduction is apparently not obligatory for tumor inhibition, the observed antitumor effectiveness of such compounds may have a component which is due to the reduction products formed. Difficulties in accommodating screening results from nitro-substituted variants could be a consequence of such reduction. As an example of the effects that nitro group reduction could produce, it is instructive to compare the properties of 3-NO_2-*m*-AMSA ($\pi_{NO_2} = -0.28$; $pK_a = 5.72$; $t_{1/2} = 1.90$ min) with the final product of reduction which could result, i.e., 3-NH_2-*m*-AMSA ($\pi_{NH_2} = -1.23$; $pK_a = 9.92$; $t_{1/2} = 1285$ min). Attendant on in vivo nitro group reduction, the changes in agent log *P*, base strength, or thiolytic stability could provide discordant measures of biologic activity in relation to the physicochemical properties of the administered nitro compound.

The findings summarized above provide a firm basis for renewed approach to the problem of developing QSAR in this series of agents. Future attempts at regression analyses can incorporate the following points: (1) measured R_m values can be justifiably utilized without modification according to agent pK_a; (2) parabolic equations in R_m provide an acceptable interelationship with the measures of biologic activity D_{40} or ILS_{max}; (3) in modeling D_{40} it may be desirable or even necessary to limit the study to close structural congeners of *m*-AMSA; (4) selection of a subgroup of variants in which covariance between $t_{1/2}$ and pK_a is minimal may assist in discerning which variable is important in modulating D_{40}; (5) nitro-containing analogues can justifiably be excluded from all such studies.

Experimental Section

Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. Analyses were performed by Dr. A. D. Campbell, Microchemical Laboratory, University of Otago, Dunedin, New Zealand. Melting points were determined on an electrothermal melting point apparatus with the maker's supplied stem corrected thermometer; melting points are as read. NMR spectra were obtained on a Varian A-60 spectrometer (Me_4Si). IR spectra (KBr) were recorded using a Beckmann 237 Infracord. UV spectra were recorded on a Shimadzu UV-200.

To monitor the progress of reactions, purification of products, etc., TLC on SiO_2 (Merck SiO_2, F_{254}) was used. The partition chromatographic methods used in measuring R_m values have been described earlier.[11]

4-Hydroxy-9(10*H*)-acridone. A convenient rapid preparation of this compound, easily capable of scale-up, is as follows. A mixture of pyridine (160 mL) and 12 N HCl (180 mL) was distilled until the internal temperature reached 210 °C. After cooling the mixture to below 100 °C, 4-methoxy-9(10*H*)-acridone (24 g, 0.11 mol) was added and the mixture further distilled until the internal temperature reached 220 °C. The clear yellow solution was then well cooled, and the product precipitated by addition of H_2O (250 mL). The required phenol was freed of traces of nonphenolic contaminants by solution in H_2O (250 mL) containing KOH (13 g), clarifying, and acidification with HOAc. Following heating, to coagulate the resulting fine precipitate, TLC-homogeneous product was collected, well washed with H_2O, and dried (21.1 g, 91%). This compound crystallizes readily from DMF–H_2O, in yellow-green needles, but the relatively insoluble Na salt, necessary for subsequent reactions, is readily obtained as follows: 4-Hydroxy-9(10*H*)-acridone (20 g) was suspended in hot water (350 mL) containing NaOH (5.7 g) and the mixture was boiled with stirring until a homogeneous solution resulted. To the boiling clear solution, solid NaCl was added in small quantities until the crimson sodium salt of the phenol started to crystallize. Following thorough cooling, the red sodium salt was collected and thoroughly dried in vacuo at 110 °C (19.2 g, 87%).

4-Ethoxy-9(10*H*)-acridone. To a suspension of the sodium salt of 4-hydroxy-9(10*H*)-acridone (2.33 g, 0.01 mol) in Me_2SO (7.5 mL) ethyl bromide (1.2 g, 0.011 mol) was added, the flask was sealed, and the whole was heated at 100 °C for 1 h. The mixture was then diluted slowly with H_2O, in order to provide crude product in readily filterable form. After stirring the crude product with 5% aqueous KOH for 30 min, to remove traces of unreacted starting material, the required ether was crystallized from EtOH–H_2O until homogeneous to TLC. Pure product was obtained as yellow needles (86% yield) of mp 291–292 °C (lit.[19] mp 291–292 °C).

4-(*n*-Propyloxy)-9(10*H*)-acridone [mp 183–185 °C; yield 87%. Anal. ($C_{16}H_{15}NO_2$) C, H, N], 4-(*n*-butyloxy)-9(10*H*)-acridone [mp 204–205 °C; yield 87%. Anal. ($C_{17}H_{17}NO_2$) C, H, N], and 4-[(3-cyanopropyl)oxy]-9(10*H*)-acridone [mp 195–197 °C; yield 86%. Anal. ($C_{17}H_{14}N_2O_2$) C, H, N] were prepared by obvious extensions of the above method.

