Potential Antitumor Agents. 36. Quantitative Relationships between Experimental Antitumor Activity, Toxicity, and Structure for the General Class of 9-Anilinoacridine Antitumor Agents

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Quantitative relationships (QSAR) have been derived between antileukemic (L1210) activity and agent physicochemical properties for 509 tumor-active members of the general class of 9-anilinoacridines. One member of this class is the clinical agent *m*-AMSA (NSC 249992). Agent hydrophobicity proved a significant but not a dominant influence on in vivo potency. The electronic properties of substituent groups proved important, but the most significant effects on drug potency were shown by the steric influence of groups placed at various positions on the 9-anilinoacridine skeleton. The results are entirely consistent with the physiologically important step in the action of these compounds being their binding to double-stranded DNA by intercalation of the acridine chromophore between the base pairs and positioning of the anilino group in the minor groove, as previously suggested. An equation was also derived for the acute toxicities of 643 derivatives of 9-anilinoacridine. This equation took a somewhat similar form to the one modeling antileukemia potency, emphasizing the usual fairly close relationship between potency and acute toxicity for antitumor agents in general. This study demonstrated the power of QSAR techniques to structure very large amounts of biological data and to allow the extraction of useful information from them bearing on the possible site of action of the compounds concerned.

A large number of derivatives of 9-anilinoacridines (I) have been prepared and tested for in vivo antitumor activity by Cain and co-workers.[1-15] While the majority of testing has employed the intraperitoneally (ip) implanted L1210 leukemia in mice, a number of the agents, particularly the 4′-(9-acridinylamino)methanesulfonanilide (AMSA) compounds, have shown a broad spectrum of action against a number of animal tumor systems. One member of this subclass, 4′-(9-acridinylamino)methanesulfon-*m*-anisidide (*m*-AMSA, NSC 249992, compound **162** in Table I), has given encouraging results in phase II clinical trials.[16]

Previous QSAR studies for in vivo antileukemic activity on subsets of the general class of 9-anilinoacridines have been published, including those for a series of 1′-alkyl acids and amides;[12] more recently, two papers have appeared[13-15] examining a large series of acridine-substituted AMSA and *m*-AMSA derivatives. The first of these[13] explored the utility of a number of modifications that have been proposed and applied[17-19] to measured values of hydrophobicity of weakly basic compounds (as the 9-anilinoacridines are) to allow for the varying degrees of ionization of such materials at physiological pH. The results[13] suggested that, over the range of pK_a values likely to be encountered among agents of this class, measured parameters such as R_m for the drug cations, determined at pH 1, could be used as an adequate measure of drug hydrophobicity, without the need of modifications to allow for the effects of varying acridine pK_a.

Relationships were subsequently shown[15] between the therapeutic potency of a series of acridine-substituted derivatives of *m*-AMSA and a number of experimentally determined drug properties, such as stability to thiolytic cleavage and binding to DNA, previously considered to be important determinants of in vivo activity. There are several measures of biological activity that can be obtained by careful testing of compounds in in vivo antitumor screens over the full dose profile from inactive to toxic.[12] For leukemia models, the most widely employed measure of in vivo antitumor activity for QSAR studies is the dose of drug needed to elicit a standard percentage increase in the lifespan (ILS) of treated, tumor-bearing animals over untreated, tumor-bearing controls. This is a measure of drug potency. A second measure of biological activity, ILS_{max} (the percentage increase in the life span of treated animals when dosed at a constant toxic load to the host, conveniently the LD_{10}), is a measure of tumor cell selectivity for the leukemia models, where the tumor growth fraction is essentially constant throughout the course of the disease and a fixed burden of tumor cells causes death.[20]

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For several series of antitumor agents of different structures, these two measures of biological activity have been shown to be essentially independent and complementary measures of the potential usefulness of antitumor agents.[13,21,22] Whereas measures of drug potency (e.g., D_{40}, the dose to achieve an ILS of 40%) are closely related to the acute toxicity of the drugs, ILS_{max} is essentially independent of such toxicity. Thus, it seems worthwhile to attempt to model both of these measures of the biological activity of antitumor compounds, for they carry complementary information essential to the drug designer. The inherently more difficult goal of modeling drug toxicity might also, if achieved, further assist in the main aim of such work, namely, the selection from a class of the most selective, rather than necessarily the most dose-potent, member.

Development of QSAR for the antitumor activity of the 9-anilinoacridines has proved a formidable task. For monosubstituted compounds there are seven nonequivalent nuclear carbon positions available for group attachment; for higher substitution, there are 12 such positions. Substituents appended to any of these positions, either in the anilino or acridine rings, have been shown to alter agent base strength.[11] It has been noted that the effect of such variations in pK_a upon measured values of hydrophobicity could be ignored for the purposes of QSAR.[13] However, the possibility of varying degrees of dependence of biological activity on the local hydrophobic, steric, and electronic effects of the substituents in each position meant that a very large number of derivatives would be needed to study QSAR in the usual way.

Initial studies have therefore utilized overall drug properties that were thought to be related to in vivo potency. It is well documented that the hydrophobicity of a compound has a major influence on its bioactivity,[23,24] and the more complex the biosystem involved the stronger this dependence becomes. In previous QSAR of the 9-anilinoacridines,[13] chromatographic R_m values for the agent cations (determined at pH 1) were used as a measure of drug hydrophobicity.

It has been shown[25-27] that the major route of breakdown for *m*-AMSA in vivo is a nonenzymatically mediated attack of thiol at the C-9 position, resulting eventually in loss of the side chain and the formation of inactive and nontoxic products. The rate of this reaction could, by influencing available drug levels in vivo, be a determinant of drug potency and toxicity. Thus, the use of log $t^{1/2}$ ($t^{1/2}$ = the half-life of agents in the presence of excess mercaptoethanol) as a parameter for modeling drug potency provided a significant reduction in variance in a study of a limited number of acridine-substituted *m*-AMSA compounds.[13] For a larger representative series of such compounds it was found[15] that log $t^{1/2}$ values were well correlated with pK_a values, in agreement with earlier observations[26] that electron-donating groups in the acridine ring confer greater stability to thiol attack.

It was clearly impractical to measure such drug properties for all members of the extensive series that have been prepared and tested. An alternative approach to modeling the antileukemic potency of all active members of the general class of 9-anilinoacridines was to use greater parameterization of the effects of groups at various positions of the 9-anilinoacridine nucleus. Although a large number of such parameters might conceivably be needed, test data had been accumulated on a very large number of congeners, and the rang of potencies shown by this data set was extraordinarily large for in vivo antitumor activity (over 3000-fold). Development of QSAR in this way might enable a picture to be built up of the structural features needed for antitumor activity in compounds of this general class, of which the *m*-AMSA derivatives form such an interesting subset. Accordingly, this paper considers the entire data base of 9-anilinoacridine congeners for which adequate biological data were available. This consisted of 535 tumor-active compounds, together with a further 241 materials which were tested but found to be inactive against the L1210 leukemia.

Chemistry. Preparation of the new agents listed in Table I followed the general procedures detailed earlier.[1-3,8-10] Jourdan–Ullmann condensation of an appropriate 2-chlorobenzoic acid and an aromatic amine gave an *N*-arylanthranilic acid. Ring closure was effected in many cases with $POCl_3$ to provide a 9-chloroacridine directly, which was then coupled with the appropriate aryl amide side chain to provide the new agents, for which physical data are given in Table IV. Where closure of the *N*-arylanthranilic acid with $POCl_3$ was not desirable, this was effected with either H_2SO_4, PPA, or PPE to give the 9-(10*H*)-acridanone. In cases where acid-labile groups were present, the use of PPE proved a new and very useful method for the ring closure of *N*-arylanthranilic acids. Reaction proceeded rapidly (ca. 1 h) and cleanly at low temperature (50–70 °C) to give high yields of products. The 9(10*H*)-acridanones so formed were then converted to the 9-chloroacridines with $SOCl_2$/DMF.

For many examples, the acridanones (or 9-chloroacridines) and the side chains are known compounds or prepared by trivial modifications of known procedures. The acridanone for preparation of compound **245** was made by condensation of 3-aminoacridanone with hydantoin-3-acetic acid and that for the preparation of compound **246** came from condensation of the 3-aminoacridanone with *N*-(ethoxycarbonyl)glycine, followed by ring closure with base. 4-[(Dimethylamino)methyl]-9-chloroacridine for the preparation of compound **284** was produced by treatment of 4-(bromomethyl)-9-chloroacridine[28] with dimethylamine. Compounds **318–321** and **329** were prepared by treatment of 4′-[[4-[(4-nitrophenyl)carbonyl]-9-acridinyl]amino]methanesulfon-*m*-anisidide[8] with the respective amines in DMF. 3-Azido-5-methylacridanone for the synthesis of compound **381** was made by NaN_3 treatment of the diazo compound derived from 3-amino-5-methylacridanone. 2,6-Diazoidoacridanones for the prepartion of compound **655** was obtained by tetrazotization of 2,6-diaminoacridanone and subsequent activation with $SOCl_2$/DMF.

1-Chloro-4-carboxyacridanone was the major product of the ring closure of 5-chloro-2′-carboxydiphenylamine-2-carboxylic acid and was purified by crystallization from

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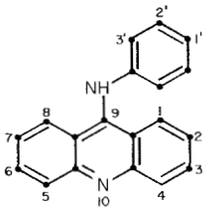
Table I. Structural Details and Physicochemical and Biological Parameters for the 9-Anilinoacridines



no.	substituents[mm]	log $(1/D_{50})$[a] obsd	log $(1/D_{50})$[a] calcd[h]	Δ log $(1/D_{50})$	log $(1/LD_{10})$[b] obsd	log $(1/LD_{10})$[b] calcd[i]	Δ log $(1/LD_{10})$	$\Sigma\pi$[c]	$\Sigma\sigma$[d]	MR_1[e]	MR_2[e]	MR_3[e]	$E_{s(3')}$[f]	R_{BS}[g]	I_{BS}	$I_{3,6}$	I_{NH_2}	I_{NO_2}
1[j]	10-CH_3; 2-NH_2	4.28	3.95	0.32	4.09	3.59	0.50	−0.73	−0.16	0.20	0.64	0.20	0.00	0	0	0	0	0
2[j]	10-CH_3; 2-$NHCOCH_3$	3.92	3.30	0.62	3.70	3.06	0.63	−0.47	0.21	0.20	1.59	0.20	0.00	0	0	0	0	0
3[k]	3-NH_2	4.07[l]	5.18	−1.11	2.99[l]	4.82	−1.83	−1.23	−0.66	0.20	0.20	0.64	0.00	0	0	0	1	0
4[j]	10-CH_3; 3-NH_2	4.85	5.12	−0.27	4.18	4.29	−0.11	−0.73	−0.66	0.20	0.20	0.64	0.00	0	0	0	0	0
5[j]	10-CH_3; 3-$NHCOCH_3$	4.58	4.65	−0.07	3.97	4.08	−0.11	−0.47	0.00	0.20	0.20	1.59	0.00	0	0	0	0	0
6[m]	1'-$COOCH_3$	3.03	3.17	−0.14	2.74	3.04	−0.30	−0.01	0.64	0.20	0.20	0.20	0.00	0	0	0	0	0
7[m]	1'-COOH	3.72	3.08	0.64	3.65	2.96	0.68	−0.32	0.77	0.20	0.20	0.20	0.00	0	0	0	0	0
8[m]	3'-OCH_3; 1'-COOH	3.39	3.68	−0.29	3.01	3.39	−0.38	−0.34	0.61	0.20	0.20	0.20	−0.55	0	0	0	0	0
9[m]	3-N_3; 1'-COOH	3.85	3.62	0.23	3.76	3.22	0.54	0.14	0.92	0.20	0.20	1.12	0.00	0	0	0	0	0
10[m]	3-NO_2; 1'-COOH	3.41	3.57	−0.16	3.41	3.12	0.29	−0.60	1.55	0.20	0.20	0.84	0.00	0	0	0	0	1
11[m]	3-I; 1'-COOH	3.22	3.54	−0.32	2.87	3.26	−0.39	0.80	0.95	0.20	0.20	1.49	0.00	0	0	0	0	0
12[m]	4-CH_3; 1'-COOH	3.72	3.08	0.64	3.68	2.98	0.70	0.24	0.70	0.20	0.20	0.20	0.00	0	0	0	0	0
13[n]	4-$OCH_2CH(OH)CH_2OH$; 1'-COOH	3.38	3.24	0.13	2.96	3.04	−0.08	−2.54	0.87	0.20	0.20	0.20	0.00	0	0	0	0	0
14[m]	4-$CONH_2$; 1'-COOH	3.23	2.97	0.25	3.21	2.86	0.35	−1.81	1.05	0.20	0.20	0.20	0.00	0	0	0	0	0
15[n]	3-NH_2; 1'-CN	3.89	4.25	−0.36	3.67	4.12	−0.45	−1.80	0.32	0.20	0.20	0.64	0.00	0	0	0	1	0
16[n]	3-NH_2; 1'-$COCH_3$	3.93	4.36	−0.43	3.88	4.20	−0.32	−1.78	0.21	0.20	0.20	0.64	0.00	0	0	0	1	0
17[n]	3-NH_2; 1'-SO_2NH_2	4.71	4.45	0.26	4.44	4.24	0.20	−3.05	0.28	0.20	0.20	0.64	0.00	0	0	0	1	0
18[n]	3-$NHCH_3$; 1'-SO_2NH_2	4.40	4.75	−0.35	4.34	4.01	0.32	−2.29	0.10	0.20	0.20	1.14	0.00	0	0	0	0	0
19[n]	3,6-$(NH_2)_2$; 1'-SO_2NH_2	5.11	4.77	0.33	4.81	4.48	0.33	−4.28	−0.38	0.20	0.20	1.08	0.00	0	0	1	1	0
20[n]	3-NH_2; 1'-SO_2NHCH_3	4.66	4.35	0.31	4.38	4.18	0.20	−2.44	0.30	0.20	0.20	0.64	0.00	0	0	0	1	0
21[n]	3-NH_2; 1'-SO_2NHEt	4.63	4.29	0.34	4.33	4.14	0.19	−1.90	0.30	0.20	0.20	0.64	0.00	0	0	0	1	0
22[n]	3-NH_2; 1'-SO_2NHPr	4.39	4.22	0.16	4.30	4.11	0.19	−1.36	0.30	0.20	0.20	0.64	0.00	0	0	0	1	0
23[n]	3-NH_2; 1'-SO_2NHBu	4.18	4.16	0.02	4.18	4.07	0.11	−0.82	0.30	0.20	0.20	0.64	0.00	0	0	0	1	0
24[n]	3-NH_2; 1'-SO_2NHPe	4.07	4.09	−0.02	4.07	4.03	0.04	−0.28	0.30	0.20	0.20	0.64	0.00	0	0	0	1	0
25[n]	3-NH_2; 1'-SO_2NHHx	<4.26[l,o]	4.03	0.23	4.26	3.99	0.26	0.26	0.30	0.20	0.20	0.64	0.00	0	0	0	1	0
26[p]	1'-OH	3.81	4.06	−0.25	3.25	3.69	−0.44	−0.67	−0.16	0.20	0.20	0.20	0.00	0	0	0	0	0
27[n]	1'-OCH_3; 2'-$NHSO_2CH_3$	4.05	3.92	0.12	3.25	3.58	−0.33	−1.20	0.04	0.20	0.20	0.20	0.00	0	0	0	0	0
28[q]	3-NH_2; 1'-OCH_3	4.94	5.34	−0.40	4.03[l]	4.94	−0.91	−1.25	−0.82	0.20	0.20	0.64	0.00	0	0	0	1	0
29[r]	1'-$O(CH_2)_3COOH$	3.82	4.02	−0.20	3.41	3.66	−0.25	−0.28	−0.16	0.20	0.20	0.20	0.00	0	0	0	0	0
30[r]	1'-$O(CH_2)_4COOH$	3.35	3.97	−0.62	2.93	3.64	−0.71	0.90	−0.16	0.20	0.20	0.20	0.00	0	0	0	0	0
31[n]	1'-α-D-glucopyranosyl	3.75	4.12	−0.37	3.58	3.69	−0.11	−2.84	0.04	0.20	0.20	0.20	0.00	0	0	0	0	0
32[n]	3-NO_2; 1'-β-D-glucopyranosyl	4.34	4.61	−0.27	3.30	3.85	−0.55	−3.12	0.82	0.20	0.20	0.84	0.00	0	0	0	0	1
33[m]	1'-CH_3	3.62	3.90	−0.28	3.41	3.60	−0.19	0.56	−0.15	0.20	0.20	0.20	0.00	0	0	0	0	0
34[k]	3'-CH_3	3.33	3.55	−0.22	3.25	3.76	−0.51	0.56	−0.15	0.20	0.20	0.20	−1.24	0	0	0	0	0
35[m]	1'-CH_2SO_3H	2.99	3.46	−0.47	2.88	3.21	−0.33	−2.42	0.64	0.20	0.20	0.20	0.00	0	0	0	0	0
36[m]	1'-$CH_2SO_2NH_2$	3.81	3.78	0.03	3.81	3.45	0.36	−2.01	0.28	0.20	0.20	0.20	0.00	0	0	0	0	0
37[m]	1'-CH_2SO_2NH-o-pyridyl	3.68	3.58	0.09	3.11	3.34	−0.23	−0.91	0.28	0.20	0.20	0.20	0.00	0	0	0	0	0
38[m]	1'-$(CH_2)_2SO_2NH_2$	3.88	4.07	−0.19	3.71	3.68	0.03	−1.51	−0.07	0.20	0.20	0.20	0.00	0	0	0	0	0
39[r]	4-CH_3; 1'-CH_2COOH	4.02	3.98	0.04	3.60	3.64	0.04	−0.16	−0.14	0.20	0.20	0.20	0.00	0	0	0	0	0
40[r]	4-Et; 1'-CH_2COOH	3.64	3.93	−0.29	3.29	3.61	0.32	0.30	−0.14	0.20	0.20	0.20	0.00	0	0	0	0	0

41[m]	1′-$(CH_2)_2$COOH	4.02	3.93	0.09	3.48	3.60	0.12	−0.29	−0.07	0.20	0.20	0.00	0	0	0	0	0	0	0
42[m]	3′-OCH$_3$; 1′-$(CH_2)_2$COOH	4.10	4.53	−0.43	3.45	4.02	0.57	−0.31	−0.23	0.20	0.20	−0.55	0	0	0	0	0	0	0
43[r]	4-CH$_3$; 1′-$(CH_2)_2$COOH	4.27	3.93	0.34	4.09	3.61	0.48	0.27	−0.14	0.20	0.20	0.00	0	0	0	0	0	0	0
44[r]	4-Et; 1′-$(CH_2)_2$COOH	3.95	3.87	0.07	3.31	3.58	0.27	0.73	−0.14	0.20	0.20	0.00	0	0	0	0	0	0	0
45[r]	1′-$(CH_2)_3$COOH	3.69	3.94	−0.25	3.31	3.62	0.31	0.25	−0.15	0.20	0.20	0.00	0	0	0	0	0	0	0
46[r]	1′-$(CH_2)_4$COOH	3.80	3.88	−0.08	3.51	3.58	0.07	0.79	−0.15	0.20	0.20	0.00	0	0	0	0	0	0	0
47[r]	1′-$(CH_2)_5$COOH	4.14	3.81	0.33	3.45	3.54	0.09	1.33	−0.15	0.20	0.20	0.00	0	0	0	0	0	0	0
48[r]	1′-$(CH_2)_6$COOH	3.79	3.75	0.04	3.68	3.51	0.17	1.87	−0.15	0.20	0.20	0.00	0	0	0	0	0	0	0
49[r]	1′-$(CH_2)_7$COOH	3.80	3.68	0.12	3.67	3.47	0.20	2.41	−0.15	0.20	0.20	0.00	0	0	0	0	0	0	0
50[r]	1′-$(CH_2)_8$COOH	3.69	3.62	0.07	3.67	3.43	0.24	2.95	−0.15	0.20	0.20	0.00	0	0	0	0	0	0	0
51[r]	1′-$(CH_2)_9$COOH	3.84	3.55	0.28	3.80	3.39	0.40	3.49	−0.15	0.20	0.20	0.00	0	0	0	0	0	0	0
52[r]	1′-CH(Et)COOH	3.42	3.89	−0.47	2.92	3.58	0.66	0.01	−0.07	0.20	0.20	0.00	0	0	0	0	0	0	0
53[m]	1′-CH_2CONH$_2$	3.97	3.95	0.02	3.89	3.59	0.30	−1.68	0.07	0.20	0.20	0.00	0	0	0	0	0	0	0
54[m]	1′-$(CH_2)_2$CONH$_2$	4.04	4.03	0.01	3.77	3.66	0.11	−1.14	−0.07	0.20	0.20	0.00	0	0	0	0	0	0	0
55[m]	3′-OCH$_3$; 1′-$(CH_2)_2$CONH$_2$	3.96	4.63	−0.67	3.71	4.08	0.37	−1.16	−0.23	0.20	0.20	−0.55	0	0	0	0	0	0	0
56[r]	1′-$(CH_2)_3$CONH$_2$	4.06	4.04	0.01	3.72	3.68	0.04	−0.60	−0.15	0.20	0.20	0.00	0	0	0	0	0	0	0
57[r]	1′-$(CH_2)_4$CONH$_2$	4.01	3.98	0.03	3.63	3.64	−0.01	−0.06	−0.15	0.20	0.20	0.00	0	0	0	0	0	0	0
58[r]	1′-$(CH_2)_5$CONH$_2$	3.72	3.91	−0.19	3.59	3.60	−0.01	0.48	−0.15	0.20	0.20	0.00	0	0	0	0	0	0	0
59[r]	1′-$(CH_2)_6$CONH$_2$	3.80	3.85	−0.05	3.65	3.57	0.08	1.02	−0.15	0.20	0.20	0.00	0	0	0	0	0	0	0
60[r]	1′-$(CH_2)_7$CONH$_2$	3.65	3.78	−0.13	3.63	3.53	0.10	1.56	−0.15	0.20	0.20	0.00	0	0	0	0	0	0	0
61[r]	1′-$(CH_2)_8$CONH$_2$	<3.94[l,o]	3.72	0.22	3.94	3.49	0.45	2.10	−0.15	0.20	0.20	0.00	0	0	0	0	0	0	0
62[m]	1′-CH=CHCOOH	3.25	3.19	0.06	2.83	3.06	−0.23	0.00	0.62	0.20	0.20	0.00	0	0	0	0	0	0	0
63[m]	1′-CH=CHCONH$_2$	3.34	3.30	0.04	2.90	3.12	−0.22	−0.89	0.62	0.20	0.20	0.00	0	0	0	0	0	0	0
64[n]	1′-CH=NNHCONH$_2$	3.36	3.52	−0.16	3.23	3.28	−0.05	−0.85	0.40	0.20	0.20	0.00	0	0	0	0	0	0	0
65[m]	1′-(CH=CH)$_2$COOH	4.06	3.74	0.32	3.23	3.48	−0.25	0.70	0.00	0.20	0.20	0.00	0	0	0	0	0	0	0
66[n]	1′-CH=CHPhCOOH	3.96	3.45	0.51	3.56	3.30	0.26	2.49	0.07	0.20	0.20	0.00	0	0	0	0	0	0	0
67[n]	1′-CH=C(CN)$_2$	3.50[l]	2.60	0.90	3.20	2.61	0.58	0.05	1.20	0.20	0.20	0.00	0	0	0	0	0	0	0
68[n]	1′,2′-(CH=NNH)	3.76	3.86	−0.10	3.43	3.55	−0.12	−0.31	0.00	0.20	0.20	0.00	0	0	0	0	0	0	0
69[p]	1′-NH_2	4.09	4.12	−0.03	3.87	3.72	0.15	−1.23	−0.15	0.20	0.20	0.00	0	0	0	0	0	0	0
70[j]	10-CH$_3$; 1′-NH_2	3.84	4.06	−0.22	3.64	3.69	−0.05	−0.73	−0.15	0.20	0.20	0.00	0	0	0	0	0	0	0
71[p]	2′-NH_2; 1′-NH_2	4.29	4.43	−0.14	3.83	3.93	−0.10	−2.46	−0.31	0.20	0.20	0.00	0	0	0	0	0	0	0
72[n]	3′-OCH$_3$; 1′-NH_2	4.43	4.72	−0.29	3.94	4.15	−0.21	−1.25	−0.31	0.20	0.20	−0.55	0	0	0	0	0	0	0
73[n]	3′-CH$_3$; 1′-NH_2	3.97	3.85	0.12	3.59	3.96	−0.37	−0.67	−0.30	0.20	0.20	−1.24	0	0	0	0	0	0	0
74[s]	3-NH_2; 1′-NH_2	5.14	5.48	−0.34	4.24	5.02	−0.78	−2.46	−0.81	0.20	0.64	0.00	0	0	0	0	0	1	0
75[n]	3-NHCOCH$_3$; 1′-NH_2	4.98	5.01	−0.03	3.98	4.32	−0.34	−2.20	−0.15	0.20	1.59	0.00	0	0	0	0	0	0	0
76[n]	4-CH$_3$; 1′-NH_2	4.23	4.12	0.10	3.48	3.74	−0.26	−0.67	−0.22	0.20	0.20	0.00	0	0	0	0	0	0	0
77[n]	4-CH$_3$-3′-OCH$_3$; 1′-NH_2	5.00	4.73	0.27	4.49	4.16	0.32	−0.69	−0.38	0.20	0.20	−0.55	0	0	0	0	0	0	0
78[j]	10-CH$_3$; 2′-NH_2	3.62	4.07	−0.45	3.38	3.70	−0.32	−0.73	−0.16	0.20	0.20	0.00	0	0	0	0	0	0	0
79[n]	2′-NH_2; 5′-CH_3	3.60	4.21	−0.61	3.49	3.80	−0.31	−0.67	−0.31	0.20	0.20	0.00	0	0	0	0	0	0	0
80[p]	2′-NH_2	3.81	4.13	−0.32	3.77	3.73	0.04	−1.23	−0.16	0.20	0.20	0.00	0	0	0	0	0	0	0
81[p]	1′-NHCH$_3$	3.79	4.08	−0.29	3.74	3.71	0.03	−0.47	−0.20	0.20	0.20	0.00	0	0	0	0	0	0	0
82[p]	1′-NHEt	3.59	3.96	−0.37	3.55	3.63	−0.08	0.08	−0.15	0.20	0.20	0.00	0	0	0	0	0	0	0
83[p]	1′-N(CH$_3$)$_2$	3.64	3.92	−0.28	3.64	3.60	0.04	0.18	−0.12	0.20	0.20	0.00	0	0	0	0	0	0	0
84[p]	1′-N(CH$_3$)COCH$_3$	3.85	3.94	−0.09	3.85	3.59	0.25	−1.01	0.00	0.20	0.20	0.00	0	0	0	0	0	0	0
85[q]	1′-N(CH_2CH_2)$_2$NCOCH$_3$	3.88	3.94	−0.06	3.12	3.62	−0.50	0.06	−0.13	0.20	0.20	0.00	0	0	0	0	0	0	0
86[q]	1′-N(CH_2CH_2)$_2$NSO$_2$CH$_3$	3.71	3.94	−0.23	3.19	3.61	−0.42	0.03	−0.12	0.20	0.20	0.00	0	0	0	0	0	0	0
87[q]	1′-N(CH_2CH_2)$_2$NCONH$_2$	4.36	4.11	0.25	4.08	3.71	0.37	−1.38	−0.12	0.20	0.20	0.00	0	0	0	0	0	0	0
88[n]	1′,2′-(NHCH=N)	4.06	4.08	−0.02	3.89	3.70	0.19	−0.79	−0.16	0.20	0.20	0.00	0	0	0	0	0	0	0
89[p]	1′-NHCOCH$_3$	4.20	3.94	0.26	3.99	3.59	0.40	−0.97	0.00	0.20	0.20	0.00	0	0	0	0	0	0	0
90[n]	10-CH$_3$; 1′-NHCOCH$_3$	3.84	3.88	−0.04	3.53	3.56	−0.03	−0.47	0.00	0.20	0.20	0.00	0	0	0	0	0	0	0
91[p]	1′-NHCOEt	3.88	3.87	0.01	3.81	3.55	0.25	−0.43	0.00	0.20	0.20	0.00	0	0	0	0	0	0	0

Table I (*Continued*)

no.	substituents[mm]	log $(1/D_{50})$[a] obsd	log $(1/D_{50})$[a] calcd[h]	Δ log $(1/D_{50})$	log $(1/LD_{10})$[b] obsd	log $(1/LD_{10})$[b] calcd[i]	Δ log $(1/LD_{10})$	$\Sigma\pi$[c]	$\Sigma\sigma$[d]	MR_1[e]	MR_2[e]	MR_3[e]	$E_{s(3')}$[f]	R_{BS}[g]	I_{BS}	$I_{3,6}$	I_{NH_2}	I_{NO_2}
92[p]	1′-NHCOPr	3.99	3.81	0.18	3.59	3.52	0.07	0.11	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
93[p]	1′-NHCOBu	3.76	3.74	0.02	3.43	3.48	−0.05	0.65	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
94[p]	1′-NHCOPe	3.58	3.68	−0.10	3.58	3.44	0.14	1.19	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
95[p]	1′-NHCOCH$(CH_3)_2$	3.81	3.84	−0.03	3.25	3.54	−0.29	−0.18	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
96[p]	1′-NHCOCH$_2$CH$(CH_3)_2$	4.00	3.78	0.22	3.56	3.50	0.06	0.36	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
97[p]	1′-NHCO$(CH_2)_2$CH$(CH_3)_2$	3.62	3.71	−0.09	3.62	3.46	0.16	0.90	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
98[p]	1′-NHCOCHEt$_2$	3.97	3.71	0.26	3.77	3.46	0.31	0.90	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
99[n]	1′-NHCO-c-C_5H_9	3.92	3.72	0.20	3.78	3.47	0.31	0.85	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
100[n]	1′-NHCO$(CH_2)_3$NHCOCH$_3$	3.56	4.03	−0.47	3.16	3.64	−0.48	−1.76	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
101[p]	1′-NHCOPh$(CH_2)_6$COOH	3.40	3.52	−0.12	2.98	3.35	−0.37	2.51	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
102[p]	2′-NHCOCH$_3$	3.54	3.72	−0.18	3.50	3.43	0.07	−0.97	0.21	0.20	0.20	0.20	0.00	0	0	0	0	0
103[j]	10-CH$_3$; 2′-NHCOCH$_3$	3.71	3.66	0.04	3.43	3.40	0.03	−0.47	0.21	0.20	0.20	0.20	0.00	0	0	0	0	0
104[s]	1′-NHCOPh	3.45	3.76	−0.31	3.52	3.49	0.03	0.49	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
105[t]	3-NH$_2$; 1′-NHCOPh	4.64	5.12	−0.48	3.65[l]	4.79	−1.14	−0.74	−0.66	0.20	0.20	0.64	0.00	0	0	0	1	0
106[n]	2-NH$_2$; 1′-NHCOPhNH$_2$[u]	3.82	4.08	−0.26	3.53	3.66	−0.13	−1.76	−0.16	0.20	0.64	0.20	0.00	0	0	0	0	0
107[p]	1′-NHCOOCH$_3$	4.08	3.97	0.11	3.85	3.62	0.22	−0.37	−0.10	0.20	0.20	0.20	0.00	0	0	0	0	0
108[p]	1′-NHCOOEt	4.05	3.90	0.15	3.78	3.59	0.19	0.17	−0.10	0.20	0.20	0.20	0.00	0	0	0	0	0
109[q]	1′-NHCOOCH$_2$CH(OH)CH$_2$OH	4.50	4.18	0.31	4.07	3.75	0.32	−2.19	−0.10	0.20	0.20	0.20	0.00	0	0	0	0	0
110[q]	1′-NHNHCOOEt	4.26	3.80	0.46	4.11	3.51	0.60	0.18	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
111[q]	1′-NHCONHCH$_3$	4.14	4.09	0.05	3.75	3.70	0.05	−1.03	−0.14	0.20	0.20	0.20	0.00	0	0	0	0	0
112[q]	3′-OCH$_3$; 1′-NHCONHCH$_3$	4.36	4.69	−0.33	3.74	4.13	−0.39	−1.05	−0.30	0.20	0.20	0.20	−0.55	0	0	0	0	0
113[n]	3′-CH$_3$; 1′-NHCONHCH$_3$	3.23	3.82	−0.58	3.18	3.94	−0.76	−0.47	−0.29	0.20	0.20	0.20	−1.24	0	0	0	0	0
114[q]	1′-NHCONHNHCOOCH$_3$	3.83	4.14	−0.31	2.90[l]	3.73	−0.83	−1.46	−0.14	0.20	0.20	0.20	0.00	0	0	0	0	0
115[q]	1′-NHCON$(CH_2CH_2)_2$NCOOEt	3.80	3.86	−0.06	3.80	3.57	0.22	0.81	−0.14	0.20	0.20	0.20	0.00	0	0	0	0	0
116[s]	1′-NHCONHPh	3.65	3.87	−0.22	2.99	3.58	−0.59	0.73	−0.14	0.20	0.20	0.20	0.00	0	0	0	0	0
117[n]	1′-NHCONHPhCH$_2$NH$_2$	4.72	4.36	0.36	4.14	3.86	0.28	−3.32	−0.14	0.20	0.20	0.20	0.00	0	0	0	0	0
118[n]	3-NO$_2$; 1′-NHCONHPhCH$_2$NH$_2$	5.14	4.84	0.29	4.00	4.02	−0.02	−3.60	0.64	0.20	0.20	0.84	0.00	0	0	0	0	1
119[n]	1′-NHCONHPh$(CH_2)_2$NH$_2$	4.44	4.35	0.09	4.06	3.85	0.21	−2.92	−0.14	0.20	0.20	0.20	0.00	0	0	0	0	0
120[n]	1′-NHCONHPh$(CH_2)_3$NH$_2$	4.49	4.29	0.20	3.85	3.82	0.03	−2.73	−0.14	0.20	0.20	0.20	0.00	0	0	0	0	0
121[n]	1′-NHCONHPh$(CH_2)_4$NH$_2$	4.39	4.23	0.15	4.09	3.79	0.30	−2.26	−0.14	0.20	0.20	0.20	0.00	0	0	0	0	0
122[n]	1′-NHCONHPh$(CH_2)_5$NH$_2$	4.19	4.18	0.01	3.92	3.75	0.16	−1.79	−0.14	0.20	0.20	0.20	0.00	0	0	0	0	0
123[n]	1′-NHCONHPh$(CH_2)_6$NH$_2$	4.11	4.12	−0.01	4.11	3.72	0.39	−1.32	−0.14	0.20	0.20	0.20	0.00	0	0	0	0	0
124[n]	1′-NHCONHPhCH$_2$CH(NH_2)-COOH	3.27[l]	4.33	−1.06	3.15[l]	3.84	−0.69	−2.83	−0.14	0.20	0.20	0.20	0.00	0	0	0	0	0
125[n]	3-NO$_2$; 1′-NHCONHPhCH$_2$CH-(NH_2)COOH	3.78[l]	4.82	−1.04	3.14[l]	4.00	−0.86	−3.34	0.64	0.20	0.20	0.84	0.00	0	0	0	0	1
126[n]	1′-NHCONHPhCOOH	4.08	3.96	0.12	3.73	3.63	0.10	0.02	−0.14	0.20	0.20	0.20	0.00	0	0	0	0	0
127[n]	1′-NHCONHPhCH$_2$COOH	3.79	3.96	−0.17	3.15	3.63	−0.48	0.01	−0.14	0.20	0.20	0.20	0.00	0	0	0	0	0
128[n]	1′-NHCONHPh$(CH_2)_2$COOH	4.01	3.90	0.11	3.06	3.59	−0.53	0.55	−0.14	0.20	0.20	0.20	0.00	0	0	0	0	0
129[n]	1′-NHCONHPh$(CH_2)_3$COOH	3.61	3.83	−0.22	3.28	3.55	−0.27	1.09	−0.14	0.20	0.20	0.20	0.00	0	0	0	0	0
130[n]	1′-NHCONHPh$(CH_2)_4$COOH	4.16	3.77	0.39	3.68	3.52	0.16	1.63	−0.14	0.20	0.20	0.20	0.00	0	0	0	0	0
131[n]	1′-NHCONHPh$(CH_2)_5$COOH	3.42	3.70	−0.28	3.52	3.48	0.04	2.17	−0.14	0.20	0.20	0.20	0.00	0	0	0	0	0
132[n]	1′-NHCONHPhNHSO$_2$CH$_3$	3.00[l]	4.02	−1.02	2.97[l]	3.66	−0.69	−0.45	−0.14	0.20	0.20	0.20	0.00	0	0	0	0	0
133[n]	1′-NHCONHPhNHC(NH)NH$_2$	4.55	4.45	0.10	4.26	3.92	0.34	−4.15	−0.14	0.20	0.20	0.20	0.00	0	0	0	0	0
134[n]	3-NO$_2$; 1′-NHCONHPhNHC(NH)NH$_2$	4.92	4.93	−0.01	3.32[l]	4.07	−0.75	−4.43	0.64	0.20	0.20	0.84	0.00	0	0	0	0	1

135[n]	1′-NHCONHPhNHC(NH)-NHC(NH)NH_2	4.85	4.48	0.36	4.22	3.94	0.27	−4.55	−0.14	0.20	0.20	0.20	0.00	0	0	0	0	0
136[n]	3-NO_2; 1′-NHCONHPhNHC-(NH)NHC(NH)NH_2	5.31	4.95	0.36	3.75	4.11	−0.36	−4.93	0.64	0.20	0.20	0.84	0.00	0	0	0	0	1
137[n]	10-CH_3; 3-NH_2; 1′NHCONH-PhNHC(NH)NHC(NH)NH_2	5.72	5.69	0.03	3.21[l]	5.22	−2.01	−5.38	−0.81	0.20	0.20	0.64	0.00	0	0	0	1	0
138[n]	1′-NHCONHPhC(CH_3)-NNHC(NH)NH_2	4.67	4.44	0.23	3.74	3.91	−0.17	−4.00	−0.14	0.20	0.20	0.20	0.00	0	0	0	0	0
139[n]	10-CH_3; 3-NH_2; 1′-NHCONH-PhC(CH_3)NNHC(NH)NH_2	6.07	5.70	0.37	4.44	4.66	−0.22	−4.50	−0.81	0.20	0.20	0.64	0.00	0	0	0	0	0
140[n]	1′-N($COCH_2CH_2SO_2$)	3.24	3.59	−0.35	3.17	3.34	−0.17	−0.63	0.30	0.20	0.20	0.20	0.00	0	0	0	0	0
141[n]	1′-N($COOCH_3$)SO_2CH_3	3.38	3.67	−0.29	3.36	3.38	−0.02	−1.24	0.30	0.20	0.20	0.20	0.00	0	0	0	0	0
142[n]	3-NH_2; 1′-N($COOCH_3$)SO_2CH_3	4.82	5.02	−0.20	3.97	4.68	−0.71	−2.47	−0.36	0.20	0.20	0.64	0.00	0	0	0	1	0
143[n]	3-$NHCOCH_3$; 1′-N($COOCH_3$)-SO_2CH_3	4.71	4.55	0.16	3.67	3.98	−0.31	−2.21	0.30	0.20	0.20	1.59	0.00	0	0	0	0	0
144[v]	1′-N(CH_3)SO_2CH_3	3.62	3.90	−0.28	3.34	3.57	−0.23	−0.62	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
145[v]	1′-$NHSO_2CH_2Cl$	3.73	3.98	−0.25	3.32	3.62	−0.30	−1.35	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
146[p]	2′-$NHSO_2CH_3$	3.76	3.76	0.00	3.17	3.45	−0.28	−1.18	0.20	0.20	0.20	0.20	0.00	0	0	0	0	0
147[n]	3′-CH_3; 2′-$NHSO_2CH_3$	3.71	3.49	0.22	3.62	3.69	−0.07	−0.62	0.05	0.20	0.20	0.20	−1.24	0	0	0	0	0
148[w]	1′-$NHSO_2CH_3$	4.27	3.96	0.31	3.78	3.61	0.17	−1.18	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
149[j]	10-CH_3; 1-$NHSO_2CH_3$	4.01	3.90	0.11	3.54	3.57	−0.03	−0.68	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
150[w]	1′-$NHSO_2Et$	3.94	3.90	0.04	3.10	3.57	−0.47	−0.64	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
151[j]	10-CH_3; 1′-$NHSO_2Et$	3.98	3.84	0.14	3.61	3.53	0.07	−0.14	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
152[w]	1′-$NHSO_2Pr$	3.63	3.83	−0.20	3.09	3.53	−0.44	−0.10	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
153[w]	1′-$NHSO_2Bu$	3.44	3.77	−0.33	3.10	3.49	−0.39	0.44	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
154[r]	1′-$NHSO_2Pe$	3.88	3.70	0.18	3.81	3.46	0.35	0.98	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
155[r]	1′-$NHSO_2Hx$	3.53	3.64	−0.11	3.59	3.42	0.17	1.52	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
156[v]	2′-Aza; 1′-$NHSO_2CH_3$	3.90	3.45	0.45	3.37	3.20	0.16	−1.96	0.60	0.20	0.20	0.20	0.00	0	0	0	0	0
157[v]	2′-NH_2; 1′-$NHSO_2CH_3$	4.28	4.27	0.01	3.82	3.81	0.01	−2.41	−0.16	0.20	0.20	0.20	0.00	0	0	0	0	0
158[p]	1′,2′-($NHSO_2CH_3$)$_2$	3.39	3.90	−0.51	3.22	3.54	−0.32	−2.36	0.20	0.20	0.20	0.20	0.00	0	0	0	0	0
159[v]	3′-NH_2; 1′-$NHSO_2CH_3$	4.58	4.69	−0.11	3.99	4.12	−0.13	−2.41	−0.15	0.20	0.20	0.20	−0.61	0	0	0	0	0
160[v]	3′-CH_3; 1′-$NHSO_2CH_3$	3.98	3.69	0.29	3.72	3.85	−0.13	−0.62	−0.15	0.20	0.20	0.20	−1.24	0	0	0	0	0
161[v]	3′-OH; 1′-$NHSO_2CH_3$	4.62	4.64	−0.02	4.02	4.08	−0.06	−1.85	−0.16	0.20	0.20	0.20	−0.55	0	0	0	0	0
162[v]	3′-OCH_3; 1′-$NHSO_2CH_3$	5.09	4.57	0.52	4.74	4.03	0.71	−1.20	−0.16	0.20	0.20	0.20	−0.55	0	0	0	0	0
163[j]	10-CH_3; 3′-OCH_3; 1′-$NHSO_2CH_3$	4.69	4.51	0.18	4.30	4.00	0.30	−0.70	−0.16	0.20	0.20	0.20	−0.55	0	0	0	0	0
164[x]	3′-OCH_3; 1′-$NHSO_2Et$	5.08	4.50	0.58	4.68	4.00	0.68	−0.66	−0.16	0.20	0.20	0.20	−0.55	0	0	0	0	0
165[x]	3′-OCH_3; 1′-$NHSO_2Pr$	4.60	4.44	0.16	4.27	3.96	0.31	−0.12	−0.16	0.20	0.20	0.20	−0.55	0	0	0	0	0
166[x]	3′-OCH_3; 1′-$NHSO_2Bu$	4.33	4.37	−0.04	3.87	3.92	−0.05	0.42	−0.16	0.20	0.20	0.20	−0.55	0	0	0	0	0
167[y]	3′-OCH_3; 1′-$NHSO_2Pe$	4.36	4.31	0.05	4.18	3.88	0.30	0.96	−0.16	0.20	0.20	0.20	−0.55	0	0	0	0	0
168[y]	3′-OCH_3; 1′-$NHSO_2Hx$	4.32	4.24	0.08	4.00	3.85	0.15	1.50	−0.16	0.20	0.20	0.20	−0.55	0	0	0	0	0
169[z]	3′-OCH_3; 1′-$NHSO_2Hp$	4.05	4.18	−0.13	3.83	3.81	0.02	2.04	−0.16	0.20	0.20	0.20	−0.55	0	0	0	0	0
170[z]	3′-OCH_3; 1′-$NHSO_2Oct$	<4.10[l,o]	4.11	−0.01	4.10	3.77	0.33	2.58	−0.16	0.20	0.20	0.20	−0.55	0	0	0	0	0
171[aa]	3′-OEt; 1′-$NHSO_2CH_3$	3.96	3.79	0.17	3.76	3.88	−0.12	−0.80	−0.16	0.20	0.20	0.20	−1.21	0	0	0	0	0
172[aa]	3′-OCH_2CH_2OH; 1′-$NHSO_2CH_3$	3.57	3.95	−0.38	3.28	3.98	−0.70	−2.15	−0.16	0.20	0.20	0.20	−1.21	0	0	0	0	0
173[w]	2-NH_2; 1′-$NHSO_2CH_3$	4.04	4.16	−0.12	4.03	3.71	0.32	−2.41	−0.16	0.20	0.64	0.20	0.00	0	0	0	0	0
174[j]	10-CH_3; 2-NH_2; 1′-$NHSO_2CH_3$	4.97[l]	4.10	0.87	4.73[l]	3.67	1.06	−1.91	−0.16	0.20	0.64	0.20	0.00	0	0	0	0	0
175[w]	2-$NHCOCH_3$; 1′-$NHSO_2CH_3$	3.17	3.50	−0.33	3.11	3.18	−0.07	−2.15	0.21	0.20	1.59	0.20	0.00	0	0	0	0	0
176[j]	10-CH_3; 2-$NHCOCH_3$; 1′-$NHSO_2CH_3$	3.97	3.44	0.53	3.97	3.14	0.82	−1.65	0.21	0.20	1.59	0.20	0.00	0	0	0	0	0
177[n]	2-N_3; 1′-$NHSO_2CH_3$	3.77	3.39	0.38	3.20	3.15	0.05	−0.72	0.27	0.20	1.12	0.20	0.00	0	0	0	0	0

Table I (*Continued*)

no.	substituents[mm]	log $(1/D_{50})$[a] obsd	log $(1/D_{50})$[a] calcd[h]	Δ log $(1/D_{50})$	log $(1/LD_{10})$[b] obsd	log $(1/LD_{10})$[b] calcd[i]	Δ log $(1/LD_{10})$	$\Sigma\pi$[c]	$\Sigma\sigma$[d]	MR_1[e]	MR_2[e]	MR_3[e]	$E_{s(3')}$[f]	R_{BS}[g]	I_{BS}	$I_{3,6}$	I_{NH_2}	I_{NO_2}
178[w]	2-$N(CH_3)_2$; 1′-$NHSO_2CH_3$	3.47	3.71	−0.24	3.47	3.36	0.11	−1.00	−0.15	0.20	1.65	0.20	0.00	0	0	0	0	0
179[w]	3-NH_2; 1′-$NHSO_2CH_3$	5.58	5.32	0.26	5.26	4.90	0.35	−2.41	−0.66	0.20	0.20	0.64	0.00	0	0	0	1	0
180[j]	10-CH_3; 3-NH_2; 1′-$NHSO_2CH_3$	5.72	5.26	0.46	5.54[l]	4.37	1.17	−1.91	−0.66	0.20	0.20	0.64	0.00	0	0	0	0	0
181[x]	3-$NHCH_3$; 1′-$NHSO_2CH_3$	5.81	5.62	0.19	4.78	4.68	0.10	−1.65	−0.84	0.20	0.20	1.13	0.00	0	0	0	0	0
182[bb]	3-$NHCOOCH_3$; 1′-$NHSO_2CH_3$	4.49	4.92	−0.43	3.68	4.30	−0.62	−1.55	−0.15	0.20	0.20	1.75	0.00	0	0	0	0	0
183[cc]	3-N_3; 1′-$NHSO_2CH_3$	4.90	4.50	0.40	4.26	3.86	0.40	−0.72	0.15	0.20	0.20	1.12	0.00	0	0	0	0	0
184[cc]	3-$N_3(CH_3)_2$;[dd] 1′-$NHSO_2CH_3$	5.57	5.33	0.24	4.63	4.07	0.55	−0.72	0.15	0.20	0.20	2.18	0.00	0	0	0	0	0
185[cc]	3-$N_3(CH_3)Pr$;[dd] 1′-$NHSO_2CH_3$	5.40	5.05	0.35	4.49	3.97	0.52	0.36	0.15	0.20	0.20	3.10	0.00	0	0	0	0	0
186[cc]	3-$N_3(Et)_2$;[dd] 1′-$NHSO_2CH_3$	5.01	5.05	−0.04	3.90	3.97	−0.07	0.36	0.15	0.20	0.20	3.10	0.00	0	0	0	0	0
187[w]	3-$NHCOCH_3$; 1′-$NHSO_2CH_3$	5.33	4.85	0.48	4.43	4.20	0.23	−2.15	0.00	0.20	0.20	1.59	0.00	0	0	0	0	0
188[j]	10-CH_3; 3-$NHCOCH_3$; 1′-$NHSO_2CH_3$	5.11	4.79	0.32	4.74	4.17	0.57	−1.65	0.00	0.20	0.20	1.59	0.00	0	0	0	0	0
189[w]	3-$NHCOCH_3$; 1′-$NHSO_2Et$	5.29	4.78	0.50	4.28	4.16	0.12	−1.61	0.00	0.20	0.20	1.59	0.00	0	0	0	0	0
190[w]	3-$NHCOCH_3$; 1′-$NHSO_2Pr$	5.13	4.72	0.41	4.22	4.13	0.09	−1.07	0.00	0.20	0.20	1.59	0.00	0	0	0	0	0
191[w]	3-$NHCOCH_3$; 1′-$NHSO_2Bu$	5.06	4.65	0.40	4.16	4.09	0.07	−0.53	0.00	0.20	0.20	1.59	0.00	0	0	0	0	0
192[w]	3-$NHCOCH_3$; 1′-$NHSO_2Pe$	4.50	4.59	−0.09	4.16	4.05	0.11	0.01	0.00	0.20	0.20	1.59	0.00	0	0	0	0	0
193[w]	3-$NHCOCH_3$; 1′-$NHSO_2Hx$	4.37	4.52	−0.15	4.37	4.01	0.36	0.55	0.00	0.20	0.20	1.59	0.00	0	0	0	0	0
194[x]	3-$N(CH_3)COCH_3$; 1′-$NHSO_2CH_3$	4.61	4.81	−0.20	4.01	4.28	−0.27	−2.19	0.00	0.20	0.20	2.06	0.00	0	0	0	0	0
195[x]	3-NHCOEt; 1′-$NHSO_2CH_3$	4.47	4.74	−0.27	3.99	4.24	−0.25	−1.61	0.00	0.20	0.20	2.06	0.00	0	0	0	0	0
196[x]	3-NHCOPr; 1′-$NHSO_2CH_3$	4.33	4.60	−0.27	3.77	4.22	−0.45	−1.07	0.00	0.20	0.20	2.52	0.00	0	0	0	0	0
197[w]	3-NO_2; 1′-$NHSO_2CH_3$	5.04	4.45	0.59	4.55[l]	3.76	0.79	−1.46	0.78	0.20	0.20	0.84	0.00	0	0	0	0	1
198[x]	3-NO_2; 1′-$NHSO_2Et$	4.88	4.38	0.50	4.67[l]	3.72	0.94	−0.92	0.78	0.20	0.20	0.84	0.00	0	0	0	0	1
199[x]	3-NO_2; 1′-$NHSO_2Pr$	4.68	4.32	0.36	3.46	3.69	−0.23	−0.38	0.78	0.20	0.20	0.84	0.00	0	0	0	0	1
200[x]	3-NO_2; 1′-$NHSO_2Bu$	4.35	4.25	0.09	3.61	3.65	−0.04	0.16	0.78	0.20	0.20	0.84	0.00	0	0	0	0	1
201[n]	3-NO_2; 1′-$NHSO_2Pe$	3.92	4.19	−0.27	3.92	3.61	0.31	0.70	0.78	0.20	0.20	0.84	0.00	0	0	0	0	1
202[n]	3-NO_2; 1′-$NHSO_2Hx$	3.87	4.12	−0.25	3.81	3.58	0.23	1.24	0.78	0.20	0.20	0.84	0.00	0	0	0	0	1
203[bb]	3-OH; 1′-$NHSO_2CH_3$	4.73	4.71	0.02	4.29	4.03	0.26	−1.85	−0.37	0.20	0.20	0.39	0.00	0	0	0	0	0
204[w]	3-OCH_3; 1′-$NHSO_2CH_3$	4.94	4.92	0.02	4.03	4.13	−0.10	−1.20	−0.27	0.20	0.20	0.89	0.00	0	0	0	0	0
205[w]	3-CH_3; 1′-$NHSO_2CH_3$	4.77	4.62	0.14	4.20	3.92	0.28	−0.62	−0.17	0.20	0.20	0.66	0.00	0	0	0	0	0
206[x]	3-CH_3; 1′-$NHSO_2Et$	4.62	4.56	0.06	4.14	3.88	0.26	−0.08	−0.17	0.20	0.20	0.66	0.00	0	0	0	0	0
207[w]	3-Cl; 1′-$NHSO_3CH_3$	4.10	4.23	−0.13	3.56	3.62	−0.06	−0.47	0.23	0.20	0.20	0.70	0.00	0	0	0	0	0
208[w]	3-Br; 1′-$NHSO_2CH_3$	4.39	4.34	0.04	4.16	3.73	0.43	−0.32	0.23	0.20	0.20	0.99	0.00	0	0	0	0	0
209[j]	10-CH_3; 3-Br; 1′-$NHSO_2CH_3$	4.35	4.28	0.06	3.84	3.69	0.15	0.18	0.23	0.20	0.20	0.99	0.00	0	0	0	0	0
210[v]	3-I; 1′-$NHSO_2CH_3$	4.36	4.42	−0.06	3.72	3.90	−0.18	−0.06	0.18	0.20	0.20	1.49	0.00	0	0	0	0	0
211[w]	4-NH_2; 1′-$NHSO_2CH_3$	3.95	4.27	−0.32	3.55	3.81	−0.26	−2.41	−0.16	0.20	0.20	0.20	0.00	0	0	0	0	0
212[w]	4-CH_3; 1′-$NHSO_2CH_3$	4.37	3.97	0.40	4.02	3.62	0.40	−0.62	−0.07	0.20	0.20	0.20	0.00	0	0	0	0	0
213[aa]	4-CH_2OH; 1′-$NHSO_2CH_3$	4.04	4.09	−0.05	3.86	3.68	0.18	−2.21	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
214[w]	4-Et; 1′-$NHSO_2CH_3$	3.59	3.91	−0.32	3.16	3.59	−0.43	−0.16	−0.07	0.20	0.20	0.20	0.00	0	0	0	0	0
215[w]	4-OCH_3; 1′-$NHSO_2CH_3$	4.35	3.84	0.51	3.55	3.52	0.03	−1.20	0.12	0.20	0.20	0.20	0.00	0	0	0	0	0
216[n]	4-OEt; 1′-$NHSO_2CH_3$	4.03	3.82	0.21	3.36	3.50	−0.14	−0.80	0.10	0.20	0.20	0.20	0.00	0	0	0	0	0
217[aa]	4-OPr; 1′-$NHSO_2CH_3$	3.72	3.73	−0.01	3.20	3.46	−0.26	−0.13	0.10	0.20	0.20	0.20	0.00	0	0	0	0	0
218[bb]	4-$CONH_2$; 1′-$NHSO_2CH_3$	2.99[l]	3.86	−0.87	2.99	3.50	−0.51	−2.67	0.28	0.20	0.20	0.20	0.00	0	0	0	0	0
219[n]	3-NO_2; 2′-aza; 1′-$NHSO_2CH_3$	4.17	3.95	0.22	3.53	3.37	0.16	−2.24	1.37	0.20	0.20	0.84	0.00	0	0	0	0	1
220[n]	3-NH_2; 2′-OCH_3; 1′-$NHSO_2CH_3$	4.95	5.20	−0.25	3.27[l]	4.32	−1.05	−2.43	−0.54	0.20	0.20	0.64	0.00	0	0	0	0	0
221[x]	2-NH_2; 3′-OCH_3; 1′-$NHSO_2CH_3$	5.35	4.76	0.59	4.75	4.13	0.62	−2.43	−0.32	0.20	0.64	0.20	−0.55	0	0	0	0	0
222[ee]	2-CH_3; 3′-OCH_3; 1′-$NHSO_2CH_3$	3.61	4.01	−0.40	3.44	3.63	−0.19	−0.64	−0.23	0.20	0.67	0.20	0.00	0	0	0	0	0