4-[9(10*H*)-Acridonyloxy]butanoic acid was prepared by hydrolysis of the corresponding nitrile (3 g) described above in boiling HOAc–12 N HCl (1:1, v/v, 35 mL) for 3 h. Crude acid, as precipitated by dilution with H_2O, was collected and stirred with excess 5% aqueous $KHCO_3$ until no further dissolved, traces of insoluble material were removed by filtration, and the product was recovered by acidification. Crystallization from EtOH–H_2O then provided TLC-homogeneous product as light yellow needles

of mp 261–262 °C (79% yield). Anal. ($C_{17}H_{15}NO_4 \cdot 0.25H_2O$) C, H, N.

79. A suspension of 4′-[9-[4-[(4-nitrophenoxy)carbonyl]-acridinyl]amino]methanesulfon-*m*-anisidide[5] (6.0 g, 0.01 mol) and 3-aminohexan-1-ol (1.5 g, 0.013 mol) in DMF (20 mL) was stirred at room temperature until a homogeneous solution resulted when Et_3N (1.8 mL, 0.014 mol) was added, and the mixture stood until TLC monitoring indicated completion of reaction (15 min). Solvent was then removed in vacuo, the product was dissolved in excess EtOAc, the resulting solution was washed with ice-cold 10% $KHCO_3$ and H_2O and dried (Na_2SO_4), and the solvent was removed. The remaining base was crystallized from 1:1 EtOH–H_2O at low temperatures. A sample of this TLC-homogeneous base was dissolved in the minimum necessary volume of hot 1 N HOAc. To the hot, clarified solution was added 0.10 volume of 20% aqueous NaCl. After thoroughly cooling the solution, the crystalline hydrochloride was collected and washed with a little ice-cold H_2O, mp 106–107 °C. Anal. ($C_{28}H_{32}N_4O_5S \cdot HCl \cdot H_2O$) C, H, N, Cl.

A solution of the foregoing base (2 g, 3.7 mmol) was prepared in refluxing pyridine (8 mL) and then thoroughly cooled in an ice–salt mixture while stirring vigorously. Methanesulfonyl chloride (0.84 g, 7.4 mmol) was then added in dropwise fashion, so the temperature remained below −5 °C. Reaction was allowed to proceed at this temperature until TLC monitoring demonstrated complete conversion of starting material to the more polar product. Light petroleum (25 mL) was then added with shaking, and the precipitated thick red gum was washed with successive quantities of light petroleum by decantation. Ice-cold EtOAc (250 mL) was then added, followed by excess cold aqueous 10% $KHCO_3$, and vigorous stirring was continued until all solids had dissolved. To the washed (H_2O) and dried (Na_2SO_4) EtOAc solution light petroleum was added until turbid, and then dry HCl was passed through the solution with ice cooling. The precipitated hydrochloride was dissolved in the minimum necessary volume of dry *n*-BuOH by stirring at room temperature and then the clarified solution was stored at refrigerator temperatures until turbid. Scratching and occasional deep-freeze cooling of a small sample finally produced seed crystals. Back seeding of the bulk solution and final cooling at −15 °C then provided TLC-homogeneous product. A further crystallization from MeOH–H_2O provided pure product as deep red crystals of mp 66–67 °C (yield 1.41 g, 61%). Anal. ($C_{29}H_{34}N_4S_2O_7 \cdot HCl \cdot 0.5H_2O$) C, H, N.

Methods of elaboration of substituted acridones to the desired products have been earlier well described.[1-8]

$t_{1/2}$ Values for Thiolytic Cleavage. Formerly,[16] half-lives for drug decay in the presence of thiol were determined in 50% MeOH–H_2O solution. In contrast, drug dissociation constants have been determined spectrophotometrically in 20% DMF–H_2O solution. To obtain $t_{1/2}$ values under conditions comparable to those used in pK_a determinations, the reaction rates assays were repeated under the following conditions. Agents were dissolved in 40% DMF–H_2O to provide 50 μM solutions. The freshly prepared buffered thiol solution contained equal volumes of 0.140 M KH_2PO_4 and 0.06 M Na_2HPO_4 and 2-mercaptoethanol to provide a 0.50 M solution. Equal volumes of temperature-equilibrated drug and thiol solutions were rapidly mixed in the cuvette of a Shimadzu UV-200 double-beam spectrophotometer having thermostated cell holders maintained at 37 ± 0.1 °C. The concentration of reagents are such that the final reaction mixture is 20% in DMF and has a pH of 7.00, as measured by a glass electrode. Absorbance (A) of the reaction mixture was monitored at an appropriate wavelength (350–500 nm) as a function of time. The slope of plots of log A against time provided values of the pseudo-first-order rate constants (k) for drug disappearance and $t_{1/2}$ values were then calculated as $0.69/k$.

Necessary values (min) recorded for this study were: **22** (Table I), 13.2; **30**, 23.6; **37**, 13.4; **48**, 1.12; **55**, 1.90; **62**, 2.52.

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Potential Antiinflammatory Compounds. 1. Antiinflammatory Phenylpiperidine Derivatives

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The syntheses of a number of amines and their derivatives, based on the phenylpiperidine nucleus, are described. Their activities on the rat paw carrageenan test are also reported. Activities comparable to that of phenylbutazone were obtained for some of the amines, notably 4-piperidino-β-methylphenethylamine.

Patent literature reports for the antiinflammatory compound fenoprofen (I, Z = CO_2H) and its close relatives have shown that antiinflammatory activity is also found in the corresponding alkanes (e.g., I, Z = Me),[1] alcohols (I, Z =

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