223[ee]	2-CH(CH$_3$)$_2$; 3′-OCH$_3$; 1-NHSO$_2$CH$_3$	3.44	4.08	−0.64	3.08	3.64	−0.56	0.33	−0.23	0.20	1.60	0.20	−0.55	0	0	0	0	0
224[ee]	2-F; 3′-OCH$_3$; 1′-NHSO$_2$CH$_3$	4.33	4.21	0.12	3.70	3.77	−0.07	−1.06	0.18	0.20	0.19	0.20	−0.55	0	0	0	0	0
225[ee]	2-I; 3′-OCH$_3$; 1′-NHSO$_2$CH$_3$	3.57	3.74	−0.17	3.51	3.38	0.13	−0.08	0.19	0.20	1.49	0.20	−0.55	0	0	0	0	0
226[z]	3-aza; 3′-OCH$_3$; 1′-NHSO$_2$CH$_3$	4.17	3.71	0.46	3.56	3.45	0.11	−2.68	0.67	0.20	0.20	0.10	−0.55	0	0	0	0	0
227[ee]	3-NHCOOCH$_3$; 3′-OCH$_3$; 1′-NHSO$_2$CH$_3$	5.22	5.53	−0.31	4.66	4.71	−0.05	−1.57	−0.31	0.20	0.20	1.65	−0.55	0	0	0	0	0
228[n]	3-NHSO$_2$CH$_3$; 3′-OCH$_3$; 1′-NHSO$_2$CH$_3$	2.95[l]	5.42	−2.47	2.85[l]	4.68	−1.83	−2.38	−0.13	0.20	0.20	1.92	−0.55	0	0	0	0	0
229[cc]	3-N$_3$; 3′-OCH$_3$; 1′-NHSO$_2$CH$_3$	5.28	5.11	0.17	4.60	4.29	0.31	−0.74	−0.01	0.20	0.20	1.12	−0.55	0	0	0	0	0
230[cc]	3-N$_3$(CH$_3$)$_2$;[dd] 3′-OCH$_3$; 1′-NHSO$_2$CH$_3$	5.70	5.96	−0.26	4.66	4.48	0.17	−0.74	−0.01	0.20	0.20	2.00	−0.55	0	0	0	0	0
231[cc]	3-N$_3$(CH$_3$)Pr;[dd] 3′-OCH$_3$; 1′-NHSO$_2$CH$_3$	5.48	5.76	−0.28	4.69	4.44	0.24	0.25	−0.01	0.20	0.20	2.56	−0.55	0	0	0	0	0
232[n]	3-NH$_2$; 1′-N(CH$_3$)SO$_2$CH$_3$	5.11	5.25	−0.14	4.37	4.86	−0.49	−1.85	−0.66	0.20	0.20	0.64	0.00	0	0	0	1	0
233[aa]	3-NH$_2$; 3′-OCH$_3$; 1′-NHSO$_2$CH$_3$	5.63	5.92	−0.29	4.53	5.33	−0.80	−2.43	−0.82	0.20	0.20	0.64	−0.55	0	0	0	1	0
234[n]	3-NH$_2$; 3-OCH$_3$; 1′-NHSO$_2$Et	5.96	5.86	0.10	5.26	5.29	−0.03	−1.89	−0.82	0.20	0.20	0.64	−0.55	0	0	0	1	0
235[aa]	3-NH$_2$; 3′-CH$_3$; 1′-NHSO$_2$CH$_3$	4.52	5.05	−0.53	4.06[l]	5.14	−1.08	−1.85	−0.81	0.20	0.20	0.64	−1.24	0	0	0	1	0
236[x]	3-NHCH$_3$; 3′-OCH$_3$; 1′-NHSO$_2$CH$_3$	6.13	6.22	−0.09	5.45	5.10	0.35	−1.67	−1.00	0.20	0.20	1.13	−0.55	0	0	0	0	0
237[z]	3-NHCOCH$_3$; 3′-OCH$_3$; 1′-NHSO$_2$CH$_3$	5.64	5.45	0.19	4.33	4.63	−0.30	−2.17	−0.16	0.20	0.20	1.59	−0.55	0	0	0	0	0
238[z]	3-NHCOCH$_3$; 3′-OCH$_3$; 1′-NHSO$_2$Et	5.49	5.39	0.10	4.54	4.59	−0.05	−1.63	−0.16	0.20	0.20	1.59	−0.55	0	0	0	0	0
239[z]	3-NHCOCH$_3$; 3′-OCH$_3$; 1′-NHSO$_2$Pr	5.20	5.32	−0.12	4.56	4.55	0.01	−1.09	−0.16	0.20	0.20	1.59	−0.55	0	0	0	0	0
240[z]	3-NHCOCH$_3$; 3′-OCH$_3$; 1′-NHSO$_2$Bu	4.88	5.26	−0.38	4.38	4.51	−0.13	−0.55	−0.16	0.20	0.20	1.59	−0.55	0	0	0	0	0
241[z]	3-NHCOCH$_3$; 3′-OCH$_3$; 1′-NHSO$_2$Pe	4.59	5.19	−0.60	3.93	4.48	−0.55	−0.01	−0.16	0.20	0.20	1.59	−0.55	0	0	0	0	0
242[z]	3-NHCOCH$_3$; 3′-OCH$_3$; 1′-NHSO$_2$Hx	4.54	5.13	−0.59	4.20	4.44	−0.24	0.53	−0.16	0.20	0.20	1.59	−0.55	0	0	0	0	0
243[z]	3-NHCOCH$_3$; 3′-OCH$_3$; 1-NHSO$_2$Hp	4.55	5.06	−0.51	4.31	4.40	−0.09	1.07	−0.16	0.20	0.20	1.59	−0.55	0	0	0	0	0
244[aa]	3-NHCOCH$_3$; 3′-CH$_3$; 1′-NHSO$_2$CH$_3$	4.50	4.58	−0.08	3.40[l]	4.44	−1.04	−1.59	−0.15	0.20	0.20	1.59	−1.24	0	0	0	0	0
245[n]	3-X$_1$;[ff] 3′-OCH$_3$; 1′-NHSO$_2$CH$_3$	5.50	5.24	0.26	4.92	4.56	0.36	−3.50	−0.16	0.20	0.20	4.00	−0.55	0	0	0	0	0
246[n]	3-X$_2$;[gg] 3′-OCH$_3$; 1′-NHSO$_2$CH$_3$	5.32	5.36	−0.04	4.82	4.76	0.06	−3.08	−0.16	0.20	0.20	3.00	−0.55	0	0	0	0	0
247[aa]	3-NO$_2$; 3′-OCH$_3$; 1′-NHSO$_2$CH$_3$	5.68	5.05	0.62	5.17[l]	4.19	0.98	−1.48	0.62	0.20	0.20	0.84	−0.55	0	0	0	0	1
248[x]	3-NO$_2$; 3′-OCH$_3$; 1′-NHSO$_2$Et	5.27	4.99	0.28	4.71	4.15	0.56	−0.94	0.62	0.20	0.20	0.84	−0.55	0	0	0	0	1
249[x]	3-NO$_2$; 3′-OCH$_3$; 1′-NHSO$_2$Pr	4.84	4.92	−0.08	3.93	4.11	−0.18	−0.40	0.62	0.20	0.20	0.84	−0.55	0	0	0	0	1
250[x]	3-NO$_2$; 3′-OCH$_3$; 1′-NHSO$_2$Bu	4.64	4.86	−0.21	4.00	4.08	−0.08	0.14	0.62	0.20	0.20	0.84	−0.55	0	0	0	0	1
251[z]	3-NO$_2$; 3′-OCH$_3$; 1′-NHSO$_2$Pe	4.31	4.79	−0.48	4.03	4.04	−0.01	0.68	0.62	0.20	0.20	0.84	−0.55	0	0	0	0	1
252[z]	3-NO$_2$; 3′-OCH$_3$; 1′-NHSO$_2$Hx	3.70[l]	4.73	−1.03	3.62	4.00	−0.38	1.22	0.62	0.20	0.20	0.84	−0.55	0	0	0	0	1
253[z]	3-NO$_2$; 3′-OCH$_3$; 1′-NHSO$_2$Hp	3.53[l]	4.66	−1.13	3.45	3.96	−0.51	1.76	0.62	0.20	0.20	0.84	−0.55	0	0	0	0	1
254[aa]	3-NO$_2$; 3′-CH$_3$; 1′-NHSO$_2$CH$_3$	4.02	4.18	−0.16	3.19	4.00	−0.81	−0.90	0.63	0.20	0.20	0.84	−1.24	0	0	0	0	1
255[v]	3-CH$_3$; 3′-OCH$_3$; 1′-NHSO$_2$CH$_3$	5.62	5.23	0.39	4.86	4.35	0.51	−0.64	−0.33	0.20	0.20	0.66	−0.55	0	0	0	0	0
256[v]	3,3′-(CH$_3$)$_2$; 1′-NHSO$_2$CH$_3$	4.48	4.35	0.12	3.93	4.16	−0.23	−0.06	−0.32	0.20	0.20	0.66	−1.24	0	0	0	0	0
257[v]	3-Et; 3′-OCH$_3$; 1′-NHSO$_2$CH$_3$	4.72	5.35	−0.63	4.08	4.48	−0.40	−0.20	−0.31	0.20	0.20	1.13	−0.55	0	0	0	0	0
258[q]	3-CH$_2$CH$_2$CONH$_2$; 3′-OCH$_3$; 1′-NHSO$_2$CH$_3$	3.44[l]	5.62	−2.18	2.96[l]	4.84	−1.88	−2.42	−0.33	0.20	0.20	1.98	−0.55	0	0	0	0	0

Table I (*Continued*)

no.	substituents[mm]	log $(1/D_{50})$[a] obsd	log $(1/D_{50})$[a] calcd[h]	Δ log $(1/D_{50})$	log $(1/LD_{10})$[b] obsd	log $(1/LD_{10})$[b] calcd[i]	Δ log $(1/LD_{10})$	$\Sigma\pi$[c]	$\Sigma\sigma$[d]	MR_1[e]	MR_2[e]	MR_3[e]	$E_{s(3')}$[f]	R_{BS}[g]	I_{BS}	$I_{3,6}$	I_{NH_2}	I_{NO_2}
259[v]	3-CH$(CH_3)_2$; 3'-OCH_3; 1'-$NHSO_2CH_3$	3.00[l]	5.30	−2.30	3.05[l]	4.57	−1.52	0.33	−0.31	0.20	0.20	1.60	−0.55	0	0	0	0	0
260[ee]	3,3'-$(OCH_3)_2$; 1'-$NHSO_2CH_3$	5.26	5.53	−0.27	4.88	4.56	0.32	−1.22	−0.43	0.20	0.20	0.89	−0.55	0	0	0	0	0
261[ee]	3-CN; 3'-OCH_3; 1'-$NHSO_2CH_3$	4.17	4.58	−0.41	3.80	3.83	−0.03	−1.77	0.50	0.20	0.20	0.74	−0.55	0	0	0	0	0
262[v]	3-CF_3; 3'-OCH_3; 1'-$NHSO_2CH_3$	4.07	4.42	−0.35	3.63	3.76	−0.13	−0.32	0.38	0.20	0.20	0.60	−0.55	0	0	0	0	0
263[ee]	3-F; 3'-OCH_3; 1'-$NHSO_2CH_3$	4.89	4.47	0.42	4.25	3.97	0.28	−1.06	−0.10	0.20	0.20	0.19	−0.55	0	0	0	0	0
264[v]	3-Cl; 3'-OCH_3; 1'-$NHSO_2CH_3$	5.15	4.83	0.31	4.59	4.05	0.54	−0.49	0.07	0.20	0.20	0.70	−0.55	0	0	0	0	0
265[j]	10-CH_3; 3-Cl; 3'-OCH_3; 1'-$NHSO_2CH_3$	4.72	4.77	−0.05	4.40	4.02	0.38	0.01	0.07	0.20	0.20	0.70	−0.55	0	0	0	0	0
266[x]	3-Cl; 3'-OCH_3; 1'-$NHSO_2Et$	4.71	4.77	−0.06	4.47	4.02	0.45	0.01	0.07	0.20	0.20	0.70	−0.55	0	0	0	0	0
267[j]	10-CH_3; 3-Cl; 3'-OCH_3; 1'-$NHSO_2CH_3$	4.52	4.71	−0.19	3.91	3.98	−0.07	0.51	0.07	0.20	0.20	0.70	−0.55	0	0	0	0	0
268[v]	3-Br; 3'-OCH_3; 1'-$NHSO_2CH_3$	5.09	4.94	0.15	4.52	4.14	0.37	−0.34	0.07	0.20	0.20	0.96	−0.55	0	0	0	0	0
269[j]	10-CH_3; 3-Br; 3'-OCH_3; 1'-$NHSO_2CH_3$	4.87	4.89	−0.02	4.52	4.12	0.40	0.16	0.07	0.20	0.20	0.99	−0.55	0	0	0	0	0
270[v]	3-I; 3'-OCH_3; 1'-$NHSO_2CH_3$	5.09	5.02	0.07	4.57	4.32	0.24	−0.08	0.02	0.20	0.20	1.49	−0.55	0	0	0	0	0
271[hh]	4-aza; 3'-OCH_3; 1'-$NHSO_2CH_3$	4.29	4.14	0.15	3.79	3.69	0.09	−2.32	0.39	0.20	0.20	0.20	−0.55	0	0	0	0	0
272[z]	4-aza; 3'-OCH_3; 1'-$NHSO_2Et$	3.98	4.08	−0.10	3.80	3.66	0.14	−1.78	0.39	0.20	0.20	0.20	−0.55	0	0	0	0	0
273[z]	4-aza; 3'-OCH_3; 1'-$NHSO_2Pr$	3.91	4.01	−0.10	3.55	3.62	−0.07	−1.24	0.39	0.20	0.20	0.20	−0.55	0	0	0	0	0
274[z]	4-aza; 3'-OCH_3; 1'-$NHSO_2Bu$	3.90	3.95	−0.05	3.58	3.58	0.00	−0.70	0.39	0.20	0.20	0.20	−0.55	0	0	0	0	0
275[z]	4-aza; 3'-OCH_3; 1'-$NHSO_2Pe$	3.91	3.88	0.02	3.74	3.54	0.19	−0.16	0.39	0.20	0.20	0.20	−0.55	0	0	0	0	0
276[z]	4-aza; 3'-OCH_3; 1'-$NHSO_2Hx$	3.41	3.82	−0.41	3.10	3.51	−0.41	0.38	0.39	0.20	0.20	0.20	−0.55	0	0	0	0	0
277[z]	4-aza; 3'-OCH_3; 1'-$NHSO_2Hp$	<3.11[l,o]	3.75	−0.64	3.11	3.47	−0.36	0.92	0.39	0.20	0.20	0.20	−0.55	0	0	0	0	0
278[n]	4-$NHCOCH_3$; 3'-OCH_3; 1'-$NHSO_2Pr$	4.14	4.34	−0.20	3.97	3.87	0.10	−1.09	0.05	0.20	0.20	0.20	−0.55	0	0	0	0	0
279[hh]	4-NO_2; 3'-OCH_3; 1'-$NHSO_2CH_3$	3.64	3.88	−0.24	3.60	3.52	0.08	−1.48	0.55	0.20	0.20	0.20	−0.55	0	0	0	0	0
280[v]	4-CH_3; 3'-OCH_3; 1'-$NHSO_2CH_3$	5.24	4.57	0.67	4.77	4.05	0.72	−0.64	−0.23	0.20	0.20	0.20	−0.55	0	0	0	0	0
281[x]	4-CH_3; 3'-OCH_3; 1'-$NHSO_2Et$	4.88	4.50	0.37	4.62	4.01	0.61	−0.10	−0.23	0.20	0.20	0.20	−0.55	0	0	0	0	0
282[v]	4,3'-$(CH_3)_2$; 1'-$NHSO_2CH_3$	4.15	3.69	0.45	4.06	3.86	0.20	−0.06	−0.22	0.20	0.20	0.20	−1.24	0	0	0	0	0
283[n]	4-CH_2OH; 3'-OCH_3; 1'-$NHSO_2CH_3$	4.36	4.69	−0.33	3.66	4.10	−0.44	−2.23	−0.16	0.20	0.20	0.20	−0.55	0	0	0	0	0
284[n]	4-CH_2OH; 3'-OCH_3; 1'-$NHSO_2CH_3$	4.54	4.58	−0.04	4.18	4.04	0.14	−1.35	−0.16	0.20	0.20	0.20	−0.55	0	0	0	0	0
285[q]	4-$(CH_2)_2CONH_2$; 3'-OCH_3; 1'-$NHSO_3CH_3$	5.32	4.78	0.53	4.61	4.17	0.44	−2.42	−0.23	0.20	0.20	0.20	−0.55	0	0	0	0	0
286[ee]	4-Ph; 3'-OCH_3; 1'-$NHSO_2CH_3$	3.75	4.27	−0.52	3.51	3.85	−0.34	0.76	−0.10	0.20	0.20	0.20	−0.55	0	0	0	0	0
287[ee]	4-F; 3'-OCH_3; 1'-$NHSO_2CH_3$	4.76	4.21	0.55	4.30	3.77	0.53	−1.06	0.18	0.20	0.20	0.20	−0.55	0	0	0	0	0
288[ee]	4-Cl; 3'-OCH_3; 1'-$NHSO_2CH_3$	4.31	4.11	0.20	4.04	3.70	0.33	−0.49	0.21	0.20	0.20	0.20	−0.55	0	0	0	0	0
289[ee]	4-Br; 3'-OCH_3; 1'-$NHSO_2CH_3$	4.38	4.07	0.31	3.80	3.68	0.12	−0.34	0.23	0.20	0.20	0.20	−0.55	0	0	0	0	0
290[ee]	4-CN; 3'-OCH_3; 1'-$NHSO_2CH_3$	3.94	4.07	−0.13	3.67	3.65	0.02	−1.77	0.40	0.20	0.20	0.20	−0.55	0	0	0	0	0
291[z]	4-OCH_3; 3'-OCH_3; 1'-$NHSO_2CH_3$	4.94	4.45	0.49	4.68	3.94	0.74	−1.22	−0.04	0.20	0.20	0.20	−0.55	0	0	0	0	0
292[z]	4-OCH_3; 3'-OCH_3; 1'-$NHSO_2Et$	4.75	4.38	0.37	4.53	3.91	0.62	−0.68	−0.04	0.20	0.20	0.20	−0.55	0	0	0	0	0
293[z]	4-OCH_3; 3'-OCH_3; 1'-$NHSO_2Pr$	4.81	4.32	0.49	4.31	3.87	0.44	−0.14	−0.04	0.20	0.20	0.20	−0.55	0	0	0	0	0
294[hh]	4-OCH_3; 3'-OCH_3; 1'-$NHSO_2Bu$	4.57	4.25	0.32	4.14	3.83	0.31	0.40	−0.04	0.20	0.20	0.20	−0.55	0	0	0	0	0
295[z]	4-OEt; 3'-OCH_3; 1'-$NHSO_2CH_3$	4.58	4.42	0.16	4.24	3.93	0.31	−0.82	−0.06	0.20	0.20	0.20	−0.55	0	0	0	0	0
296[z]	4-OPr; 3'-OCH_3; 1'-$NHSO_2CH_3$	4.59	4.34	0.25	4.33	3.88	0.44	−0.15	−0.06	0.20	0.20	0.20	−0.55	0	0	0	0	0
297[z]	4-OBu; 3'-OCH_3; 1'-$NHSO_2CH_3$	4.51	4.27	0.23	4.14	3.85	0.29	0.39	−0.06	0.20	0.20	0.20	−0.55	0	0	0	0	0

298[z]	4-OBu; 3′-OCH_3; 1′-$NHSO_2Pr$	4.07	4.14	−0.07	3.98	3.77	0.21	1.47	−0.06	0.20	0.20	0.20	−0.55	0	0	0	0	0
299[z]	4-OBu; 3′-OCH_3; 1′-$NHSO_2Pe$	3.67	4.01	−0.34	3.67	3.70	−0.03	2.55	−0.06	0.20	0.20	0.20	−0.55	0	0	0	0	0
300[n]	4-OCH_2COOH; 3′-OCH_3; 1′-$NHSO_2CH_3$	4.16	4.57	−0.41	3.27	4.02	−0.75	−2.07	−0.06	0.20	0.20	0.20	−0.55	0	0	0	0	0
301[z]	4-$OCH_2CONHCH_3$; 3′-OCH_3; 1′-$NHSO_2CH_3$	4.54	4.58	−0.04	3.01[l]	4.02	−1.01	−2.17	−0.06	0.20	0.20	0.20	−0.55	0	0	0	0	0
302[q]	4-OCH_2CH_2OH; 3′-OCH_3; 1′-$NHSO_2CH_3$	4.94	4.56	0.38	4.64	4.01	0.63	−2.17	−0.04	0.20	0.20	0.20	−0.55	0	0	0	0	0
303[q]	4-$OCH_2CH(OH)CH_2OH$; 3′-OCH_3; 1′-$NHSO_2CH_3$	5.26	4.71	0.55	4.35	4.10	0.25	−3.42	−0.04	0.20	0.20	0.20	−0.55	0	0	0	0	0
304[q]	4-$OCH_2CH(OH)CH_2OH$; 3′-OCH_3; 1′-$NHSO_2CH_3$	4.44	3.84	0.60	3.59	3.91	−0.32	−2.90	−0.03	0.20	0.20	0.20	−1.24	0	0	0	0	0
305[z]	4-$O(CH_2)_3CONH_2$; 3′-OCH_3; 1′-$NHSO_2CH_3$	4.98	4.58	0.39	4.33	4.03	0.30	−2.20	−0.06	0.20	0.20	0.20	−0.55	0	0	0	0	0
306[n]	4-$CONH_2$; 3′-CH_3; 1′-$NHSO_2CH_3$	3.21	3.60	−0.39	2.96	3.74	−0.78	−2.11	0.12	0.20	0.20	0.20	−1.24	0	0	0	0	0
307[q]	4-$CONH_2$; 3′-OCH_3; 1′-$NHSO_2CH_3$	4.58	4.46	0.12	4.08	3.92	0.15	−2.69	0.12	0.20	0.20	0.20	−0.55	0	0	0	0	0
308[z]	4-$CONH_2$; 3′-OCH_3; 1′-$NHSO_2Et$	4.61	4.40	0.21	4.36	3.89	0.47	−2.15	0.12	0.20	0.20	0.20	−0.55	0	0	0	0	0
309[z]	4-$CONH_2$; 3′-OCH_3; 1′-$NHSO_2Pr$	4.68	4.33	0.35	4.16	3.85	0.31	−1.61	0.12	0.20	0.20	0.20	−0.55	0	0	0	0	0
310[z]	4-$CONH_2$; 3′-OCH_3; 1′-$NHSO_2Bu$	4.33	4.27	0.06	3.60	3.81	−0.21	−1.07	0.12	0.20	0.20	0.20	−0.55	0	0	0	0	0
311[z]	4-$CONH_2$; 3′-OCH_3; 1′-$NHSO_2Pe$	4.08	4.20	−0.12	3.68	3.77	−0.09	−0.53	0.12	0.20	0.20	0.20	−0.55	0	0	0	0	0
312[z]	4-$CONH_2$; 3′-OCH_3; 1′-$NHSO_2Hx$	3.92	4.14	−0.22	3.50	3.74	−0.24	0.01	0.12	0.20	0.20	0.20	−0.55	0	0	0	0	0
313[z]	4-$CONH_2$; 3′-OCH_3; 1′-$NHSO_2Hp$	3.63	4.07	−0.44	3.20	3.70	−0.50	0.55	0.12	0.20	0.20	0.20	−0.55	0	0	0	0	0
314[q]	4-$CONHCH_3$; 3′-OCH_3; 1′-$NHSO_2CH_3$	4.90	4.36	0.54	3.71	3.85	−0.14	−2.45	0.19	0.20	0.20	0.20	−0.55	0	0	0	0	0
315[z]	4-CONHBu; 3′-OCH_3; 1′-$NHSO_2CH_3$	4.25	4.18	0.06	3.96	3.75	0.21	−0.97	0.19	0.20	0.20	0.20	−0.55	0	0	0	0	0
316[z]	4-CONHBu; 3′-OCH_3; 1′-$NHSO_2Pr$	3.66	4.05	−0.39	3.56	3.68	−0.12	0.11	0.19	0.20	0.20	0.20	−0.55	0	0	0	0	0
317[z]	4-CONHBu; 3′-OCH_3; 1′-$NHSO_2Pe$	3.29	3.92	−0.63	3.28	3.60	−0.32	1.19	0.19	0.20	0.20	0.20	−0.55	0	0	0	0	0
318[n]	4-$CONH(CH_2)_2OH$; 3′-OCH_3; 1′-$NHSO_2CH_3$	4.63	4.44	0.19	4.17	3.90	0.27	−3.10	0.19	0.20	0.20	0.20	−0.55	0	0	0	0	0
319[n]	4-$CONHCH_2CH(OH)CH_3$; 3′-OCH_3; 1′-$NHSO_2CH_3$	5.33[l]	4.38	0.95	3.84	3.86	−0.02	−2.70	0.19	0.20	0.20	0.20	−0.55	0	0	0	0	0
320[n]	4-$CONH(CH_2)_3OH$; 3′-OCH_3; 1′-$NHSO_2CH_3$	4.56	4.44	0.11	3.89	3.90	−0.01	−3.03	0.19	0.20	0.20	0.20	−0.55	0	0	0	0	0
321[q]	4-$CONHCH_2CH(OH)CH_2OH$; 3′-OCH_3; 1′-$NHSO_2CH_3$	4.40	4.55	−0.15	3.70	3.97	−0.27	−4.07	0.19	0.20	0.20	0.20	−0.55	0	0	0	0	0
322[q]	4-CONH-Y;[ii] 3′-OCH_3; 1′-$NHSO_2CH_3$	4.32	4.56	−0.24	3.50	3.98	−0.48	−4.24	0.19	0.20	0.20	0.20	−0.55	0	0	0	0	0
323[q]	4-CONH-Y;[ii] 3′-OCH_3; 1′-$NHSO_2Pr$	4.20	4.45	−0.25	3.20	3.91	−0.71	−3.24	0.19	0.20	0.20	0.20	−0.55	0	0	0	0	0
324[q]	4-$CONHCH_2CONH_2$; 3′-OCH_3; 1′-$NHSO_2CH_3$	4.48	4.46	0.02	3.75	3.91	−0.16	−3.32	0.19	0.20	0.20	0.20	−0.55	0	0	0	0	0

Table I (*Continued*)

no.	substituents[mm]	log $(1/D_{50})$[a] obsd	log $(1/D_{50})$[a] calcd[h]	Δ log $(1/D_{50})$	log $(1/LD_{10})$[b] obsd	log $(1/LD_{10})$[b] calcd[i]	Δ log $(1/LD_{10})$	$\Sigma\pi$[c]	$\Sigma\sigma$[d]	MR_1[e]	MR_2[e]	MR_3[e]	$E_{s(3')}$[f]	R_{BS}[g]	I_{BS}	$I_{3,6}$	I_{NH_2}	I_{NO_2}
325[z]	4-CONHCH$_2$CONHCH$_3$; 3′-OCH$_3$; 1′-NHSO$_2$CH$_3$	4.74	4.39	0.35	3.66	3.87	−0.21	−2.86	0.19	0.20	0.20	0.20	−0.55	0	0	0	0	0
326[z]	4-CONH(CH$_2$)$_6$OSO$_2$CH$_3$; 3′-OCH$_3$; 1′-NHSO$_2$CH$_3$	4.05	4.14	−0.09	3.39	3.73	−0.34	−0.64	0.19	0.20	0.20	0.20	−0.55	0	0	0	0	0
327[n]	4-CONHCH$_2$CONH(CH$_2$)$_2$NH-(CH$_2$)$_2$OH; 3′-OCH$_3$; 1′-NHSO$_2$CH$_3$	4.21	4.46	−0.25	3.58	3.91	−0.33	−3.02	0.19	0.20	0.20	0.20	−0.55	0	0	0	0	0
328[q]	4-CON(CH$_3$)$_2$; 3′-OCH$_3$; 1′-NHSO$_2$CH$_3$	4.56	4.39	0.16	4.33	3.87	0.46	−2.71	0.19	0.20	0.20	0.20	−0.55	0	0	0	0	0
329[n]	4-CON(CH$_2$CH$_2$)$_2$O; 3′-OCH$_3$; 1′-NHSO$_2$CH$_3$	3.84	4.39	−0.55	3.39	3.87	−0.48	−2.66	0.19	0.20	0.20	0.20	−0.55	0	0	0	0	0
330[x]	2-NH$_2$; 3-Cl; 1′-NHSO$_2$CH$_3$	4.06	4.42	−0.36	3.71	3.72	−0.01	−1.70	0.07	0.20	0.64	0.70	0.00	0	0	0	0	0
331[w]	2,6-(NH$_2$)$_2$; 1′-NHSO$_2$CH$_3$	5.40	5.51	−0.11	4.56	4.50	0.05	−3.64	−0.82	0.20	0.64	0.64	0.00	0	0	0	0	0
332[x]	2-NH$_2$; 6-Cl; 1′-NHSO$_2$CH$_3$	4.36	4.42	−0.06	3.88	3.72	0.15	−1.70	0.07	0.20	0.64	0.70	0.00	0	0	0	0	0
333[aa]	3-NH$_2$; 4-CH$_3$; 1′-NHSO$_2$CH$_3$	5.57	5.32	0.24	4.56	4.92	−0.36	−1.85	−0.73	0.20	0.20	0.64	0.00	0	0	0	1	0
334[aa]	3-NHCOCH$_3$; 4-CH$_3$; 1′-NHSO$_2$CH$_3$	4.67	4.85	−0.18	4.13	4.21	−0.08	−1.59	−0.07	0.20	0.20	1.59	0.00	0	0	0	0	0
335[n]	3-NHCHO; 4-CH$_3$; 1′-NHSO$_2$CH$_3$	5.51	4.96	0.55	5.18[l]	4.18	1.00	−1.60	−0.19	0.20	0.20	1.13	0.00	0	0	0	0	0
336[aa]	3-NO$_2$; 4-CH$_3$; 1′-NHSO$_2$CH$_3$	3.92	4.45	−0.53	3.56	3.78	−0.22	−0.90	0.71	0.20	0.20	0.84	0.00	0	0	0	0	1
337[w]	3,4-(CH$_3$)$_2$; 1′-NHSO$_2$CH$_3$	4.53	4.63	−0.10	3.85	3.93	−0.08	−0.06	−0.24	0.20	0.20	0.66	0.00	0	0	0	0	0
338[w]	3,4-(OCH$_3$)$_2$; 1′-NHSO$_2$CH$_3$	3.49[l]	4.75	−1.26	3.18[l]	4.00	0.82	−1.02	−0.12	0.20	0.20	0.89	0.00	0	0	0	0	0
339[aa]	3-NH$_2$; 5-CH$_3$; 1′-NHSO$_2$CH$_3$	5.85	5.32	0.52	5.33	4.92	0.41	−1.85	−0.73	0.20	0.20	0.64	0.00	0	0	0	1	0
340[w]	3-NH$_2$; 5-OCH$_3$; 1′-NHSO$_2$CH$_3$	5.64	5.20	0.44	5.05	4.81	0.23	−2.43	−0.54	0.20	0.20	0.64	0.00	0	0	0	1	0
341[x]	3-NHCH$_3$; 5-CH$_3$; 1′-NHSO$_2$CH$_3$	6.14	5.62	0.52	5.31	4.69	0.62	−1.09	−0.91	0.20	0.20	1.13	0.00	0	0	0	0	0
342[aa]	3-NHCOCH$_3$; 5-CH$_3$; 1′-NHSO$_2$CH$_3$	5.63[l]	4.85	0.78	4.50	4.21	0.28	−1.59	−0.07	0.20	0.20	1.59	0.00	0	0	0	0	0
343[n]	3-NHCOCH$_3$; 5-OCH$_3$; 1′-NHSO$_2$CH$_3$	5.08	4.73	0.35	3.26[l]	4.11	−0.85	−2.17	0.12	0.20	0.20	1.59	0.00	0	0	0	0	0
344[aa]	3-NO$_2$; 5-CH$_3$; 1′-NHSO$_2$CH$_3$	4.36	4.45	−0.09	3.58	3.78	−0.20	−0.90	0.71	0.20	0.20	0.84	0.00	0	0	0	0	1
345[n]	3-NO$_2$; 5-CH$_3$; 1′-NHSO$_2$Et	4.83	4.39	0.44	3.93	3.74	0.19	−0.36	0.71	0.20	0.20	0.84	0.00	0	0	0	0	1
346[w]	3-NO$_2$; 5-OCH$_3$; 1′-NHSO$_2$CH$_3$	3.99	4.33	−0.34	3.20	3.67	−0.47	−1.48	0.90	0.20	0.20	0.84	0.00	0	0	0	0	1
347[x]	3,5-(CH$_3$)$_2$; 1′-NHSO$_2$CH$_3$	5.00	4.63	0.37	4.61	3.93	0.67	−0.06	−0.24	0.20	0.20	0.66	0.00	0	0	0	0	0
348[x]	3,5-(CH$_3$)$_2$; 1′-NHSO$_2$Et	4.74	4.56	0.17	4.59	3.90	0.69	0.48	−0.24	0.20	0.20	0.66	0.00	0	0	0	0	0
349[n]	3-OCH$_3$; 5-CH$_3$; 1′-NHSO$_2$CH$_3$	5.32	4.93	0.39	4.39	4.14	0.24	−0.64	−0.34	0.20	0.20	0.89	0.00	0	0	0	0	0
350[x]	3-Cl; 5-CH$_3$; 1′-NHSO$_2$CH$_3$	4.11	4.23	−0.12	3.75	3.64	0.11	0.09	0.16	0.20	0.20	0.70	0.00	0	0	0	0	0
351[w]	3-Cl; 5-OCH$_3$; 1′-NHSO$_2$CH$_3$	4.37	4.11	0.26	3.44	3.54	−0.10	−0.49	0.35	0.20	0.20	0.70	0.00	0	0	0	0	0
352[aa]	3-I; 5-CH$_3$; 1′-NHSO$_2$CH$_3$	4.67	4.42	0.25	4.24	3.91	0.33	0.50	0.11	0.20	0.20	1.49	0.00	0	0	0	0	0
353[aa]	3-I; 5-OCH$_3$; 1′-NHSO$_2$CH$_3$	4.60	4.30	0.30	3.90	3.81	0.09	−0.08	0.30	0.20	0.20	1.49	0.00	0	0	0	0	0
354[w]	3,6-(NH$_2$)$_2$; 1′-NHSO$_2$CH$_3$	5.82	5.66	0.16	5.50	5.15	0.35	−3.64	−1.32	0.20	0.20	1.08	0.00	0	0	1	1	0
355[w]	3-NH$_2$; 6-NO$_2$; 1′-NHSO$_2$CH$_3$	4.87	4.70	0.17	4.48	4.48	0.00	−2.69	0.12	0.20	0.20	1.28	0.00	0	0	1	1	1
356[w]	3-NH$_2$; 6-OCH$_3$; 1′-NHSO$_2$CH$_3$	5.05	5.15	−0.10	3.57[l]	4.84	−1.27	−2.43	−0.93	0.20	0.20	1.33	0.00	0	0	1	1	0
357[w]	3,6-(NHCOCH$_3$)$_2$; 1′-NHSO$_2$CH$_3$	4.80	4.10	0.70	3.38	3.83	−0.45	−3.12	0.00	0.20	0.20	2.98	0.00	0	0	1	0	0
358[w]	3-NHCOCH$_3$; 6-NO$_2$; 1′-NHSO$_2$CH$_3$	5.49[l]	3.93	1.56	4.52[l]	3.64	0.88	−2.43	0.78	0.20	0.20	2.23	0.00	0	0	1	0	1
359[n]	3-NHCOCH$_3$; 6-OCH$_3$; 1′-NHSO$_2$CH$_3$	3.50[l]	4.37	−0.87	3.26	3.99	−0.73	−2.17	−0.27	0.20	0.20	2.28	0.00	0	0	1	0	0

360[n]	3-NHCOCH$_3$; 6-Cl; 1′-NHSO$_2$CH$_3$	3.65	3.81	−0.16	3.39	3.55	−0.16	−1.44	0.23	0.20	0.20	2.10	0.00	0	0	1	0	0
361[aa]	3-NO$_2$; 6-CH$_3$; 1′-NHSO$_2$CH$_3$	4.06	3.99	0.07	2.92	3.50	−0.58	−0.90	0.61	0.20	0.20	1.30	0.00	0	0	1	0	1
362[w]	3-NO$_2$; 6-OCH$_3$; 1′-NHSO$_2$CH$_3$	3.95	4.16	−0.21	2.98	3.67	−0.69	−1.48	0.51	0.20	0.20	1.53	0.00	0	0	1	0	1
363[n]	3,6-(N$_3$)$_2$; 1′-NHSO$_2$CH$_3$	4.24	3.60	0.64	4.08	3.40	0.67	−0.26	0.30	0.20	0.20	2.04	0.00	0	0	1	0	0
364[w]	3,6-(OCH$_3$)$_2$; 1′-NHSO$_2$CH$_3$	4.06	4.61	−0.55	3.95	4.03	−0.08	−1.22	−0.54	0.20	0.20	1.58	0.00	0	0	1	0	0
365[w]	3-Cl; 6-OCH$_3$; 1′-NHSO$_2$CH$_3$	3.67	4.02	−0.35	3.12	3.56	−0.44	−0.49	−0.04	0.20	0.20	1.39	0.00	0	0	1	0	0
366[aa]	3,6-(Br)$_2$; 1′-NHSO$_2$CH$_3$	3.04	3.37	−0.33	3.04	3.19	−0.15	0.53	0.46	0.20	0.20	1.78	0.00	0	0	1	0	0
367[x]	4,5-(CH$_3$)$_2$; 1′-NHSO$_2$CH$_3$	3.86	3.97	−0.11	3.57	3.63	−0.06	−0.06	−0.14	0.20	0.20	0.20	0.00	0	0	0	0	0
368[x]	2-NH$_2$; 3-Br; 3′-OCH$_3$; 1′-NHSO$_2$CH$_3$	5.22	5.14	0.08	4.42	4.25	0.17	−1.57	−0.09	0.20	0.64	0.99	−0.55	0	0	0	0	0
369[x]	2-NH$_2$; 3-CF$_3$; 3′-OCH$_3$; 1′-NHSO$_2$CH$_3$	4.45	4.62	−0.17	4.03	3.86	0.17	−1.55	0.22	0.20	0.64	0.60	−0.55	0	0	0	0	0
370[x]	3,4,3′-(CH$_3$)$_3$; 1′-NHSO$_2$CH$_3$	4.48	4.36	0.12	4.17	4.17	0.00	0.50	−0.39	0.20	0.20	0.66	−1.24	0	0	0	0	0
371[x]	3,4-(CH$_3$)$_2$; 3′-OCH$_3$; 1′-NHSO$_2$CH$_3$	5.15	5.23	−0.08	4.80	4.36	0.44	−0.08	−0.40	0.20	0.20	0.66	−0.55	0	0	0	0	0
372[n]	3,4-benz; 3′-OCH$_3$; 1′-NHSO$_2$CH$_3$	4.54	5.01	−0.47	3.94	4.20	−0.26	0.12	−0.07	0.20	0.20	0.91	−0.55	0	0	0	0	0
373[n]	3,4-(CH=CHCH=N); 3′-OCH$_3$; 1′-NHSO$_2$CH$_3$	5.10	5.12	−0.02	4.80	4.25	0.55	−1.36	0.00	0.20	0.20	0.91	−0.55	0	0	0	0	0
374[n]	3,4-(OC(CH$_3$)CH$_2$); 3′-OCH$_3$; 1′-NHSO$_2$CH$_3$	4.71	5.19	−0.48	4.17	4.32	−0.15	−0.68	−0.16	0.20	0.20	0.90	−0.55	0	0	0	0	0
375[n]	3-Cl, 4-CH$_3$; 3′-OCH$_3$; 1′-NHSO$_2$CH$_3$	4.65	4.84	−0.19	4.55	4.07	0.48	0.07	0.00	0.20	0.20	0.71	−0.55	0	0	0	0	0
376[aa]	2-NH$_2$; 6-NO$_2$; 3′-OCH$_3$; 1′-NHSO$_2$CH$_3$	5.40	5.25	0.15	4.46	4.29	0.17	−2.71	0.46	0.20	0.64	0.84	−0.55	0	0	0	0	1
377[n]	2-NH$_2$; 6-I; 3′-OCH$_3$; 1′-NHSO$_2$CH$_3$	5.46	5.22	0.24	4.26	4.43	−0.17	−1.31	−0.14	0.20	0.64	1.50	−0.55	0	0	0	0	0
378[aa]	3-NH$_2$; 5-CH$_3$; 3′-OCH$_3$; 1′-NHSO$_2$CH$_3$	6.06	5.93	0.13	5.58	5.34	0.23	−1.87	−0.89	0.20	0.20	0.64	−0.55	0	0	0	1	0
379[x]	3-NHCH$_3$; 5-CH$_3$; 3′-OCH$_3$; 1′-NHSO$_2$CH$_3$	6.50	6.23	0.27	5.78	5.12	0.66	−1.11	−1.07	0.20	0.20	1.13	−0.55	0	0	0	0	0
380[n]	3-NHCOOCH$_3$; 5-CH$_3$; 3′-OCH$_3$; 1′-NHSO$_2$CH$_3$	5.01	5.52	−0.51	4.62	4.74	−0.12	−1.01	−0.38	0.20	0.20	1.75	−0.55	0	0	0	0	0
381[n]	3-N$_3$; 5-CH$_3$; 3′-OCH$_3$; 1′-NHSO$_2$CH$_3$	5.14	5.11	0.03	4.85	4.30	0.55	−0.18	−0.08	0.20	0.20	1.12	−0.55	0	0	0	0	0
382[aa]	3-NO$_2$; 5,3′-(CH$_3$)$_2$; 1′-NHSO$_2$CH$_3$	3.97	4.18	−0.21	2.97[l]	4.02	−1.05	−0.34	0.56	0.20	0.20	0.84	−1.24	0	0	0	0	1
383[aa]	3-NO$_2$; 5,3′-(OCH$_3$)$_2$; 1′-NHSO$_2$CH$_3$	5.10	4.93	0.16	4.40	4.10	0.30	−1.50	0.74	0.20	0.20	0.84	−0.55	0	0	0	0	1
384[n]	3-NO$_2$; 5-CH$_3$; 3′-OCH$_3$; 1′-NHSO$_2$Et	5.30	5.00	0.30	4.75	4.17	0.58	−0.42	0.55	0.20	0.20	0.84	−0.55	0	0	0	0	1
385[aa]	3-NO$_2$; 5-CH$_3$; 3′-OCH$_3$; 1′-NHSO$_2$CH$_3$	5.05	5.06	−0.01	4.51	4.20	0.31	−0.92	0.55	0.20	0.20	0.84	−0.55	0	0	0	0	1
386[x]	3,5,3′-(CH$_3$)$_3$; 1′-NHSO$_2$CH$_3$	4.67	4.36	0.31	4.02	4.17	−0.15	0.50	−0.39	0.20	0.20	0.66	−1.24	0	0	0	0	0
387[x]	3,5-(CH$_3$)$_2$; 3′-OCH$_3$; 1′-NHSO$_2$CH$_3$	5.20	5.23	−0.03	5.13	4.36	0.77	−0.08	−0.40	0.20	0.20	0.66	−0.55	0	0	0	0	0
388[n]	3-CH$_3$; 5-OCH$_3$; 3′-OCH$_3$; 1′-NHSO$_2$CH$_3$	5.21	5.12	0.09	4.95	4.26	0.69	−0.66	−0.21	0.20	0.20	0.67	−0.55	0	0	0	0	0
389[n]	3-OCH$_3$; 5-CH$_3$; 3′-OCH$_3$; 2′-NHSO$_2$CH$_3$	5.67	5.53	0.14	5.20	4.57	0.63	−0.66	−0.50	0.20	0.20	0.89	−0.55	0	0	0	0	0

Table I (*Continued*)

no.	substituents[mm]	log $(1/D_{50})$[a] obsd	log $(1/D_{50})$[a] calcd[h]	Δ log $(1/D_{50})$	log $(1/LD_{10})$[b] obsd	log $(1/LD_{10})$[b] calcd[i]	Δ log $(1/LD_{10})$	$\Sigma\pi$[c]	$\Sigma\sigma$[d]	MR_1[e]	MR_2[e]	MR_3[e]	$E_{s(3')}$[f]	R_{BS}[g]	I_{BS}	$I_{3,6}$	I_{NH_2}	I_{NO_2}
390[x]	3-Cl; 5-CH_3; 3'-OCH_3; 1'-$NHSO_2CH_3$	4.98	4.84	0.14	4.45	4.07	0.38	0.07	0.00	0.20	0.20	0.70	−0.55	0	0	0	0	0
391[x]	3-Cl; 5,3'-$(OCH_3)_2$; 1'-$NHSO_2CH_3$	4.90	4.71	0.18	4.60	3.96	0.64	−0.51	0.19	0.20	0.20	0.70	−0.55	0	0	0	0	0
392[n]	3-Br; 5-CH_3; 3'-OCH_3; 1'-$NHSO_2CH_3$	5.23	4.95	0.28	4.69	4.17	0.52	0.22	0.00	0.20	0.20	0.99	−0.55	0	0	0	0	0
393[n]	3-Br; 5-OCH_3; 3'-OCH_3; 1'-$NHSO_2CH_3$	5.19	4.83	0.36	4.69	4.07	0.62	−0.36	0.19	0.20	0.20	0.99	−0.55	0	0	0	0	0
394[aa]	3-I; 5-CH_3; 3'-OCH_3; 1'-$NHSO_2CH_3$	4.98	5.03	−0.05	4.71	4.34	0.37	0.48	−0.05	0.20	0.20	1.49	−0.55	0	0	0	0	0
395[aa]	3-I; 5,3'-$(OCH_3)_2$; 1'-$NHSO_2CH_3$	5.04	4.90	0.13	4.70	4.23	0.46	−0.10	0.14	0.20	0.20	1.49	−0.55	0	0	0	0	0
396[q]	3-I; 5-$OCH_2CH(OH)CH_2OH$; 3'-OCH_3; 1'-$NHSO_2CH_3$	5.33	5.19	0.14	3.73	4.40	−0.67	−2.30	0.12	0.20	0.20	1.49	−0.55	0	0	0	0	0
397	3,6-$(NHCOCH_3)_2$; 3'-OCH_3; 1'-$NHSO_2CH_3$	4.17	4.70	−0.53	4.08	4.25	−0.17	−3.14	−0.16	0.20	0.20	2.99	−0.55	0	0	1	0	0
398[aa]	3,6-$(NO_2)_2$; 3'-OCH_3; 1'-$NHSO_2CH_3$	3.51	3.74	−0.23	3.34	3.31	0.03	−1.76	1.40	0.20	0.20	1.48	−0.55	0	0	1	0	1
399[aa]	3-NO_2; 6-CH_3; 3'-OCH_3; 1'-$NHSO_2CH_3$	4.92	4.59	0.33	4.16	3.92	0.24	−0.92	0.45	0.20	0.20	1.30	−0.55	0	0	1	0	1
400[n]	3-Cl; 6-OCH_3; 3'-OCH_3; 1'-$NHSO_2CH_3$	4.32	4.63	−0.31	4.32	3.98	0.34	−0.51	−0.20	0.20	0.20	1.39	−0.55	0	0	1	0	0
401[aa]	3,6-Cl_2; 3'-OCH_3; 1'-$NHSO_2CH_3$	3.97	4.02	−0.05	3.72	3.50	0.22	0.22	0.30	0.20	0.20	1.20	−0.55	0	0	1	0	0
402[aa]	3,6-Br_2; 3'-OCH_3; 1'-$NHSO_2CH_3$	3.72	3.98	−0.26	3.46	3.62	−0.16	0.52	0.30	0.20	0.20	1.78	−0.55	0	0	1	0	0
403[x]	4,5,3'-$(CH_3)_3$; 1'-$NHSO_2CH_3$	3.75	3.70	0.05	3.53	3.87	−0.34	0.50	−0.29	0.20	0.20	0.20	−1.24	0	0	0	0	0
404[x]	4,5-$(CH_3)_2$; 3'-OCH_3; 1'-$NHSO_2CH_3$	4.60	4.57	0.03	3.92	4.06	−0.14	−0.08	−0.30	0.20	0.20	0.20	−0.55	0	0	0	0	0
405[x]	4,5-$(CH_3)_2$; 3'-OCH_3; 1'-$NHSO_2Et$	4.77	4.51	0.26	4.42	4.02	0.40	0.46	−0.30	0.20	0.20	0.20	−0.55	0	0	0	0	0
406[n]	4,5-$(OCH_3)_2$; 3'-OCH_3; 1'-$NHSO_2CH_3$	4.76	4.33	0.43	4.74[l]	3.85	0.89	−1.24	0.08	0.20	0.20	0.20	−0.55	0	0	0	0	0
407[x]	2-NH_2; 3-Br; 5-CH_3; 1'-$NHSO_2CH_3$	4.80	4.54	0.26	4.19	3.84	0.35	−0.99	0.00	0.20	0.64	0.99	0.00	0	0	0	0	0
408[aa]	3-NH_2; 4,5-$(CH_3)_2$; 1'-$NHSO_2CH_3$	5.54	5.33	0.21	5.04	4.93	0.11	−1.29	−0.80	0.20	0.20	0.64	0.00	0	0	0	1	0
409[aa]	3-$NHCOCH_3$; 4,5-$(CH_3)_2$; 1'-$NHSO_2CH_3$	4.67	4.85	−0.18	4.44	4.23	0.21	−1.03	−0.14	0.20	0.20	1.59	0.00	0	0	0	0	0
410[aa]	3-NO_2; 4,6-$(CH_3)_2$; 1'-$NHSO_2CH_3$	3.60	3.99	−0.39	3.11	3.51	−0.40	−0.34	0.54	0.20	0.20	1.30	0.00	0	0	1	0	1
411[aa]	3-NH_2; 5,6-$(CH_3)_2$; 1'-$NHSO_2CH_3$	5.52	4.96	0.56	4.67	4.67	0.00	−1.29	−0.90	0.20	0.20	1.10	0.00	0	0	1	1	0
412[x]	3-$NHCH_3$; 5,6-$(CH_3)_2$; 1'-$NHSO_2CH_3$	5.19	5.08	0.11	4.70	4.39	0.31	−0.53	−1.08	0.20	0.20	1.59	0.00	0	0	1	0	0
413[aa]	3-NO_2; 5,6-$(CH_3)_2$; 1'-$NHSO_2CH_3$	4.44	3.99	0.45	3.42	3.51	−0.09	−0.34	0.54	0.20	0.20	1.30	0.00	0	0	1	0	1
414[x]	3,4,5-$(CH_3)_3$; 1'-$NHSO_2CH_3$	4.64	4.63	0.01	3.35	3.95	−0.60	0.50	−0.31	0.20	0.20	0.66	0.00	0	0	0	0	0
415[x]	3,4,6-$(CH_3)_3$; 1'-$NHSO_2CH_3$	4.14	4.25	−0.11	3.84	3.69	0.15	0.50	−0.41	0.20	0.20	1.12	0.00	0	0	1	0	0

416[x]	2-NH_2; 3,4-$(CH_3)_2$; 3′-OCH_3; 1′-$NHSO_2CH_3$	5.19	5.43	−0.24	4.12	4.46	−0.34	−1.31	−0.56	0.20	0.64	0.66	−0.55	0	0	0	0	0
417[x]	2-NH_2; 3-Br; 5-CH_3; 3′-OCH_3; 1′-$NHSO_2CH_3$	5.07	5.15	−0.08	4.39	4.27	0.12	−1.01	−0.16	0.20	0.64	0.99	−0.55	0	0	0	0	0
418[x]	3-NH_2; 4,5-$(CH_3)_2$; 3′-OCH_3; 1′-$NHSO_2CH_3$	5.85	5.93	−0.08	5.40	5.36	0.04	−1.31	−0.96	0.20	0.20	0.64	−0.55	0	0	0	1	0
419[aa]	3-NO_2; 4,5-$(CH_3)_2$; 3′-OCH_3; 1′-$NHSO_2CH_3$	3.30[l]	5.06	−1.76	3.00[l]	4.22	−1.22	−0.36	0.48	0.20	0.20	0.84	−0.55	0	0	0	0	1
420[w]	3,4,5-$(CH_3)_3$; 3′-OCH_3; 1′-$NHSO_2CH_3$	4.74	5.24	−0.50	4.22	4.38	−0.16	0.48	−0.47	0.20	0.20	0.66	−0.55	0	0	0	0	0
421[x]	3-NO_2; 5,6-$(CH_3)_2$; 3′-OCH_3; 1′-$NHSO_2Et$	4.72	4.53	0.19	4.04	3.90	0.14	0.18	0.38	0.20	0.20	1.30	−0.55	0	0	1	0	1
422[aa]	3-NH_2; 5,6-$(CH_3)_2$; 3′-OCH_3; 1′-$NHSO_2Et$	5.67	5.56	0.11	4.98	5.10	−0.12	−1.31	−1.06	0.20	0.20	1.10	−0.55	0	0	1	1	0
423[x]	3-$NHCH_3$; 5,6-$(CH_3)_2$; 3′-OCH_3; 1′-$NHSO_2CH_3$	5.70	5.68	0.02	5.05	4.82	0.23	−0.55	−1.24	0.20	0.20	1.59	−0.55	0	0	1	0	0
424[aa]	3-NO_2; 5,6-$(CH_3)_2$; 3′-CH_3; 1′-$NHSO_2CH_3$	3.39	3.72	−0.33	3.08	3.75	−0.67	0.22	0.39	0.20	0.20	1.30	−1.24	0	0	1	0	1
425[aa]	3-NO_2; 5,6-$(CH_3)_2$; 3′-OCH_3; 1′-$NHSO_2CH_3$	4.59	4.60	−0.01	4.07	3.94	0.13	−0.36	0.38	0.20	0.20	1.30	−0.55	0	0	1	0	1
426[aa]	3,4,6-$(CH_3)_3$; 3′-OCH_3; 1′-$NHSO_2CH_3$	5.10	4.86	0.24	4.63	4.12	0.51	0.48	−0.57	0.20	0.20	1.12	−0.55	0	0	1	0	0
427[n]	3-NO_2; 1′-$NHSO_2(CH_2)_2NHCHO$	4.16	4.54	−0.38	3.44	3.81	−0.37	−2.18	0.78	0.20	0.20	0.84	0.00	0	0	0	0	1
428[q]	1′-$NHSO_2(CH_2)_2NHCOCH_3$	4.10	4.03	0.07	3.80	3.65	0.15	−1.78	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
429[q]	1′-$NHSO_2(CH_2)_2N(CH_3)COCH_3$	3.48	3.97	−0.49	3.21	3.61	−0.40	−1.25	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
430[n]	3-NO_2; 1′-$NHSO_2(CH_2)_2$-$NHCOCH(CH_3)NH_2$	4.19	4.45	−0.26	4.19	3.76	0.43	−1.47	0.78	0.20	0.20	0.84	0.00	0	0	0	0	1
431[q]	1′-$NHSO_2(CH_2)_2NHCOOCH_3$	3.59	3.95	−0.36	2.99	3.60	−0.61	−1.10	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
432[q]	1′-$NHSO_2(CH_2)_2NHCONH_2$	3.49	4.08	−0.59	3.22	3.67	−0.45	−2.15	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
433[n]	3,5-$(CH_3)_2$; 1′-$NHSO_2(CH_2)_2$-$NHCONH_2$	4.40	4.75	−0.35	3.80	4.00	−0.20	−1.04	−0.24	0.20	0.20	0.66	0.00	0	0	0	0	0
434[q]	1′-$NHSO_2(CH_2)_2NHSO_2CH_3$	3.66	4.02	−0.36	3.66	3.64	0.02	−1.70	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
435[q]	1′-$NHSO_2(CH_2)_2$-$N(CONHCH_2CO)$	3.93	4.11	−0.18	3.37	3.69	−0.32	−2.42	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
436[q]	1′-$NHSO_2(CH_2)_2OCH_3$	3.72	3.93	−0.21	3.17	3.59	−0.42	−0.91	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
437[q]	1′-$NHSO_2(CH_2)_2CONH_2$	3.18[l]	4.08	−0.90	2.96[l]	3.67	−0.71	−2.16	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
438[q]	1′-$NHSO_2(CH_2)_2CON(CH_3)_2$	3.82	3.97	−0.15	3.44	3.61	−0.17	−1.25	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
439[n]	1′-$(CH_2)_3NHSO_2CH_3$	3.85	4.04	−0.19	3.52	3.68	−0.16	−0.44	−0.16	0.20	0.20	0.20	0.00	0	0	0	0	0
440[n]	3-NO_2; 1′-$NHSO_2(CH_2)_2NHCHO$	4.11	4.51	−0.40	2.97[l]	3.80	−0.83	−1.93	0.78	0.20	0.20	0.84	0.00	0	0	0	0	1
441[jj]	1′-$NHSO_2(CH_2)_2NHCOCH_2NH_2$	3.84	4.06	−0.22	3.54	3.66	−0.12	−2.01	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
442[jj]	3-NO_2; 1′-$NHSO_2(CH_2)_2$-$NHCOCH_2NH_2$	4.27	4.55	−0.28	3.36	3.82	−0.46	−2.29	0.78	0.20	0.20	0.84	0.00	0	0	0	0	1
443[jj]	3-NO_2; 1′-$NHSO_2(CH_2)_2$-$NHCO(CH_2)_2NH_2$	4.75	4.78	−0.03	3.59	3.96	−0.37	−4.39	0.78	0.20	0.20	0.84	0.00	0	0	0	0	1
444[jj]	3-NO_2; 1′-$NHSO_2(CH_2)_2NH_2$	4.24	4.75	−0.51	4.24	3.94	0.30	−4.01	0.78	0.20	0.20	0.84	0.00	0	0	0	0	1
445[jj]	10-CH_3; 3-NH_2; 1′-$NHSO_2$-$(CH_2)_2NH_2$	5.29	5.55	−0.26	4.22	4.55	−0.33	−4.46	−0.66	0.20	0.20	0.64	0.00	0	0	0	0	0
446[jj]	3-NO_2; 1′-$NHSO_2(CH_2)_3NH_2$	4.64	4.73	−0.09	4.28	3.93	0.35	−3.88	0.78	0.20	0.20	0.84	0.00	0	0	0	0	1
447[jj]	10-CH_3; 1′-$NHSO_2(CH_2)_4NH_2$	4.06	4.16	−0.10	4.05	3.72	0.33	−2.84	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
448[jj]	10-CH_3; 3-NH_2; 1′-$NHSO_2(CH_2)_4NH_2$	5.64	5.51	0.13	4.45	4.52	−0.07	−4.07	−0.66	0.20	0.20	0.64	0.00	0	0	0	0	0

Table I (*Continued*)

no.	substituents[mm]	log $(1/D_{50})$[a] obsd	log $(1/D_{50})$[a] calcd[h]	Δ log $(1/D_{50})$	log $(1/LD_{10})$[b] obsd	log $(1/LD_{10})$[b] calcd[i]	Δ log $(1/LD_{10})$	$\Sigma\pi$[c]	$\Sigma\sigma$[d]	MR_1[e]	MR_2[e]	MR_3[e]	$E_{s(3')}$[f]	R_{BS}[g]	I_{BS}	$I_{3,6}$	I_{NH_2}	I_{NO_2}
449[jj]	3-NHCOCH$_3$; 1′-NHSO$_2$-(CH$_2$)$_4$NH$_2$	4.52	5.09	−0.57	4.01	4.35	−0.34	−4.33	0.00	0.20	0.20	1.59	0.00	0	0	0	0	0
450[jj]	3-NO$_2$; 1′-NHSO$_2$(CH$_2$)$_4$NH$_2$	4.89	4.71	0.18	3.78	3.91	−0.13	−3.64	0.78	0.20	0.20	0.84	0.00	0	0	0	0	1
451[n]	4,5-(CH$_3$)$_2$; 1′-NHSO$_2$-(CH$_2$)$_4$NH$_2$	4.44	4.23	0.21	4.30	3.79	0.51	−2.24	−0.14	0.20	0.20	0.20	0.00	0	0	0	0	0
452[jj]	3-NO$_2$; 3′-OCH$_3$; 1′-NHSO$_2$(CH$_2$)$_4$NH$_2$	5.21	5.31	−0.10	5.06	4.34	0.72	−3.66	0.62	0.20	0.20	0.84	−0.55	0	0	0	0	1
453[jj]	3-NO$_2$; 5,6-(CH$_3$)$_2$; 1′-NHSO$_2$(CH$_2$)$_4$NH$_2$	4.10	4.25	−0.15	4.20	3.66	0.54	−2.52	0.54	0.20	0.20	1.30	0.00	0	0	1	0	1
454[jj]	3-NO$_2$; 1′-NHSO$_2$(CH$_2$)$_4$-N(CH$_3$)$_2$	4.67	4.76	−0.09	4.52	3.95	0.57	−4.10	0.78	0.20	0.20	0.84	0.00	0	0	0	0	1
455[jj]	3-NO$_2$; 1′-NHSO$_2$(CH$_2$)$_5$NH$_2$	4.74	4.64	0.10	3.70	3.87	−0.17	−3.08	0.78	0.20	0.20	0.84	0.00	0	0	0	0	1
456[jj]	3-NO$_2$; 1′-NHSO$_2$(CH$_2$)$_6$NH$_2$	5.50[l]	4.59	0.91	5.27[l]	3.84	1.43	−2.61	0.78	0.20	0.20	0.84	0.00	0	0	0	0	1
457[jj]	3-NO$_2$; 1′-NHSO$_2$(CH$_2$)$_7$NH$_2$	4.21	4.53	−0.32	4.16	3.81	0.35	−2.14	0.78	0.20	0.20	0.84	0.00	0	0	0	0	1
458[jj]	3-NO$_2$; 1′-NHSO$_2$(CH$_2$)$_2$-NHC(NH)NH$_2$	4.90	4.79	0.11	4.00	4.03	−0.03	−5.34	0.78	0.20	0.20	0.84	0.00	0	0	0	0	1
459[n]	3-NO$_2$; 3′-OCH$_3$; 1′-NHSO$_2$-(CH$_2$)$_2$NHC(NH)NH$_2$	4.09[l]	5.38	−1.29	3.84	4.46	−0.62	−5.36	0.62	0.20	0.20	0.84	−0.55	0	0	0	0	1
460[n]	2,6-(NH$_2$)$_2$; 1′-NHSO$_2$-(CH$_2$)$_2$NHC(NH)NH$_2$	4.25	4.39	−0.14	4.13[l]	5.29	−1.16	−7.82	−0.82	0.20	0.64	0.64	0.00	0	0	0	1	0
461[jj]	3-NHCOCH$_3$; 6-NO$_2$; 1′-NHSO$_2$-(CH$_2$)$_2$NHC(NH)NH$_2$	5.48	3.84	1.64	4.31	3.91	0.40	−6.31	0.78	0.20	0.20	2.23	0.00	0	0	1	0	1
462[jj]	10-CH$_3$; 3-NH$_2$; 1′-NHSO$_2$-(CH$_2$)$_3$NHC(NH)NH$_2$	5.23	5.43	−0.20	4.47	4.64	−0.17	−5.83	−0.66	0.20	0.20	0.64	0.00	0	0	0	0	0
463[jj]	3-NO$_2$; 1′-NHSO$_2$(CH$_2$)$_3$-NHC(NH)NH$_2$	4.75	4.81	−0.06	3.89	4.00	−0.11	−4.94	0.78	0.20	0.20	0.84	0.00	0	0	0	0	1
464[n]	2,6-(NH$_2$)$_2$; 1′-NHSO$_2$(CH$_2$)$_3$-NHC(NH)NH$_2$	4.91	4.70	0.21	4.17[l]	5.26	−1.09	−7.32	−0.82	0.20	0.64	0.64	0.00	0	0	0	1	0
465[jj]	3-NHCOCH$_3$; 6-NO$_2$; 1′-NHSO$_2$-(CH$_2$)$_3$NHC(NH)NH$_2$	5.25[l]	4.04	1.21	4.23	3.87	0.36	−5.81	0.78	0.20	0.20	2.23	0.00	0	0	1	0	1
466[jj]	3,6-(NO$_2$)$_2$; 1′-NHSO$_2$(CH$_2$)$_3$-NHC(NH)NH$_2$	3.46	3.45	0.01	3.06	3.12	−0.06	−5.12	1.56	0.20	0.20	1.47	0.00	0	0	1	0	1
467[jj]	10-CH$_3$; 3-NH$_2$; 1′-NHSO$_2$-(CH$_2$)$_4$NHC(NH)NH$_2$	5.44	5.54	−0.10	4.58	4.61	−0.03	−5.33	−0.66	0.20	0.20	0.64	0.00	0	0	0	0	0
468[jj]	3-NO$_2$; 1′-NHSO$_2$(CH$_2$)$_4$-NHC(NH)NH$_2$	4.68	4.78	−0.10	3.86	3.96	−0.10	−4.34	0.78	0.20	0.20	0.84	0.00	0	0	0	0	1
469[jj]	4,5-(CH$_3$)$_2$; 1′-NHSO$_2$(CH$_2$)$_4$-NHC(NH)NH$_2$	3.90	4.35	−0.45	3.80	3.85	−0.05	−3.28	−0.14	0.20	0.20	0.20	0.00	0	0	0	0	0
470[jj]	3-NO$_2$; 1′-NHSO$_2$(CH$_2$)$_5$-NHC(NH)NH$_2$	4.73	4.73	0.00	3.73	3.93	−0.20	−3.84	0.78	0.20	0.20	0.84	0.00	0	0	0	0	1
471[jj]	3-NO$_2$; 1′-NHSO$_2$(CH$_2$)$_6$-NHC(NH)NH$_2$	4.05	4.67	−0.62	3.88	3.89	−0.01	−3.34	0.78	0.20	0.20	0.84	0.00	0	0	0	0	1
472[p]	1′-NHSO$_2$Ph	4.62	4.28	0.34	3.79	3.49	0.30	0.45	0.00	0.20	0.20	0.20	0.00	0	1	0	0	0
473[n]	2-NH$_2$; 1′-NHSO$_2$Ph	4.63	4.59	0.04	3.38	3.70	−0.32	−0.78	−0.16	0.20	0.20	0.20	0.00	0	1	0	0	0
474[n]	2-NH$_2$; 1′-NHSO$_2$Ph	4.56	4.48	0.08	4.11	3.59	0.52	−0.78	−0.16	0.20	0.64	0.20	0.00	0	1	0	0	0
475[n]	3-NO$_2$; 1′-NHSO$_2$Ph	4.70	4.77	−0.07	3.27	3.65	−0.38	0.17	0.78	0.20	0.20	0.84	0.00	0	1	0	0	1

476[n]	4-CH_3; 1′-$NHSO_2Ph$	4.19	3.77	0.42	4.19	3.51	0.68	1.01	−0.07	0.20	0.20	0.20	0.00	0	1	0	0	0
477[n]	3-$NHCOCH_3$; 5-CH_3; 1′-$NHSO_2Ph$	5.13	5.17	0.04	4.42	4.10	0.32	0.04	−0.07	0.20	0.20	1.59	0.00	0	1	0	0	0
478[v]	1′-$NHSO_2PhNH_2$	5.83	5.23	0.60	4.78	4.33	0.45	−0.57	0.00	0.20	0.20	0.20	0.00	−0.68	1	0	0	0
479[n]	2′-aza; 1′-$NHSO_2PhNH_2$	4.82	4.71	0.11	4.06	3.93	0.13	−1.35	0.60	0.20	0.20	0.20	0.00	−0.68	1	0	0	0
480[n]	3′-CH_3; 1′-$NHSO_2PhNH_2$	5.42	4.96	0.46	4.25	4.57	−0.32	−0.01	−0.15	0.20	0.20	0.20	−1.24	−0.68	1	0	0	0
481[n]	3′-OCH_3; 1′-$NHSO_2PhNH_2$	6.30	5.83	0.47	5.62	4.76	0.86	−0.59	−0.16	0.20	0.20	0.20	−0.55	−0.68	1	0	0	0
482[n]	3-NH_2; 1′-$NHSO_2PhNH_2$	6.25	6.59	−0.34	5.03	5.63	−0.60	−1.80	−0.66	0.20	0.20	0.64	0.00	−0.68	1	0	1	0
483[n]	3-Cl; 1′-$NHSO_2PhNH_2$	5.41	5.50	−0.09	4.48	4.35	0.13	0.15	0.23	0.20	0.20	0.71	0.00	−0.68	1	0	0	0
484[n]	4-CH_3; 3′-CH_3; 1′-$NHSO_2PhNH_2$	4.92	4.96	−0.04	4.41	4.58	−0.17	0.55	−0.22	0.20	0.20	0.20	−1.24	−0.68	1	0	0	0
485[n]	4-CH_3; 3′-OCH_3; 1′-$NHSO_2PhNH_2$	5.76	5.84	−0.08	5.11	4.77	0.34	−0.03	−0.23	0.20	0.20	0.20	−0.55	−0.68	1	0	0	0
486[n]	3-Cl; 5-CH_3; 1′-$NHSO_2PhNH_2$	4.88	5.51	−0.63	4.25	4.37	−0.12	0.70	0.16	0.20	0.20	0.71	0.00	−0.68	1	0	0	0
487[n]	4,5-$(CH_3)_2$; 1′-$NHSO_2PhNH_2$	4.83	5.23	−0.40	4.04	4.36	−0.32	0.55	−0.14	0.20	0.20	0.20	0.00	−0.68	1	0	0	0
488[n]	1′-$NHSO_2PhNHCOCH_3$	4.54	4.65	−0.11	3.11	3.81	−0.70	0.05	0.00	0.20	0.20	0.20	0.00	−0.26	1	0	0	0
489[n]	3-NO_2; 1′-$NHSO_2Ph$-*m*-$NHC(NH)NH_2$	4.68	5.27	−0.59	4.04	3.94	0.10	−4.08	0.78	0.20	0.20	0.84	0.00	0.00	1	0	0	1
490[n]	3-NO_2; 1′-$NHSO_2PhNO_2$	4.65	4.54	0.11	3.47	3.45	0.02	0.48	0.78	0.20	0.20	0.84	0.00	0.16	1	0	0	1
491[n]	3-$NHCOCH_3$; 5-CH_3; 1′-$NHSO_2PhCH_3$	5.08	4.75	0.33	3.66	4.21	−0.55	0.60	−0.07	0.20	0.20	1.59	0.00	−0.13	1	0	0	0
492[n]	1′-$NHSO_2PhCOOH$	4.10	4.09	0.01	2.96	3.32	−0.36	0.53	0.00	0.20	0.20	0.20	0.00	0.15	1	0	0	0
493[n]	3-NO_2; 1′-$NHSO_2PhCONHCH_3$	5.21	4.81	0.40	4.18	3.65	0.53	−0.62	0.78	0.20	0.20	0.84	0.00	0.05	1	0	0	1
494[n]	3-NO_2; 1′-$NHSO_2PhCONHC_2NH_2$	4.80	5.18	−0.38	3.80	3.86	−0.06	−3.74	0.78	0.20	0.20	0.84	0.00	0.05	1	0	0	1
495[n]	1′-$NHSO_2PhSO_2CH_3$	4.30	4.14	0.16	3.48	3.32	0.16	−0.59	0.00	0.20	0.20	0.20	0.00	0.22	1	0	0	0
496[cc]	1′-$N(COCH_3)SO_2CH_3$	4.15	4.04	0.11	3.37	3.65	−0.28	−1.84	0.00	0.20	0.20	0.20	0.00	0.00	0	0	0	0
497[cc]	1′-N(COEt)SO_2CH_3	3.81	3.98	−0.17	3.06	3.61	−0.55	−1.30	0.00	0.20	0.20	0.20	0.00	0.00	0	0	0	0
498[cc]	1′-N(COPr)SO_2CH_3	3.50	3.91	−0.41	2.97	3.58	−0.61	−0.76	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
499[cc]	1′-N(COBu)SO_2CH_3	3.36	3.85	−0.49	2.98	3.54	−0.56	−0.22	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
500[cc]	1′-N(COPe)SO_2CH_3	3.40	3.78	−0.38	3.40	3.50	−0.10	0.32	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
501[cc]	1′-N(COHx)SO_2CH_3	3.70	3.72	−0.02	3.01	3.46	−0.45	0.86	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
502[cc]	1′-N(COHp)SO_2CH_3	<3.02[l,o]	3.65	−0.63	3.02	3.43	−0.41	1.40	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
503[cc]	1′-N(CO-Oct)SO_2CH_3	<3.03[l,o]	3.59	−0.56	3.03	3.39	−0.36	1.94	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
504[cc]	3′-OCH_3; 1′-$N(COCH_3)SO_2CH_3$	5.07	4.65	0.42	4.80	4.08	0.72	−1.86	−0.16	0.20	0.20	0.20	−0.55	0	0	0	0	0
505[cc]	3-NH_2; 1′-$N(COCH_3)SO_2CH_3$	5.48	5.40	0.08	5.18	4.95	0.23	−3.07	−0.66	0.20	0.20	0.64	0.00	0	0	0	1	0
506[cc]	3-NH_2; 1′-N(COEt)SO_2CH_3	5.37	5.34	0.03	5.13	4.91	0.22	−2.53	−0.66	0.20	0.20	0.64	0.00	0	0	0	1	0
507[cc]	3-NH_2; 1′-N(COPr)SO_2CH_3	5.60	5.27	0.33	5.21	4.88	0.33	−1.99	−0.66	0.20	0.20	0.64	0.00	0	0	0	1	0
508[cc]	3-NH_2; 1′-N(COBu)SO_2CH_3	5.44	5.21	0.23	5.22	4.84	0.38	−1.45	−0.66	0.20	0.20	0.64	0.00	0	0	0	1	0
509[cc]	3-NH_2; 1′-N(COPe)SO_2CH_3	5.23	5.14	0.09	5.17	4.80	0.37	−0.91	−0.66	0.20	0.20	0.64	0.00	0	0	0	1	0
510[cc]	3-NH_2; 1′-N(COHx)SO_2CH_3	5.24	5.08	0.16	5.18	4.76	0.42	−0.37	−0.66	0.20	0.20	0.64	0.00	0	0	0	1	0
511[cc]	3-NH_2; 1′-N(COHp)SO_2CH_3	5.69	5.01	0.68	5.16	4.73	0.43	0.17	−0.66	0.20	0.20	0.64	0.00	0	0	0	1	0
512[cc]	3-NH_2; 1′-N(CO-Oct)SO_2CH_3	5.74	4.95	0.79	5.14	4.69	0.45	0.71	−0.66	0.20	0.20	0.64	0.00	0	0	0	1	0
513[cc]	3-$NHCOCH_3$; 1′-$N(COCH_3)SO_2CH_3$	4.79	4.93	−0.14	4.00	4.25	−0.25	−2.81	0.00	0.20	0.20	1.59	0.00	0	0	0	0	0
514[cc]	3-$NHCOCH_3$; 1′-N(COEt)SO_2CH_3	5.10	4.86	0.24	4.01	4.21	−0.20	−2.27	0.00	0.20	0.20	1.59	0.00	0	0	0	0	0
515[cc]	3-$NHCOCH_3$; 1′-N(COPr)SO_2CH_3	4.57	4.80	−0.23	3.68	4.17	−0.49	−1.73	0.00	0.20	0.20	1.59	0.00	0	0	0	0	0
516[cc]	3-$NHCOCH_3$; 1′-N(COBu)SO_2CH_3	4.99	4.73	0.26	3.78	4.13	−0.35	−1.19	0.00	0.20	0.20	1.59	0.00	0	0	0	0	0

Table I (*Continued*)

no.	substituents[mm]	log $(1/D_{50})$[a] obsd	log $(1/D_{50})$[a] calcd[h]	Δ log $(1/D_{50})$	log $(1/LD_{10})$[b] obsd	log $(1/LD_{10})$[b] calcd[i]	Δ log $(1/LD_{10})$	$\Sigma\pi$[c]	$\Sigma\sigma$[d]	MR_1[e]	MR_2[e]	MR_3[e]	$E_{s(3')}$[f]	R_{BS}[g]	I_{BS}	$I_{3,6}$	I_{NH_2}	I_{NO_2}
517[cc]	3-NHCOCH$_3$; 1′-N(COPe)SO$_2$CH$_3$	4.63	4.67	−0.04	3.79	4.10	−0.31	−0.65	0.00	0.20	0.20	1.59	0.00	0	0	0	0	0
518[cc]	3-NHCOCH$_3$; 1′-N(COHx)SO$_2$CH$_3$	4.90	4.60	0.30	4.18	4.06	0.12	−0.11	0.00	0.20	0.20	1.59	0.00	0	0	0	0	0
519[cc]	3-NHCOCH$_3$; 1′-N(COHp)SO$_2$CH$_3$	4.72	4.54	0.18	3.86	4.02	−0.16	0.43	0.00	0.20	0.20	1.59	0.00	0	0	0	0	0
520[cc]	3-NHCOCH$_3$; 1′-N(CO-Oct)SO$_2$CH$_3$	4.96	4.47	0.49	3.82	3.98	−0.16	0.97	0.00	0.20	0.20	1.59	0.00	0	0	0	0	0
521[cc]	3-NHCOCH$_3$; 1′-N(COC$_9$H$_{19}$)SO$_2$CH$_3$	4.80	4.41	0.39	3.91	3.95	−0.04	1.51	0.00	0.20	0.20	1.59	0.00	0	0	0	0	0
522[cc]	3-NHCOCH$_3$; 1′-N(COC$_{10}$H$_{21}$)SO$_2$CH$_3$	4.45	4.34	0.11	4.14	3.91	0.23	2.05	0.00	0.20	0.20	1.59	0.00	0	0	0	0	0
523[cc]	3-NHCOCH$_3$; 1′-N(COC$_{11}$H$_{23}$)SO$_2$CH$_3$	4.44	4.28	0.16	4.16	3.87	0.29	2.59	0.00	0.20	0.20	1.59	0.00	0	0	0	0	0
524[cc]	3-NHCOCH$_3$; 1′-N(COC$_{17}$H$_{35}$)SO$_2$CH$_3$	3.90	3.88	0.02	3.16	3.64	−0.48	5.89	0.00	0.20	0.20	1.59	0.00	0	0	0	0	0
525[cc]	3-NHCOCH$_3$; 1′-N[COCH(CH$_3$)$_2$]SO$_2$CH$_3$	4.41	4.81	−0.40	3.94	4.18	−0.24	−1.86	0.00	0.20	0.20	1.59	0.00	0	0	0	0	0
526[cc]	3-NHCOCH$_3$; 1′-N[COCH(CH$_3$)Et]SO$_2$CH$_3$	4.18	4.75	−0.57	3.65	4.14	−0.49	−1.32	0.00	0.20	0.20	1.59	0.00	0	0	0	0	0
527[cc]	3-NO$_2$; 1′-N(COCH$_3$)SO$_2$CH$_3$	4.95	4.53	0.42	3.78	3.81	−0.03	−2.12	0.78	0.20	0.20	0.84	0.00	0	0	0	0	1
528[cc]	3-NO$_2$; 1′-N(COEt)SO$_2$CH$_3$	4.67	4.46	0.21	3.76	3.77	−0.01	−1.58	0.78	0.20	0.20	0.84	0.00	0	0	0	0	1
529[cc]	3-NO$_2$; 1′-N(COPr)SO$_2$CH$_3$	4.14	4.40	−0.26	3.28	3.73	−0.45	−1.04	0.78	0.20	0.20	0.84	0.00	0	0	0	0	1
530[cc]	3-NO$_2$; 1′-N(COBu)SO$_2$CH$_3$	4.46	4.33	0.13	4.12	3.70	0.42	−0.50	0.78	0.20	0.20	0.84	0.00	0	0	0	0	1
531[cc]	3-NO$_2$; 1′-N(COPe)SO$_2$CH$_3$	4.80	4.27	0.53	4.53[l]	3.66	0.87	0.04	0.78	0.20	0.20	0.84	0.00	0	0	0	0	1
532[cc]	3-NO$_2$; 1′-N(COHx)SO$_2$CH$_3$	4.71	4.20	0.51	4.32[l]	3.62	0.70	0.58	0.78	0.20	0.20	0.84	0.00	0	0	0	0	1
533[cc]	3-NO$_2$; 1′-N(COHp)SO$_2$CH$_3$	4.57	4.14	0.43	4.55[l]	3.58	0.97	1.12	0.78	0.20	0.20	0.84	0.00	0	0	0	0	1
534[cc]	3-NO$_2$; 1′-N(CO-Oct)SO$_2$CH$_3$	4.19	4.08	0.11	3.78[l]	3.55	0.23	1.66	0.78	0.20	0.20	0.84	0.00	0	0	0	0	1
535[cc]	3-NO$_2$; 5-CH$_3$; 1′-N(COCH$_3$)SO$_2$CH$_3$	4.49	4.53	−0.04	3.27	3.82	−0.55	−1.56	0.71	0.20	0.20	0.84	0.00	0	0	0	0	1
536[n]	3-NO$_2$; 5-CH$_3$; 1′-N(COEt)SO$_2$CH$_3$	4.37	4.47	−0.10	3.80	3.79	0.01	−1.02	0.71	0.20	0.20	0.84	0.00	0	0	0	0	1
537[n]	3-NO$_2$; 5-CH$_3$; 1′-N(COPr)SO$_2$CH$_3$	4.44	4.40	0.04	3.80	3.75	0.05	−0.48	0.71	0.20	0.20	0.84	0.00	0	0	0	0	1
538[cc]	3-NO$_2$; 5-CH$_3$; 3′-OCH$_3$; 1′-N(COEt)SO$_2$CH$_3$	3.26	5.07	−1.81	3.06[l]	4.21	−1.15	−1.04	0.55	0.20	0.20	0.84	−0.55	0	0	0	0	1
539[cc]	3-NO$_2$; 5-CH$_3$; 3′-OCH$_3$; 1′-N(COPr)SO$_2$CH$_3$	5.24	5.01	0.23	4.06	4.17	−0.11	−0.50	0.55	0.20	0.20	0.84	−0.55	0	0	0	0	1
540[n]	3-NH$_2$; 4,5-(CH$_3$)$_2$; 1′-N(COCH$_3$)SO$_2$CH$_3$	5.64	5.41	0.23	4.78	4.98	−0.20	−1.95	−0.80	0.20	0.20	0.64	0.00	0	0	0	1	0
541[cc]	1′-N[COC(CH$_3$)$_2$]SO$_2$CH$_3$	3.35	3.91	−0.56	3.10	3.58	−0.48	−0.76	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
542[p]	H	<3.19[kk]	3.82	−0.63	3.19	3.52	−0.33	0.00	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
543[j]	10-CH$_3$; 2-NO$_2$	<3.14	2.91	0.23	3.14	2.82	0.32	0.22	0.71	0.20	0.84	0.20	0.00	0	0	0	0	0
544[n]	2′-N(CH$_3$)COCH$_3$	<3.62	3.73	−0.11	3.62	3.44	0.18	−1.01	0.21	0.20	0.20	0.20	0.00	0	0	0	0	0
545[p]	2′-NHCH$_3$	<3.18	4.18	−1.00	3.18	3.78	−0.60	−0.47	−0.30	0.20	0.20	0.20	0.00	0	0	0	0	0
546[s]	2′-CH$_3$	<2.93	3.82	−0.89	2.93	3.54	−0.61	0.56	−0.07	0.20	0.20	0.20	0.00	0	0	0	0	0

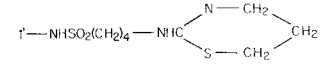
547[n]	2′-$CH_2N(CH_3)_2$	<3.70	4.29	−0.59	3.70	3.80	−0.10	−3.99	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
548[m]	2′-CH_2COOH	<3.96	3.92	0.04	3.96	3.58	0.38	−0.72	−0.01	0.20	0.20	0.20	0.00	0	0	0	0	0
549[p]	2′-OH	<3.11	3.78	−0.67	3.11	3.48	−0.37	−0.67	0.12	0.20	0.20	0.20	0.00	0	0	0	0	0
550[s]	2′-OCH_3	<3.15	3.70	−0.55	3.15	3.43	−0.28	−0.02	0.12	0.20	0.20	0.20	0.00	0	0	0	0	0
551[s]	3′-aza	<3.01	2.73	0.28	3.01	2.68	0.33	−1.51	1.26	0.20	0.20	0.20	0.00	0	0	0	0	0
552[p]	3′-NH_2	<3.74	4.55	−0.81	3.74	4.04	−0.30	−1.23	−0.15	0.20	0.20	0.20	−0.61	0	0	0	0	0
553[s]	3′-$NHCOCH_3$	<3.42	0.97	2.45	3.42	2.93	0.49	−0.97	0.00	0.20	0.20	0.20	−2.00	0	0	0	0	0
554[s]	3′-NO_2	<2.94	2.64	0.30	2.94	2.87	0.07	−0.28	1.26	0.20	0.20	0.20	−1.02	0	0	0	0	0
555[s]	3′-$NHSO_2CH_3$	<3.12	1.00	2.12	3.12	2.95	0.17	−1.18	0.00	0.20	0.20	0.20	−2.00	0	0	0	0	0
556[s]	3′-$N(CH_3)SO_2CH_3$	<3.14	−0.04	3.18	3.14	2.58	0.56	−0.75	0.00	0.20	0.20	0.20	−2.20	0	0	0	0	0
557[s]	3′-Et	<3.05	3.33	−0.28	3.05	3.69	−0.64	1.03	−0.15	0.20	0.20	0.20	−1.31	0	0	0	0	0
558[s]	3′-$CH(CH_3)_2$	<3.37	2.03	1.34	3.37	3.27	0.10	1.53	−0.15	0.20	0.20	0.20	−1.71	0	0	0	0	0
559[s]	3′-$C(CH_3)_3$	<3.27	−3.80	7.07	3.27[l]	1.27	2.00	1.98	−0.15	0.20	0.20	0.20	−2.78	0	0	0	0	0
560[m]	3′-CH_2COOH	<3.24	2.09	1.15	3.24	3.25	−0.01	−0.72	0.10	0.20	0.20	0.20	−1.70	0	0	0	0	0
561[m]	3′-CH=CHCOOH	<3.04	1.83	1.21	3.04	2.92	0.12	0.00	0.62	0.20	0.20	0.20	−1.60	0	0	0	0	0
562[m]	3′-$(CH_2)_2COOH$	<3.32	0.00	3.32	3.32	2.65	0.67	−0.02	−0.15	0.20	0.20	0.20	−2.21	0	0	0	0	0
563[s]	3′-OCH_3	<3.70	4.42	−0.72	3.70	3.95	−0.25	−0.20	−0.16	0.20	0.20	0.20	−0.55	0	0	0	0	0
564[s]	3′-OEt	<3.61	4.01	−0.40	3.61	3.88	−0.27	0.38	−0.14	0.20	0.20	0.20	−1.00	0	0	0	0	0
565[m]	3′-COOH	<3.67	2.70	0.97	3.67	3.12	0.55	−0.32	0.77	0.20	0.20	0.20	−1.25	0	0	0	0	0
566[s]	3′-F	<3.13	4.18	−1.05	3.13	3.75	−0.62	0.14	0.06	0.20	0.20	0.20	−0.46	0	0	0	0	0
567[n]	3′,5′-$(CH_3)_2$	<3.05	3.63	−0.58	3.05	3.84	−0.79	1.12	−0.30	0.20	0.20	0.20	−1.24	0	0	0	0	0
568[n]	3′,5′-$(OH)_2$	<2.83	4.74	−1.91	2.83[l]	4.16	−1.33	−1.34	−0.32	0.20	0.20	0.20	−0.55	0	0	0	0	0
569[n]	3′,5′-$(OCH_3)_2$	<4.13	4.59	−0.46	4.13	4.07	0.06	−0.04	−0.32	0.20	0.20	0.20	−0.55	0	0	0	0	0
570[n]	1′-NH_2; 2′-CH_3	<3.70	4.12	−0.42	3.70	3.74	−0.04	−0.67	−0.22	0.20	0.20	0.20	0.00	0	0	0	0	0
571[n]	1′-NH_2; 2′-OCH_3	<3.44	4.00	−0.56	3.44	3.63	−0.19	−1.25	−0.03	0.20	0.20	0.20	0.00	0	0	0	0	0
572[n]	2-CH_3; 1′-NH_2	<3.70	4.00	−0.30	3.70	3.62	0.08	−0.67	−0.22	0.20	0.67	0.20	0.00	0	0	0	0	0
573[n]	2-OCH_3; 1′-NH_2	<3.41	3.82	−0.41	3.41	3.47	−0.06	−1.25	−0.03	0.20	0.89	0.20	0.00	0	0	0	0	0
574[n]	3-NO_2; 1′-NH_2	<3.69	4.61	−0.92	3.69	3.88	−0.19	−1.51	0.63	0.20	0.20	0.84	0.00	0	0	0	0	1
575[n]	3-OCH_3; 1′-NH_2	<4.11	5.08	−0.97	4.11	4.25	−0.14	−1.25	−0.42	0.20	0.20	0.89	0.00	0	0	0	0	0
576[y]	1′-NHBu	<3.77	3.81	−0.04	3.77	3.55	0.22	1.45	−0.16	0.20	0.20	0.20	0.00	0	0	0	0	0
577[y]	1′-NHPr	<3.95	3.87	−0.08	3.95	3.58	0.37	0.91	−0.16	0.20	0.20	0.20	0.00	0	0	0	0	0
578[y]	1′-NH-Hx	<3.69	3.68	0.01	3.69	3.47	0.22	2.53	−0.16	0.20	0.20	0.20	0.00	0	0	0	0	0
579[n]	1′-NEt_2	<4.08	3.84	0.24	4.08	3.56	0.52	1.18	−0.16	0.20	0.20	0.20	0.00	0	0	0	0	0
580[q]	1′-$N(CH_2CH_2)_2NH$	<3.99	4.31	−0.32	3.99	3.83	0.16	−3.04	−0.12	0.20	0.20	0.20	0.00	0	0	0	0	0
581[q]	3-NO_2; 1′-$N(CH_2CH_2)_2NH$	<4.46	4.83	−0.37	4.46	4.01	0.45	−3.32	0.62	0.20	0.20	0.84	0.00	0	0	0	0	1
582[q]	1′-$N(CH_2CH_2)_2NCH_3$	<3.91	4.44	−0.53	3.91	3.91	0.00	−3.86	−0.16	0.20	0.20	0.20	0.00	0	0	0	0	0
583[q]	3-NO_2; 1′-$N(CH_2CH_2)_2NCH_3$	<3.98	4.92	−0.94	3.98	4.07	−0.09	−4.09	0.62	0.20	0.20	0.84	0.00	0	0	0	0	1
584[n]	1′-$NHCOCH_2Ph$	<4.05	3.75	0.30	4.05	3.48	0.57	0.58	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
585[n]	1′,2′-(N=C[$(CH_2)_3COOH$]NH)	<2.98	2.90	0.08	2.98	2.82	0.16	−0.68	1.00	0.20	0.20	0.20	0.00	0	0	0	0	0
586[n]	1′,2′-(N=C[$(CHOH)_4CHOH$]NH)	<4.09	3.33	0.76	4.09[l]	3.08	1.01	−4.53	1.00	0.20	0.20	0.20	0.00	0	0	0	0	0
587[t]	3-NH_2; 1′-NO_2	<3.52	3.87	−0.35	3.52	3.86	−0.34	−1.51	0.58	0.20	0.20	0.54	0.00	0	0	0	1	0
588[n]	4-$CONH_2$; 1′-CH_3	<3.26	3.80	−0.54	3.26	3.49	−0.23	−0.93	0.13	0.20	0.20	0.20	0.00	0	0	0	0	0
589[n]	1′-CH_2NH_2	<3.87	4.10	−0.23	3.87	3.71	0.16	−1.04	−0.15	0.20	0.20	0.20	0.00	0	0	0	0	0
590[n]	3-NO_2; 1′-CH_2NH_2	<4.31	4.58	−0.27	4.31	3.87	0.44	−1.32	0.63	0.20	0.20	0.84	0.00	0	0	0	0	1
591[n]	1′-$CH_2N(CH_3)_2$	<3.67	4.29	−0.62	3.67	3.80	−0.13	−3.99	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
592[n]	1′-$(CH_2)_2NH_2$	<4.40	4.41	−0.01	4.40	3.89	0.51	−3.65	−0.15	0.20	0.20	0.20	0.00	0	0	0	0	0
593[n]	3-NO_2; 1′-$(CH_2)_2NH_2$	<4.66	4.89	−0.23	4.66	4.05	0.61	−3.93	0.63	0.20	0.20	0.84	0.00	0	0	0	0	1
594[n]	1′-$(CH_2)_2OH$	<3.59	4.01	−0.42	3.59	3.65	−0.06	−0.77	−0.10	0.20	0.20	0.20	0.00	0	0	0	0	0
595[n]	1′-$(CH_2)_3NH_2$	<4.12	4.35	−0.23	4.12	3.86	0.26	−3.18	−0.15	0.20	0.20	0.20	0.00	0	0	0	0	0
596[n]	3-NO_2; 1′-$(CH_2)_3NH_2$	<4.47	4.84	−0.37	4.47	4.01	0.46	−3.46	0.63	0.20	0.20	0.84	0.00	0	0	0	0	1
597[n]	1′-$(CH_2)_4NH_2$	<4.07	4.30	−0.23	4.07	3.83	0.24	−2.71	−0.15	0.20	0.20	0.20	0.00	0	0	0	0	0

Table I (*Continued*)

no.	substituents[mm]	log $(1/D_{50})$[a] obsd	log $(1/D_{50})$[a] calcd[h]	Δ log $(1/D_{50})$	log $(1/LD_{10})$[b] obsd	log $(1/LD_{10})$[b] calcd[i]	Δ log $(1/LD_{10})$	$\Sigma\pi$[c]	$\Sigma\sigma$[d]	MR_1[e]	MR_2[e]	MR_3[e]	$E_{s(3')}$[f]	R_{BS}[g]	I_{BS}	$I_{3,6}$	I_{NH_2}	I_{NO_2}
598[n]	3-NO_2; 1′-$(CH_2)_4NH_2$	<4.36	4.78	−0.38	4.36	3.98	0.38	−2.99	0.63	0.20	0.20	0.84	0.00	0	0	0	0	1
599[n]	1′-$(CH_2)_5NH_2$	<4.15	4.24	−0.09	4.15	3.79	0.36	−2.24	−0.15	0.20	0.20	0.20	0.00	0	0	0	0	0
600[n]	3-NO_2; 1′-$(CH_2)_5NH_2$	<4.11	4.73	−0.62	4.11	3.95	0.16	−2.52	0.63	0.20	0.20	0.84	0.00	0	0	0	0	1
601[n]	1′-$(CH_2)_6NH_2$	<4.04	4.19	−0.15	4.04	3.76	0.28	−1.77	−0.15	0.20	0.20	0.20	0.00	0	0	0	0	0
602[n]	3-NO_2; 1′-$(CH_2)_6NH_2$	<4.29	4.67	−0.38	4.29	3.92	0.37	−2.05	0.63	0.20	0.20	0.84	0.00	0	0	0	0	1
603[m]	1′-CH_2COOH	<3.04	3.60	−0.56	3.04	3.35	−0.31	−0.72	0.30	0.20	0.20	0.20	0.00	0	0	0	0	0
604[m]	3-$NHCH_3$; 1′-CH_2COOH	<3.12	5.26	−2.14	3.12[l]	4.42	−1.30	−1.19	−0.54	0.20	0.20	1.13	0.00	0	0	0	0	0
605[n]	3-$NHCOCH_3$; 1′-$(CH_2)_2COOH$	<3.64	4.81	−1.17	3.64	4.19	−0.55	−1.26	−0.07	0.20	0.20	1.59	0.00	0	0	0	0	0
606[m]	3-OCH_3; 1′-CH_2COOH	<3.69	4.21	−0.52	3.69	3.77	−0.08	−0.74	0.14	0.20	0.20	0.20	−0.55	0	0	0	0	0
607[r]	3-$NHCH_3$; 1′-$(CH_2)_3COOH$	<2.97	4.85	−1.88	2.97[l]	4.29	−1.32	−0.22	−0.99	0.20	0.20	0.20	0.00	0	0	0	0	0
608[m]	3′-OCH_3; 1′-CH=$CHCONH_2$	<3.38	4.51	−1.13	3.38	4.00	−0.62	−0.74	−0.16	0.20	0.20	0.20	−0.55	0	0	0	0	0
609[m]	1′-$CH_2CH(NH_2)COOH$	<3.42	4.26	−0.84	3.42	3.78	−0.36	−3.67	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
619[m]	3-NO_2; 1′-$CH_2CH(NH_2)COOH$	<3.34	4.74	−1.40	3.34	3.94	−0.60	−3.95	0.78	0.20	0.20	0.84	0.00	0	0	0	0	1
611[n]	1′-CH=CHPh	<3.91	2.87	1.04	3.91[l]	2.87	1.04	2.68	0.62	0.20	0.20	0.20	0.00	0	0	0	0	0
612[m]	3′-OCH_3; 1′-CH=CHCOOH	<2.87	3.80	−1.12	2.87	3.48	−0.61	−0.02	0.46	0.20	0.20	0.20	−0.55	0	0	0	0	0
613[p]	1′-OCH_3	<3.48	3.98	−0.50	3.48	3.65	−0.17	−0.02	−0.16	0.20	0.20	0.20	0.00	0	0	0	0	0
614[q]	3-NO_2; 1′-OCH_3	<3.60	4.47	−0.87	3.60	3.80	−0.20	−0.30	0.62	0.20	0.20	0.84	0.00	0	0	0	0	1
615[r]	1′-OCH(Et)COOH	<2.95	3.98	−1.03	2.95	3.64	−0.69	0.05	−0.16	0.20	0.20	0.20	0.00	0	0	0	0	0
616[m]	1′-OCH_2COOH	<2.87	4.08	−1.21	2.87	3.70	−0.83	−0.79	−0.16	0.20	0.20	0.20	0.00	0	0	0	0	0
617[m]	3-NH_2; 1′-COOH	<3.91	4.44	−0.53	3.91	4.26	−0.35	−1.55	0.11	0.20	0.20	0.64	0.00	0	0	0	1	0
618[m]	1′-CN	<3.12	2.90	0.22	3.12	2.82	0.30	−0.57	0.98	0.20	0.20	0.20	0.00	0	0	0	0	0
619[s]	1′-F	<3.26	3.75	−0.49	3.26	3.48	−0.22	0.14	0.05	0.20	0.20	0.20	0.00	0	0	0	0	0
620[n]	3-NH_2; 1′-Br	<4.43	4.79	−0.36	4.43	4.55	−0.12	−0.37	−0.38	0.20	0.20	0.64	0.00	0	0	0	1	0
621[s]	1′-I	<3.68	3.38	0.30	3.68	3.22	0.46	1.12	0.30	0.20	0.20	0.20	0.00	0	0	0	0	0
622[n]	1′-CONHPr	<3.34	3.22	0.12	3.34	3.07	0.27	−0.27	0.63	0.20	0.20	0.20	0.00	0	0	0	0	0
623[n]	1′-$SO_2NH(CH_2)_6NH_2$	<3.24	3.24	0.00	3.24	3.03	0.21	−3.31	0.96	0.20	0.20	0.20	0.00	0	0	0	0	0
624[v]	2′-OCH_3; 1′-$NHSO_2CH_3$	<3.69	3.84	−0.15	3.69	3.52	0.17	−1.20	0.12	0.20	0.20	0.20	0.00	0	0	0	0	0
625[v]	2′-CH_3; 1′-$NHSO_2CH_3$	<3.38	3.97	−0.59	3.38	3.62	−0.24	−0.62	−0.07	0.20	0.20	0.20	0.00	0	0	0	0	0
626[v]	2′-Cl; 1′-$NHSO_2CH_3$	<2.99	3.50	−0.51	2.99	3.28	−0.29	−0.47	0.37	0.20	0.20	0.20	0.00	0	0	0	0	0
627[n]	3′-$OCH(CH_3)_2$; 1′-$NHSO_2CH_3$	<2.96	1.12	1.84	2.96	3.04	−0.08	−0.82	−0.16	0.20	0.20	0.20	−2.00	0	0	0	0	0
628[v]	3′-Cl; 1′-$NHSO_2CH_3$	<2.98	3.74	−0.76	2.98	3.64	−0.66	−0.47	0.27	0.20	0.20	0.20	−0.97	0	0	0	0	0
629[w]	1-NO_2; 1′-$NHSO_2CH_3$	<3.78	3.86	−0.08	3.78	3.16	0.62	−1.46	0.71	0.84	0.20	0.20	0.00	0	0	0	0	1
630[w]	1-CH_3; 1′-$NHSO_2CH_3$	<3.00	4.07	−1.07	3.00	3.43	−0.43	−0.62	−0.17	0.67	0.20	0.20	0.00	0	0	0	0	0
631[w]	1-OCH_3; 1′-$NHSO_2CH_3$	<3.33	3.84	−0.51	3.33	3.13	0.20	−1.20	0.12	0.89	0.20	0.20	0.00	0	0	0	0	0
632[n]	2-$NHSO_2CH_3$; 1′-$NHSO_2CH_3$	<3.52	3.45	0.07	3.52	3.12	0.40	−2.36	0.20	0.20	1.92	0.20	0.00	0	0	0	0	0
633[w]	2-CH_3; 1′-$NHSO_2CH_3$	<3.37	3.84	−0.47	3.37	3.51	−0.14	−0.62	−0.07	0.20	0.67	0.20	0.00	0	0	0	0	0
634[w]	2-Cl; 1′-$NHSO_2CH_3$	<3.31	3.37	−0.06	3.31	3.16	0.15	−0.47	0.37	0.20	0.70	0.20	0.00	0	0	0	0	0
635[n]	2-I; 1′-$NHSO_2CH_3$	<3.17	3.13	0.03	3.17	2.95	0.22	−0.06	0.35	0.20	1.49	0.20	0.00	0	0	0	0	0
636[w]	3-F; 1′-$NHSO_2CH_3$	<3.14	3.87	−0.73	3.14	3.54	−0.40	−1.04	0.06	0.20	0.20	0.19	0.00	0	0	0	0	0
637[n]	3-NHCOPh; 1′-$NHSO_2CH_3$	<4.11	4.57	−0.46	4.11	4.21	−0.10	−0.69	−0.19	0.20	0.20	3.56	0.00	0	0	0	0	0
638[n]	3-NHCOCH=CHPh; 1′-$NHSO_2CH_3$	<3.83	3.85	−0.02	3.83	3.53	0.30	0.00	0.30	0.20	0.20	4.34	0.00	0	0	0	0	0
639[w]	3-CN; 1′-$NHSO_2CH_3$	<3.19	3.97	−0.78	3.19	3.40	−0.21	−1.75	0.66	0.20	0.20	0.73	0.00	0	0	0	0	0
640[w]	3-SO_2NH_2; 1′-$NHSO_2CH_3$	<3.73	4.37	−0.64	3.73	3.76	−0.03	−3.00	0.57	0.20	0.20	1.33	0.00	0	0	0	0	0
641[n]	4-$CONH_2$; 2′-OCH_3; 1′-$NHSO_2CH_3$	<3.07	3.74	−0.67	3.07	3.41	−0.34	−2.69	0.40	0.20	0.20	0.20	0.00	0	0	0	0	0

642[z]	1-aza; 3′-OCH_3; 1′-$NHSO_2CH_3$	<3.54	3.95	−0.41	3.54	3.55	−0.01	−2.68	0.62	0.20	0.20	0.20	−0.55	0	0	0	0	0
643[n]	1-NO_2; 3′-OCH_3; 1′-$NHSO_2CH_3$	<3.60	4.39	−0.79	3.60	3.53	0.07	−1.48	0.62	0.84	0.20	0.20	−0.55	0	0	0	0	1
644[n]	1-CH_3; 3′-OCH_3; 1′-$NHSO_2CH_3$	<3.37	4.57	−1.20	3.37	3.78	−0.41	−0.64	−0.23	0.67	0.20	0.20	−0.55	0	0	0	0	0
645[n]	1-OCH_3; 3′-OCH_3; 1′-$NHSO_2CH_3$	<3.28	4.45	−1.17	3.28	3.55	−0.27	−1.22	−0.04	0.89	0.20	0.20	−0.55	0	0	0	0	0
646[z]	2-aza; 3′-OCH_3; 1′-$NHSO_2CH_3$	<2.94	4.02	−1.08	2.94	3.60	−0.66	−2.68	0.55	0.20	0.20	0.20	−0.55	0	0	0	0	0
647[n]	2-$C(CH_3)_3$; 3′-OCH_3; 1′-$NHSO_2CH_3$	<3.14	3.94	−0.80	3.14	3.52	−0.38	0.78	−0.26	0.20	2.06	0.20	−0.55	0	0	0	0	0
648[n]	2-OCH_3; 3′-OCH_3; 1′-$NHSO_2CH_3$	<3.26	4.27	−1.01	3.26	3.78	−0.52	−1.22	−0.04	0.20	0.89	0.20	−0.55	0	0	0	0	0
649[n]	2-Cl; 3′-OCH_3; 1′-$NHSO_2CH_3$	<3.19	3.97	−0.78	3.19	3.58	−0.39	−0.49	0.21	0.20	0.70	0.20	−0.55	0	0	0	0	0
650[n]	2-$CONH_2$; 3′-OCH_3; 1′-$NHSO_2CH_3$	<3.38	4.23	−0.85	3.38	3.71	−0.33	−2.69	0.12	0.20	1.08	0.20	−0.55	0	0	0	0	0
651[n]	3-$N(CH_3)SO_2CH_3$; 3′-OCH_3; 1′-$NHSO_2CH_3$	<4.08	5.16	−1.08	4.08	4.59	−0.51	−1.95	0.00	0.20	0.20	2.44	−0.55	0	0	0	0	0
652[v]	3-$C(CH_3)_3$; 3′-OCH_3; 1′-$NHSO_2CH_3$	<3.00	5.25	−2.25	3.00[l]	4.65	−1.65	0.78	−0.36	0.20	0.20	2.06	−0.55	0	0	0	0	0
653[n]	3-SO_2CH_3; 3′-OCH_3; 1′-$NHSO_2Hx$	<3.37	4.48	−1.11	3.37	3.91	−0.54	−0.13	0.56	0.20	0.20	1.45	−0.55	0	0	0	0	0
654[w]	2,7-$(NH_2)_2$; 1′-$NHSO_2CH_3$	<4.90	4.32	0.58	4.90[l]	3.78	1.12	−3.64	−0.32	0.20	1.18	0.20	0.00	0	0	0	0	0
655[n]	2,6-$(N_3)_2$; 1′-$NHSO_2CH_3$	<3.14	3.93	−0.79	3.14	3.40	−0.26	−0.26	0.42	0.20	1.12	1.12	0.00	0	0	0	0	0
656[p]	2-OCH_3; 6-NH_2; 1′-$NHSO_2CH_3$	<4.25	5.02	−0.77	4.25	4.65	−0.40	−2.43	−0.54	0.20	0.89	0.64	0.00	0	0	0	1	0
657[n]	2-OCH_3; 6-$NHCOCH_3$; 1′-$NHSO_2CH_3$	<3.21	4.55	−1.34	3.21	3.94	−0.73	−2.17	0.12	0.20	0.89	1.59	0.00	0	0	0	0	0
658[w]	2-OCH_3; 6-NO_2; 1′-$NHSO_2CH_3$	<3.38	4.15	−0.77	3.20	3.51	−0.31	−1.48	0.90	0.20	0.89	0.84	0.00	0	0	0	0	1
659[w]	2-OCH_3; 6-Cl; 1′-$NHSO_2CH_3$	<3.12	3.93	−0.81	3.12	3.37	−0.25	−0.49	0.35	0.20	0.89	0.70	0.00	0	0	0	0	0
660[w]	3,4-benz; 1′-$NHSO_2CH_3$	<3.18	4.41	−1.23	3.18	3.78	−0.60	0.14	0.08	0.20	0.20	0.91	0.00	0	0	0	0	0
661[n]	1-Cl; 4-$CONH_2$; 3′-OCH_3; 1′-$NHSO_2CH_3$	<3.93	4.14	−0.21	3.93	3.70	0.23	−1.98	0.35	0.20	0.20	0.20	−0.55	0	0	0	0	0
662[n]	2,3-benz; 3′-OCH_3; 1′-$NHSO_2CH_3$	<3.66	4.56	−0.90	3.66	4.00	−0.34	0.12	0.00	0.20	1.85	1.85	−0.55	0	0	0	0	0
663[n]	2-OCH_3; 6-Cl; 3′-OCH_3; 1′-$NHSO_2CH_3$	<3.52	4.53	−1.01	3.52	3.80	−0.28	−0.51	0.19	0.20	0.89	0.70	−0.55	0	0	0	0	0
664[aa]	3-NO_2; 4,5-$(CH_3)_2$; 1′-$NHSO_2CH_3$	<3.13	4.46	−1.33	3.13	3.79	−0.66	−0.34	0.64	0.20	0.20	0.84	0.00	0	0	0	0	1
665[q]	1′-$N[CH_2CH(OH)CH_2OH]$-SO_2CH_3	<4.06	4.05	0.01	4.06	3.66	0.40	−1.93	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
666[cc]	4-CH_3; 3′-OCH_3; 1′-$N(COCH_3)SO_2CH_3$	<4.43	4.65	−0.22	4.43	4.09	0.34	−1.30	−0.23	0.20	0.20	0.20	−0.55	0	0	0	0	0
667[cc]	4-CH_3; 3′-OCH_3; 1′-$N(COEt)SO_2CH_3$	<4.31	4.58	−0.27	4.31	4.06	0.25	−0.76	−0.23	0.20	0.20	0.20	−0.55	0	0	0	0	0
668[cc]	4-CH_3; 3′-OCH_3; 1′-$N(COPr)SO_2CH_3$	<3.84	4.52	−0.68	3.84	4.02	−0.18	−0.22	−0.23	0.20	0.20	0.20	−0.55	0	0	0	0	0
669[cc]	4-CH_3; 3′-OCH_3; 1′-$N(COBu)SO_2CH_3$	<3.44	4.45	−1.01	3.32	3.98	−0.66	0.32	−0.23	0.20	0.20	0.20	−0.55	0	0	0	0	0
670[cc]	4-CH_3; 3′-OCH_3; 1′-$N(COPe)SO_2CH_3$	<3.76	4.39	−0.63	3.76	3.94	−0.18	0.86	−0.23	0.20	0.20	0.20	−0.55	0	0	0	0	0
671[cc]	4-CH_3; 1′-$N[CO(CH_2)_2COOEt]$-SO_2CH_3	<4.84	3.21	1.63	4.84[l]	3.06	1.78	0.06	−0.07	0.20	0.20	0.20	0.00	0	0	0	0	0
672[cc]	4-CH_3; 3′-OCH_3; 1′-$N[CO(CH_2)_2COOPr]SO_2CH_3$	<3.96	4.36	−0.40	3.96	3.92	0.04	1.14	−0.23	0.20	0.20	0.20	−0.55	0	0	0	0	0
673[q]	1′-$NHSO_2CH(CH_3)CONH_2$	<3.78	4.03	−0.25	3.78	3.65	0.13	−1.77	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
674[n]	1′-$NHSO_2(CH_2)_2PhNH_2$	<3.00	3.86	−0.86	3.00	3.55	−0.55	−0.32	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0

Table I (*Continued*)

no.	substituents[mm]	log $(1/D_{50})$[a] obsd	log $(1/D_{50})$[a] calcd[h]	Δ log $(1/D_{50})$	log $(1/LD_{10})$[b] obsd	log $(1/LD_{10})$[b] calcd[i]	Δ log $(1/LD_{10})$	$\Sigma\pi$[c]	$\Sigma\sigma$[d]	MR_1[e]	MR_2[e]	MR_3[e]	$E_{s(3')}$[f]	R_{BS}[g]	I_{BS}	$I_{3,6}$	I_{NH_2}	I_{NO_2}
675[ij]	1'-$NHSO_2(CH_2)_2NH_2$	<4.16	4.26	−0.10	4.16	3.78	0.38	−3.73	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
676[ij]	1'-$NHSO_2(CH_2)_3NH_2$	<4.01	4.25	−0.24	4.01	3.77	0.24	−3.60	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
677[ij]	1'-$NHSO_2(CH_2)_4NH_2$	<4.02	4.22	−0.20	4.02	3.76	0.26	−3.36	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
678[n]	10-CH_3; 3-NO_2; 1'-$NHSO_2(CH_2)_4NH_2$	<4.26	4.65	−0.39	4.26	3.88	0.38	−3.14	0.78	0.20	0.20	0.84	0.00	0	0	0	0	1
679[n]	4-$CONH_2$; 3'-OCH_3; 1'-$NHSO_2(CH_2)_4NH_2$	<4.21	4.67	−0.46	4.21	4.08	0.13	−4.87	0.12	0.20	0.20	0.20	−0.55	0	0	0	0	0
680[ij]	3-NO_2; 5-CH_3; 1'-$NHSO_2(CH_2)_4NH_2$	<3.34	4.71	−1.37	3.34	3.93	−0.59	−3.08	0.71	0.20	0.20	0.84	0.00	0	0	0	0	1
681[ij]	1'-$NHSO_2(CH_2)_5NH_2$	<4.02	4.17	−0.15	4.02	3.72	0.30	−2.89	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
682[ij]	1'-$NHSO_2(CH_2)_6NH_2$	<4.03	4.12	−0.09	4.03	3.70	0.33	−2.46	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
683[ij]	3-NO_2; 1'-$NHSO_2(CH_2)_5NH_2$	<4.30	4.48	−0.18	4.30	3.78	0.52	−1.75	0.78	0.20	0.20	0.84	0.00	0	0	0	0	1
684[n]	4-$CONH_2$; 1'-$NHSO_2(CH_2)_3NHC(NH)NH_2$	<4.05	3.85	0.20	4.05	3.73	0.32	−6.05	0.28	0.20	0.20	0.20	0.00	0	0	0	0	0
685[ij]	1'-$NHSO_2(CH_2)_4NHC(NH)NH_2$	<3.98	4.30	−0.32	3.98	3.81	0.17	−4.06	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
686[ij]	10-CH_3; 1'-$NHSO_2(CH_2)_4NHC(NH)NH_2$	<3.61	4.30	−0.69	3.61	3.81	−0.20	−4.06	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
687[ij]	3-Cl; 1'-$NHSO_2(CH_2)_4NHC(NH)NH_2$	<3.57	4.57	−1.00	3.57	3.82	−0.25	−3.35	0.23	0.20	0.20	0.70	0.00	0	0	0	0	0
688[n]	4,5-$(CH_3)_2$; 	<4.23	4.20	0.03	4.23	3.77	0.46	−2.00	−0.14	0.20	0.20	0.20	0.00	0	0	0	0	0
689[n]	3-NO_2; 1'-$NHSO_2(CH_2)_5NHC(NH)NH_2$	<3.96	4.55	−0.60	3.96	3.82	0.14	−2.34	0.78	0.20	0.20	0.84	0.00	0	0	0	0	1
690[ij]	1'-$NHSO_2(CH_2)_2NHCO(CH_2)_2NH_2$	<3.89	4.33	−0.44	3.89	3.83	0.06	−4.39	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
691[ij]	10-CH_3; 1'-$NHSO_2(CH_2)_2NHCO(CH_2)_2NH_2$	<3.56	4.28	−0.72	3.56	3.79	−0.23	−3.89	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
692[j]	10-CH_3	<3.00[mm]	3.76	−0.76	<3.00[mm]	3.49	−0.49	0.50	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
693[n]	3-$NHSO_2CH_3$	<3.00	4.67	−1.67	<3.00	4.17	−1.17	−1.18	0.03	0.20	0.20	1.92	0.00	0	0	0	0	0
694[s]	2'-aza	<3.00	3.28	−0.28	<3.00	3.09	−0.09	−1.51	0.71	0.20	0.20	0.20	0.00	0	0	0	0	0
695[n]	2'-$NHSO_2Ph$	<3.00	3.60	−0.60	<3.00	3.37	−0.37	0.45	0.16	0.20	0.20	0.20	0.00	0	0	0	0	0
696[s]	2-NO_2	<3.00	3.14	−0.14	<3.00	3.01	−0.01	−0.28	0.71	0.20	0.20	0.20	0.00	0	0	0	0	0
697[m]	2'-CH_2CH_2COOH	<3.00	3.89	−0.89	<3.00	3.57	−0.57	−0.29	−0.03	0.20	0.20	0.20	0.00	0	0	0	0	0
698[m]	2'-CH=CHCOOH	<3.00	3.68	−0.68	<3.00	3.42	−0.42	0.00	0.14	0.20	0.20	0.20	0.00	0	0	0	0	0
699[m]	2'-$(CH=CH)_2COOH$	<3.00	3.53	−0.53	<3.00	3.32	−0.32	0.70	0.20	0.20	0.20	0.20	0.00	0	0	0	0	0
700[s]	2'-Cl	<3.00	3.36	−0.36	<3.00	3.20	−0.20	0.71	0.37	0.20	0.20	0.20	0.00	0	0	0	0	0
701[m]	2'-COOH	<3.00	3.48	−0.48	<3.00	3.27	−0.27	−0.32	0.37	0.20	0.20	0.20	0.00	0	0	0	0	0
702[s]	3'-$NHCOOCH_3$	<3.00	1.00	2.00	<3.00	2.97	0.03	−0.37	−0.10	0.20	0.20	0.20	−2.00	0	0	0	0	0
703[s]	3'-$CH_2NHSO_2CH_3$	<3.00	1.12	1.88	<3.00	3.04	−0.04	−1.37	−0.10	0.20	0.20	0.20	−2.00	0	0	0	0	0
704[p]	3'-OH	<3.00	4.50	−1.50	<3.00	4.00	−1.00	−0.67	−0.16	0.20	0.20	0.20	−0.55	0	0	0	0	0
705[s]	3'-Cl	<3.00	3.60	−0.60	<3.00	3.56	−0.56	0.71	0.27	0.20	0.20	0.20	−0.97	0	0	0	0	0
706[s]	3'-Br	<3.00	3.25	−0.25	<3.00	3.46	−0.46	0.86	0.28	0.20	0.20	0.20	−1.16	0	0	0	0	0

707[s]	3′-I	<3.00	2.75	0.25	<3.00	3.36	−0.36	1.12	0.18	0.20	0.20	0.20	−1.40	0	0	0	0	0
708[s]	3′-$CONH_2$	<3.00	0.40	2.60	<3.00	2.49	0.51	−1.49	0.63	0.20	0.20	0.20	−2.00	0	0	0	0	0
709[s]	3′-$COOCH_3$	<3.00	0.21	2.79	<3.00	2.38	0.62	−0.01	0.64	0.20	0.20	0.20	−2.00	0	0	0	0	0
710[s]	3′-SO_2NH_2	<3.00	−2.59	5.59	<3.00	1.36	1.64	−1.82	0.94	0.20	0.20	0.20	−2.50	0	0	0	0	0
711[n]	3-$NHSO_3CH_3$; 1′-NH_2	<3.00	4.97	−1.97	<3.00	4.37	−1.37	−2.41	−0.12	0.20	0.20	1.92	0.00	0	0	0	0	0
712[n]	1′-N(CONHNHCO)	<3.00	3.92	−0.92	<3.00	3.58	−0.58	−0.80	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
713[v]	1′-$N(SO_2CH_3)_2$	<3.00	4.00	−1.00	<3.00	3.63	−0.63	−1.51	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
714[m]	1′-NO_2	<3.00	2.60	0.40	<3.00	2.61	0.39	−0.28	1.24	0.20	0.20	0.20	0.00	0	0	0	0	0
715[m]	4-$OCH_2CH(OH)CH_2OH$; 1′-COOH	<3.00	3.13	−0.13	<3.00	2.97	0.03	−1.75	0.89	0.20	0.20	0.20	0.00	0	0	0	0	0
716[m]	1′-$(CH_2)_2SO_3H$	<3.00	4.13	−1.13	<3.00	3.71	−0.71	−1.96	−0.07	0.20	0.20	0.20	0.00	0	0	0	0	0
717[m]	3-NO_2; 1′-$(CH_2)_2SO_3H$	<3.00	4.69	−1.69	<3.00	3.93	−0.93	−2.24	0.63	0.20	0.20	0.84	0.00	0	0	0	0	1
718[r]	3-$NHCOCH_3$; 1′-$(CH_2)_5COOH$	<3.00	4.70	−1.70	<3.00	4.14	−1.14	0.39	−0.15	0.20	0.20	1.59	0.00	0	0	0	0	0
719[r]	1′-$OCH(CH_3)COOH$	<3.00	4.04	−1.04	<3.00	3.68	−0.68	−0.49	−0.16	0.20	0.20	0.20	0.00	0	0	0	0	0
720[r]	1′-$O(CH_2)_2COOH$	<3.00	4.05	−1.05	<3.00	3.68	−0.68	−0.54	−0.16	0.20	0.20	0.20	0.00	0	0	0	0	0
721[r]	1′-OCH(Pr)COOH	<3.00	3.91	−0.91	<3.00	3.60	−0.60	0.59	−0.16	0.20	0.20	0.20	0.00	0	0	0	0	0
722[r]	3-$NHCH_3$; 1′-$O(CH_2)_3COOH$	<3.00	5.67	−2.67	<3.00	4.73	−1.73	−0.75	−1.00	0.20	0.20	1.13	0.00	0	0	0	0	0
723[m]	3′-OH; 1′-COOH	<3.00	3.76	−0.76	<3.00	3.44	−0.44	−0.99	0.61	0.20	0.20	0.20	−0.55	0	0	0	0	0
724[m]	3′-CH_3; 1′-COOH	<3.00	2.81	0.19	<3.00	3.20	−0.20	0.24	0.62	0.20	0.20	0.20	−1.24	0	0	0	0	0
725[m]	3-$NHCOCH_3$; 1′-COOH	<3.00	3.97	−0.97	<3.00	3.56	−0.56	−1.29	0.77	0.20	0.20	1.59	0.00	0	0	0	0	0
726[m]	1′-$COCH_3$	<3.00	3.01	−0.01	<3.00	2.91	0.09	−0.55	0.87	0.20	0.20	0.20	0.00	0	0	0	0	0
727[j]	10-CH_3; 1′-$CONH_2$	<3.00	3.30	−0.30	<3.00	3.12	−0.12	0.99	0.63	0.20	0.20	0.20	0.00	0	0	0	0	0
728[m]	1′-SO_3H	<3.00	3.08	−0.08	<3.00	2.92	0.08	−2.23	1.00	0.20	0.20	0.20	0.00	0	0	0	0	0
729[s]	1′-SO_2CH_3	<3.00	3.02	−0.02	<3.00	2.90	0.10	−1.63	0.98	0.20	0.20	0.20	0.00	0	0	0	0	0
730[p]	1′-SO_2NH_2	<3.00	3.09	−0.09	<3.00	2.94	0.06	−1.82	0.94	0.20	0.20	0.20	0.00	0	0	0	0	0
731[r]	1′-$CONH_2$	<3.00	3.36	−0.36	<3.00	3.15	−0.15	−1.49	0.63	0.20	0.20	0.20	0.00	0	0	0	0	0
732[j]	10-CH_3; 1′-SO_2CH_3	<3.00	2.96	0.04	<3.00	2.86	0.14	−1.13	0.98	0.20	0.20	0.20	0.00	0	0	0	0	0
733[s]	1′-SO_2NHCH_3	<3.00	2.99	0.01	<3.00	2.88	0.12	−1.21	0.96	0.20	0.20	0.20	0.00	0	0	0	0	0
734[n]	1′-$SO_2NH(CH_2)_2NH_2$	<3.00	3.29	−0.29	<3.00	3.06	−0.06	−3.75	0.96	0.20	0.20	0.20	0.00	0	0	0	0	0
735[m]	1′-Cl	<3.00	3.46	−0.46	<3.00	3.27	−0.27	0.71	0.27	0.20	0.20	0.20	0.00	0	0	0	0	0
736[m]	1′-Br	<3.00	3.43	−0.43	<3.00	3.25	−0.25	0.86	0.28	0.20	0.20	0.20	0.00	0	0	0	0	0
737[n]	2′,6′-$(NHSO_2CH_3)_2$	<3.00	3.70	−0.70	<3.00	3.38	−0.38	−2.36	0.40	0.20	0.20	0.20	0.00	0	0	0	0	0
738[n]	5′-CH_3; 2′-$NHSO_2CH_3$	<3.00	3.49	−0.49	<3.00	3.69	−0.69	−0.62	0.05	0.20	0.20	0.20	−1.24	0	0	0	0	0
739[n]	2′,5′-$(NHSO_2CH_3)_2$	<3.00	−1.77	4.77	<3.00	1.95	1.05	−2.36	0.20	0.20	0.20	0.20	−2.50	0	0	0	0	0
740[p]	2′-NO_2; 1′-$NHSO_2CH_3$	<3.00	3.28	−0.28	<3.00	3.09	−0.09	−1.46	0.71	0.20	0.20	0.20	0.00	0	0	0	0	0
741[v]	2′-F; 1′-$NHSO_2CH_3$	<3.00	3.60	−0.60	<3.00	3.34	−0.34	−1.04	0.34	0.20	0.20	0.20	0.00	0	0	0	0	0
742[v]	3′-aza; 1′-$NHSO_2CH_3$	<3.00	2.82	0.18	<3.00	2.73	0.27	−2.30	1.26	0.20	0.20	0.20	0.00	0	0	0	0	0
743[p]	1′,3′-$(NHSO_2CH_3)_2$	<3.00	1.14	1.86	<3.00	3.03	−0.03	−2.36	0.00	0.20	0.20	0.20	−2.00	0	0	0	0	0
744[v]	3′-NO_2; 1′-$NHSO_2CH_3$	<3.00	2.80	0.20	<3.00	2.96	0.04	−1.46	1.24	0.20	0.20	0.20	−1.02	0	0	0	0	0
745[v]	3′-F; 1′-$NHSO_2CH_3$	<3.00	4.33	−1.33	<3.00	3.84	−0.84	−1.04	0.05	0.20	0.20	0.20	−0.46	0	0	0	0	0
746	1-aza; 1′-$NHSO_2CH_3$	<3.00	3.38	−0.38	<3.00	3.15	−0.15	−2.30	0.71	0.20	0.20	0.20	0.00	0	0	0	0	0
747	2-aza; 1′-$NHSO_2CH_3$	<3.00	3.33	−0.33	<3.00	3.10	−0.10	−2.66	0.80	0.20	0.20	0.20	0.00	0	0	0	0	0
748[n]	2-NHCOPh; 1′-$NHSO_2CH_3$	<3.00	3.00	0.00	<3.00	2.75	0.25	−0.69	0.02	0.20	3.56	0.20	0.00	0	0	0	0	0
749[w]	2-NO_2; 1′-$NHSO_2CH_3$	<3.00	3.11	−0.11	<3.00	2.93	0.07	−1.46	0.71	0.20	0.84	0.20	0.00	0	0	0	0	0
750[j]	10-CH_3; 2-NO_2; 1′-$NHSO_2CH_3$	<3.00	3.05	−0.05	<3.00	2.90	0.10	−0.96	0.71	0.20	0.84	0.20	0.00	0	0	0	0	0
751[w]	2-OCH_3; 1′-$NHSO_2CH_3$	<3.00	3.66	−0.66	<3.00	3.35	−0.35	−1.20	0.12	0.20	0.89	0.20	0.00	0	0	0	0	0
752[w]	2-F; 1′-$NHSO_2CH_3$	<3.00	3.60	−0.60	<3.00	3.34	−0.34	−1.04	0.34	0.20	0.19	0.20	0.00	0	0	0	0	0
753[bb]	2-$CONH_2$; 1′-$NHSO_2CH_3$	<3.00	3.63	−0.63	<3.00	3.28	−0.28	−2.67	0.28	0.20	1.08	0.20	0.00	0	0	0	0	0
754	3-aza; 1′-$NHSO_2CH_3$	<3.00	3.54	−0.54	<3.00	3.27	−0.27	−2.30	0.55	0.20	0.20	0.20	0.00	0	0	0	0	0
755[v]	3-CF_3; 1′-$NHSO_2CH_3$	<3.00	3.82	−0.82	<3.00	3.33	−0.33	−0.30	0.54	0.20	0.20	0.60	0.00	0	0	0	0	0
756[w]	3-SO_2CH_3; 1′-$NHSO_2CH_3$	<3.00	4.20	−1.20	<3.00	3.67	−0.67	−2.81	0.72	0.20	0.20	1.45	0.00	0	0	0	0	0

Table I (*Continued*)

no.	substituents[mm]	log $(1/D_{50})$[a] obsd	log $(1/D_{50})$[a] calcd[h]	Δ log $(1/D_{50})$	log $(1/LD_{10})$[b] obsd	log $(1/LD_{10})$[b] calcd[i]	Δ log $(1/LD_{10})$	$\Sigma\pi$[c]	$\Sigma\sigma$[d]	MR_1[e]	MR_1[e]	MR_3[e]	$E_{s(3')}$[f]	R_{BS}[g]	I_{BS}	$I_{3,6}$	I_{NH_2}	I_{NO_2}
757	4-aza; 1′-$NHSO_2CH_3$	<3.00	3.38	−0.38	<3.00	3.15	−0.15	−2.30	0.71	0.20	0.20	0.20	0.00	0	0	0	0	0
758[w]	4-$NHCOCH_3$; 1′-$NHSO_2CH_3$	<3.00	3.87	−0.87	<3.00	3.51	−0.51	−2.15	0.21	0.20	0.20	0.20	0.00	0	0	0	0	0
759[w]	4-NO_2; 1′-$NHSO_2CH_3$	<3.00	3.28	−0.28	<3.00	3.09	−0.09	−1.46	0.71	0.20	0.20	0.20	0.00	0	0	0	0	0
760[w]	4-F; 1′-$NHSO_2CH_3$	<3.00	3.60	−0.60	<3.00	3.34	−0.34	−1.04	0.34	0.20	0.20	0.20	0.00	0	0	0	0	0
761[w]	4-Cl; 1′-$NHSO_2CH_3$	<3.00	3.50	−0.50	<3.00	3.28	−0.28	−0.47	0.37	0.20	0.20	0.20	0.00	0	0	0	0	0
762[w]	4-COOEt; 1′-$NHSO_2CH_3$	<3.00	3.53	−0.53	<3.00	3.29	−0.29	−0.67	0.37	0.20	0.20	0.20	0.00	0	0	0	0	0
763[n]	3′,5′-$(CH_3)_2$; 1′-$NHSO_2CH_3$	<3.00	3.78	−0.78	<3.00	3.92	−0.92	−0.06	−0.30	0.20	0.20	0.20	−1.24	0	0	0	0	0
764[n]	3′,5′-$(OCH_3)_2$; 1′-$NHSO_2CH_3$	<3.00	4.73	−1.73	<3.00	4.15	−1.15	−1.22	−0.32	0.20	0.20	0.20	−0.55	0	0	0	0	0
765[n]	1-Cl; 3′-OCH_3; 1′-$NHSO_2CH_3$	<3.00	4.25	−1.25	<3.00	3.53	−0.53	−0.49	0.07	0.70	0.20	0.20	−0.55	0	0	0	0	0
766[hh]	2-NO_2; 3′-OCH_3; 1′-$NHSO_2CH_3$	<3.00	3.71	−0.71	<3.00	3.36	−0.36	−1.48	0.55	0.20	0.84	0.20	−0.55	0	0	0	0	0
767[n]	2-Et; 3′-OCH_3; 1′-$NHSO_2CH_3$	<3.00	4.27	−1.27	<3.00	3.79	−0.79	−0.18	−0.23	0.20	1.13	0.20	−0.55	0	0	0	0	0
768[n]	3-SO_2CH_3; 3′-OCH_3; 1′-$NHSO_2CH_3$	<3.00	4.81	−1.81	<3.00	4.10	−1.10	−2.83	0.56	0.20	0.20	1.45	−0.55	0	0	0	0	0
769[w]	2,6-$(NHCOCH_3)_2$; 1′-$NHSO_2CH_3$	<3.00	4.65	−1.65	<3.00	4.01	−1.01	−3.22	0.21	0.20	0.64	1.59	0.00	0	0	0	0	0
770[w]	2,7-$(NHCOCH_3)_2$; 1′-$NHSO_2CH_3$	<3.00	3.51	−0.51	<3.00	3.19	−0.19	−3.12	0.42	0.20	1.18	0.20	0.00	0	0	0	0	0
771[aa]	3-Cl; 6-CF_3; 1′-$NHSO_2CH_3$	<3.00	3.06	−0.06	<3.00	2.80	0.20	0.41	0.77	0.20	0.20	1.10	0.00	0	0	1	0	0
772[aa]	3,6-$(Cl)_2$; 1′-$NHSO_2CH_3$	<3.00	3.41	−0.41	<3.00	3.07	−0.07	0.24	0.46	0.20	0.20	1.20	0.00	0	0	1	0	0
773[aa]	3-Cl; 6-CF_3; 3′-OCH_3; 1′-$NHSO_2CH_3$	<3.00	3.67	−0.67	<3.00	3.22	−0.22	0.39	0.61	0.20	0.20	1.10	−0.55	0	0	1	0	0
774[q]	1′-$NHSO_2(CH_2)_2COOCH_3$	<3.00	3.93	−0.93	<3.00	3.58	−0.58	−0.88	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
775[q]	1′-$NHSO_2(CH_2)_2COOH$	<3.00	3.98	−0.98	<3.00	3.62	−0.62	−1.36	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0
776[q]	1′-$NHSO_2(CH_2)_3NHCOCH_3$	<3.00	4.05	−1.05	<3.00	3.66	−0.66	−1.95	0.00	0.20	0.20	0.20	0.00	0	0	0	0	0

[a] D_{50}; drug dose in moles per kilogram per day providing a 50% extension of life in L1210 assays when given on a qd 1–5 schedule; see ref 12. [b] LD_{10}; drug dose in moles per kilogram per day proving lethal to 10% of animals, determined by the method of ref 12. [c] $\Sigma\pi$; sum of π values for all 9-anilinoacridine side chains; determined by the fragment constant summation technique discussed in the text and in ref 37. [d] $\Sigma\sigma$; sum of σ values for all 9-anilinoacridine side chains, as discussed in the text. [e] MR values are taken from ref 37, and scaled by 0.1. [f] $E_{s(3')}$; E_s values for 3′-substituents taken from ref 37. [g] R_{BS}; Swain and Lupton's parameter for groups in the para position of the 1′-benzenesulfonanilide side chain; values taken from ref 37. [h] Log $(1/D_{50})$ values calculated using eq 8. [i] Log $(1/LD_{10})$ values calculated using eq 10. [j] Reference 4. [k] Reference 14. [l] Observed activity value not used to compute equation. [m] Reference 11. [n] New compound; see Table X for physical and analytical details. [o] Value recorded is actually log $(1/LD_{10})$ value. [p] Reference 1. [q] Reference 8. [r] Reference 12. [s] Reference 14. [t] Reference 57. [u] Group -XPhY implies para disposition of X and Y functions unless otherwise noted. [v] Reference 3. [w] Reference 2. [x] Reference 6. [y] Reference 58. [z] Reference 13. [aa] Reference 5. [bb] Reference 54. [cc] Reference 7. [dd] Compounds possess a 3-alkyltriazene moiety; indicator variable $I_{DAT} = 1$. [ee] Reference 15. [ff] X_1 = -$NHCOH_2N$(-$CONHCH_2CO$-). [gg] X_2 = -N(-$COCH_2NHCO$-). [hh] Reference 10. [ii] -CONHY; amide derived from α-methyl-D-glucosaminide; see ref 8. [jj] Reference 9. [kk] Compounds **542–776** tumor-inactive but toxic; activity values recorded are log $(1/LD_{10})$ values and not used to compute eq 8. [ll] Toxic dose levels could not be reached for compounds **692–776**; for visual convenience both log $(1/D_{50})$ and log $(1/LD_{10})$ values are recorded as <3.00, corresponding approximately to a dose of 500 (mg/kg)/day and have not been used to compute eq 8 and 10. [mm] Abbreviations used are: Ph, phenyl, Et, ethyl; Pr, propyl; Bu, butyl; Pe, pentyl; Hx, hexyl; Hp, heptyl; Oct, octyl; benz, benzylidene.

EtOH. Elaboration to compound **661** was effected by methods already published[8] for the 4-carboxamido analogue.

Side chains for the preparation of compounds **23–25** were prepared from *p*-acetamidobenzenesulfonyl chloride and the appropriate alkylamine, followed by alkaline hydrolysis; those for compounds **623** and **734** utilized *p*-nitrobenzensulfonyl chloride and a tenfold excess of the appropriate diamine.

The substituted nitrobenzenes needed for compounds **27, 147,** and **737–739** were prepared from methanesulfonyl chloride and the appropriate arylamines, which were commercially available, or prepared by known methods.[29-32]

Side chains for compounds **117–123, 127–131,** and **589–602** were elaborated from the ω-(4′-nitrophenyl)alkanoic acids prepared previously.[12,33] Catalytic hydrogenation of these intermediates and coupling of the resulting amines with *p*-nitrophenyl isocyanate afforded the ω-[[(4′-nitrophenyl)ureido]phenyl]alkanoic acids for compounds **127–131.** Curtius reaction[34] of the ω-(4′-nitrophenyl)alkanoic acids gave the (ω − 1)-(4′-nitrophenyl)-alkanamines, which were used for compounds **589–602.** These alkanamines, protected as the phthalimide derivatives, were also catalytically reduced and coupled to *p*-nitrophenyl isocyanate to give the (ω − 1)-[[(4′-nitrophenyl)ureido]phenyl]alkanamines for compounds **117–123.**

The side chains for compounds **763** and **764** were elaborated[35] from 2,6-dimethylaniline and resorcinol dimethyl ether.

Biological Parameters. Choice of the appropriate measures of biological response for antitumor testing has been discussed previously at some length.[22,36] In the present study, all tumor-active compounds were tested over dose ranges from the inactive to acutely toxic. Approximate LD_{10} values were determined by probit-log dose analysis of mortality data in the toxic dose range, while linear regression of percentage increase in life span data [ILS = 100(T/C)/C] vs. log dose in the active dose range provided the two measures of antitumor response. ILS_{max}, the percentage increase in life span specified by the linear correlation at the LD_{10} dose for each drug, is a measure of tumor cell selectivity.[22,36] D_{50}, the dose of drug needed to elicit an increase in life span at 50%, is a measure of dose potency. In previous QSAR studies with subsets of the 9-anilinoacridines, we have used D_{40} as a measure of dose potency in order to be able to include in the analyses as many derivatives as possible, including weakly active ones. However, D_{40} values invariably lie toward the lower end of the range of data (see diagram in ref 12) and are inherently less accurately determined than more centrally situated ones. In the present study, with a large amount of active compounds available, it was decided to use D_{50} values—the loss of a few weakly active compounds from the analysis should be more than offset by the increased accuracy of the biological parameter. Of course, it is to be hoped that similar conclusions would emerge from studies using slightly differing end points and that the choice of value Dx should not be critical, an assumption substantiated by the results of the present study.

Inactive agents were tested at a minimum of three dose levels that spanned the toxic range in order for approximate LD_{10} values to be determined. A number of derivatives were found to be inactive and nontoxic at all dose levels tested up to the arbitrary limit of 500 (mg/kg)/day; LD_{10} values for these compounds are recorded (in molar terms) as "greater than" the highest dose tested.

Physicochemical Parameters. In previous QSAR studies of subsets of the 9-anilinoacridines, we have used R_m values from partition chromatography as a measure of agent hydrophobicity. Because of the many complex substituents employed at many differing sites on the 9-anilinoacridine skeleton, it was felt that experimentally determined measures of hydrophobicity might be more relevant than summed π values derived from the benzene system. The main drawback to this approach is of course that all congeners to be considered then have to be synthesized so that measurements can be made. For a small set of 9-anilinoacridines bearing simple substituents, the measured R_m values were found to be well correlated with measured partition coefficients (log *P*) of the cations in *n*-BuOH/water (eq 1).

$$\log P_{n\text{-BuOH}} = 1.99\ (\pm 0.15)\ \Delta R_m + 0.51\ (\pm 0.10) \quad (1)$$

$$n = 21;\ r = 0.991;\ s = 0.07$$

Recent advances[37] in the calculation of partition coefficients by the fragment constant technique now permit reasonably accurate calculation of log *P* values for complex molecules as an appropriate summation of fragment constants. In the present study, the measure of hydrophobicity used is the sum of π values for the various side chains on the acridine and anilino rings. π values are either taken from the compilations that exist[37,38] or, in many cases, calculated by the fragment constant technique.[37]

Although π values determined in this way from values based on the benzene system may differ from those actually expected to apply for the anilinoacridine system, such differences are expected to be slight. More serious is the assumption that a particular side chain will have the same π value, regardless of the position it is attached to. Measured R_m values for substituted 9-anilinoacridines show that this is not the case; groups at shielded positions (e.g., 3 and 4 positions) do not exert the same effect on drug hydrophobicity as the same groups in exposed positions (e.g., 2 and 3 positions). However, such differences are still relatively small compared to the noise in even the most carefully determined biological data.

Values for steric parameters MR and E_s are taken from recent compilations.[37-39] E_s values are scaled so that H is assigned the value of zero. An important determinant of activity in previous studies of 9-anilinoacridines was found to be the pK_a for ionization of the acridine nitrogen. In the present work it was not feasible to measure pK_a

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Table II. Measured pK_a Values for Selected 9-Anilinoacridines

entry no. in table I	group	pK_a[a] obsd	pK_a[a] calcd[d]	$\|\Delta$ p$K_a\|$	$\Sigma\sigma_{acridine}$[b]	$\Sigma\sigma_{aniline}$[c]
542	1′-H	7.46	7.10	0.36	0.00	0.00
69	1′-NH_2	8.36	8.05	0.31	0.00	−0.66
81	1′-$NHCH_3$	8.42	8.31	0.11	0.00	−0.84
82	1′-NHEt	8.30	7.98	0.32	0.00	−0.61
577	1′-NHPr	8.24	7.82	0.42	0.00	−0.50
83	1′-$N(CH_3)_2$	8.46	8.30	0.16	0.00	−0.83
89	1′-$NHCOCH_3$	7.51	7.10	0.41	0.00	0.00
104	1′-NHCOPh	7.39	7.38	0.01	0.00	−0.19
148	1′-$NHSO_2CH_3$	7.19	7.06	0.13	0.00	0.03
472	1′-$NHSO_2Ph$	7.09	7.06	0.03	0.00	0.03
478	1′-$NHSO_2PhNH_2$	7.15	7.06	0.09	0.00	0.03
107	1′-$NHCOOCH_3$	7.64	7.32	0.32	0.00	−0.15
111	1′-$NHCONHCH_3$	7.77	7.45	0.32	0.00	−0.24
116	1′-NHCONHPh	7.67	7.45	0.22	0.00	−0.24
144	1′-$N(CH_3)SO_2CH_3$	6.95	7.10	0.15	0.00	0.00
33	1′-CH_3	7.72	7.35	0.37	0.00	−0.17
716	1′-$CH_2CH_2SO_3H$	7.77	7.35	0.42	0.00	−0.17
36	1′-$CH_2SO_2NH_2$	7.05	7.10	0.05	0.00	0.00
38	1′-$(CH_2)_2SO_2NH_2$	7.43	7.35	0.08	0.00	−0.17
41	1′-$(CH_2)_2COOH$	7.91	7.35	0.56	0.00	−0.17
53	1′-CH_2CONH_2	7.43	7.00	0.43	0.00	0.07
54	1′-$(CH_2)_2CONH_2$	7.63	7.35	0.28	0.00	−0.17
56	1′-$(CH_2)_3CONH_2$	7.67	7.35	0.32	0.00	−0.17
6	1′-$COOCH_3$	6.21	6.45	0.24	0.00	0.45
731	1′-$CONH_2$	6.47	6.58	0.11	0.00	0.36
613	1′-OCH_3	7.94	7.49	0.45	0.00	−0.27
618	1′-CN	5.93	6.15	0.22	0.00	0.66
714	1′-NO_2	5.58	5.98	0.40	0.00	0.78
726	1′-$COCH_3$	6.12	6.38	0.26	0.00	0.50
729	1′-SO_2CH_3	5.81	6.07	0.26	0.00	0.72
730	1′-SO_2NH_2	6.11	6.28	0.17	0.00	0.57
739	1′-SO_2NHCH_3	6.02	6.28	0.26	0.00	0.57
619	1′-F	7.50	7.02	0.48	0.00	0.06
735	1′-Cl	7.06	6.77	0.29	0.00	0.23
736	1′-Br	7.00	6.77	0.23	0.00	0.23
621	1′-I	6.90	6.84	0.06	0.00	0.18
104	2′-$NHCOCH_3$	7.16	6.80	0.36	0.00	0.21
148	2′-$NHSO_2CH_3$	6.85	6.82	0.03	0.00	0.20
80	2′-NH_2	7.58	7.33	0.25	0.00	−0.16
545	2′-$NHCH_3$	7.61	7.54	0.07	0.00	−0.30
546	2′-CH_3	7.52	7.20	0.32	0.00	−0.07
549	2′-OH	7.30	6.96	0.34	0.00	0.10
550	2′-OCH_3	7.21	6.93	0.28	0.00	0.12
694	2′-aza	6.46	6.08	0.38	0.00	0.71
696	2′-NO_2	6.26	6.08	0.18	0.00	0.71
700	2′-Cl	6.76	6.57	0.19	0.00	0.37
551	3′-aza	6.32	5.98	0.34	0.00	0.78
552	3′-NH_2	7.87	8.05	0.18	0.00	−0.66
553	3′-$NHCOCH_3$	7.24	7.10	0.14	0.00	0.00
555	3′-$NHSO_2CH_3$	6.86	7.06	0.20	0.00	0.03
556	3′-$N(CH_3)SO_2CH_3$	6.97	7.10	0.13	0.00	0.00
34	3′-CH_3	7.76	7.35	0.41	0.00	−0.17
557	3′-Et	7.68	7.32	0.36	0.00	−0.15
558	3′-$CH(CH_3)_2$	7.64	7.32	0.32	0.00	−0.15
559	3′-$C(CH_3)_3$	7.62	7.39	0.23	0.00	−0.20
702	3′-$NHCOOCH_3$	7.24	7.32	0.08	0.00	−0.15
703	3′-$CH_2NHSO_2CH_3$	7.17	7.32	0.15	0.00	−0.15
704	3′-OH	7.80	7.64	0.16	0.00	−0.37
563	3′-OCH_3	7.74	7.49	0.25	0.00	−0.27
564	3′-OEt	7.85	7.45	0.40	0.00	−0.24
566	3′-F	6.84	7.02	0.18	0.00	0.06
705	3′-Cl	6.55	6.77	0.22	0.00	0.23
706	3′-Br	6.41	6.77	0.36	0.00	0.23
707	3′-I	6.47	6.84	0.37	0.00	0.18
709	3′-$COOCH_3$	6.30	6.45	0.15	0.00	0.45
624	2′-OCH_3; 1′-$NHSO_2CH_3$	7.03	6.89	0.14	0.00	0.15
625	2′-CH_3; 1′-$NHSO_2CH_3$	7.08	7.16	0.08	0.00	−0.04
626	2′-Cl; 1′-$NHSO_2CH_3$	6.44	6.53	0.09	0.00	0.40
159	3′-NH_2; 1′-$NHSO_2CH_3$	7.65	8.01	0.36	0.00	−0.63
160	3′-CH_3; 1′-$NHSO_2CH_3$	7.36	7.31	0.07	0.00	−0.14
162	3′-OCH_3; 1′-$NHSO_2CH_3$	7.43	7.45	0.02	0.00	−0.24
628	3′-Cl; 1′-$NHSO_2CH_3$	6.34	6.67	0.33	0.00	0.30
744	3′-NO_2; 1′-$NHSO_2CH_3$	4.86[e]	5.94	1.08	0.00	0.81
629	1-NO_2; 1′-$NHSO_2CH_3$	4.79[e]	5.24	0.45	0.78	0.03
630	1-CH_3; 1′-$NHSO_2CH_3$	6.43[e]	7.46	1.03	−0.17	0.03
746	1-aza; 1′-$NHSO_2CH_3$	6.90[e]	5.40	1.50	0.71	0.03

Table II (*Continued*)

entry no. in table I	group	pK_a[a] obsd	pK_a[a] calcd[d]	$\|\Delta pK_a\|$	$\Sigma\sigma_{acridine}$[b]	$\Sigma\sigma_{aniline}$[c]
747	2-aza; 1′-$NHSO_2CH_3$	5.73[e]	5.19	0.54	0.80	0.03
173	2-NH_2; 1′-$NHSO_2CH_3$	7.15	7.43	0.28	−0.16	0.03
178	2-$N(CH_3)_2$; 1′-$NHSO_2CH_3$	7.27	7.41	0.14	−0.15	0.03
740	2-NO_2; 1′-$NHSO_2CH_3$	5.42	5.40	0.02	0.71	0.03
751	2-OCH_3; 1′-$NHSO_2CH_3$	6.87	6.78	0.09	0.12	0.03
753	2-$CONH_2$; 1′-$NHSO_2CH_3$	6.34	6.41	0.07	0.28	0.03
634	2-Cl; 1′-$NHSO_2CH_3$	6.42	6.20	0.22	0.37	0.03
754	3-aza; 1′-$NHSO_2CH_3$	5.32	5.24	0.08	0.78	0.03
179	3-NH_2; 1′-$NHSO_2CH_3$	9.80[e]	8.60	1.20	−0.66	0.03
181	3-$NHCH_3$; 1′-$NHSO_2CH_3$	9.30	9.02	0.28	−0.84	0.03
182	3-$NHCOOCH_3$; 1′-$NHSO_2CH_3$	7.48	7.41	0.07	−0.15	0.03
813	3-N_3; 1′-$NHSO_2CH_3$	7.00	6.71	0.29	0.15	0.03
184	3-$N_3(CH_3)_2$; 1′-$NHSO_2CH_3$	7.13	6.71	0.42	0.15	0.03
187	3-$NHCOCH_3$; 1′-$NHSO_2CH_3$	7.34	7.06	0.28	0.00	0.03
195	3-NHCOEt; 1′-$NHSO_2CH_3$	7.35	7.06	0.29	0.00	0.03
196	3-NHCOPr; 1′-$NHSO_2CH_3$	7.37	7.06	0.31	0.00	0.03
197	3-NO_2; 1′-$NHSO_2CH_3$	5.52	5.24	0.28	0.78	0.03
204	3-OCH_3; 1′-$NHSO_2CH_3$	7.57	7.69	0.12	−0.27	0.03
205	3-CH_3; 1′-$NHSO_2CH_3$	7.49	7.46	0.03	−0.17	0.03
636	3-F; 1′-$NHSO_2CH_3$	6.77	6.92	0.15	0.06	0.03
207	3-Cl; 1′-$NHSO_2CH_3$	6.57	6.52	0.05	0.23	0.03
208	3-Br; 1′-$NHSO_2CH_3$	6.56	6.52	0.04	0.23	0.03
210	3-I; 1′-$NHSO_2CH_3$	6.52	6.64	0.12	0.18	0.03
639	3-CN; 1′-$NHSO_2CH_3$	5.75	5.52	0.23	0.66	0.03
756	3-SO_2CH_3; 1′-$NHSO_2CH_3$	5.65	5.38	0.27	0.72	0.03
757	4-aza; 1′-$NHSO_2CH_3$	5.93[f]	5.40	0.53	0.71	0.03
761	4-Cl; 1′-$NHSO_2CH_3$	5.92	6.20	0.28	0.37	0.03
759	4-NO_2; 1′-$NHSO_2CH_3$	4.88[e]	5.40	0.52	0.71	0.03
212	4-CH_3; 1′-$NHSO_2CH_3$	7.15	7.22	0.07	−0.07	0.03
213	4-CH_2OH; 1′-$NHSO_2CH_3$	6.68	7.06	0.38	0.00	0.03
214	4-Et; 1′-$NHSO_2CH_3$	7.14	7.22	0.08	−0.07	0.03
215	4-OCH_3; 1′-$NHSO_2CH_3$	7.15	6.78	0.37	0.12	0.03
218	4-$CONH_2$; 1′-$NHSO_2CH_3$	6.12	6.41	0.29	0.28	0.03
330	2-NH_2; 3-Cl; 1′-$NHSO_2CH_3$	6.71	6.90	0.19	0.07	0.03
332	2-NH_2; 6-Cl; 1′-$NHSO_2CH_3$	6.56	6.90	0.34	0.07	0.03
347	3,5-$(CH_3)_2$; 1′-$NHSO_2CH_3$	7.46	7.62	0.16	−0.24	0.03
357	3,6-$(NHCOCH_3)_2$; 1′-$NHSO_2CH_3$	7.55	7.06	0.49	0.00	0.03
361	3-NO_2; 6-CH_3; 1′-$NHSO_2CH_3$	5.81	5.64	0.17	0.61	0.03
365	3-Cl; 6-OCH_3; 1′-$NHSO_2CH_3$	6.91	7.15	0.24	−0.04	0.03
642	1-aza; 3′-OCH_3; 1′-$NHSO_2CH_3$	7.19[e]	5.63	1.56	0.78	−0.24
643	1-NO_2; 3′-OCH_3; 1′-$NHSO_2CH_3$	4.98[e]	5.63	0.65	0.78	−0.24
644	1-CH_3; 3′-OCH_3; 1′-$NHSO_2CH_3$	6.71[e]	7.84	1.13	−0.17	−0.24
646	2-aza; 3′-OCH_3; 1′-$NHSO_2CH_3$	5.94[e]	5.79	0.15	0.71	−0.24
221	2-NH_2; 3′-OCH_3; 1′-$NHSO_2CH_3$	7.37	7.82	0.45	−0.16	−0.24
222	2-CH_3; 3′-OCH_3; 1′-$NHSO_2CH_3$	7.45	7.61	0.16	−0.07	−0.24
767	2-Et; 3′-OCH_3; 1′-$NHSO_2CH_3$	7.46	7.61	0.15	−0.07	−0.24
223	2-$CH(CH_3)_2$; 3′-OCH_3; 1′-$NHSO_2CH_3$	7.40	7.61	0.21	−0.07	−0.24
647	2-$C(CH_3)_3$; 3′-OCH_3; 1′-$NHSO_2CH_3$	7.38	7.68	0.30	−0.10	−0.24
648	2-OCH_3; 3′-OCH_3; 1′-$NHSO_2CH_3$	7.10	7.17	0.07	0.12	−0.24
649	2-Cl; 3′-OCH_3; 1′-$NHSO_2CH_3$	6.69	6.59	0.10	0.37	−0.24
650	2-$CONH_2$; 3′-OCH_3; 1′-$NHSO_2CH_3$	6.59	6.61	0.02	0.36	−0.24
766	2-NO_2; 3′-OCH_3; 1′-$NHSO_2CH_3$	5.63	5.79	0.16	0.71	−0.24
224	2-F; 3′-OCH_3; 1′-$NHSO_2CH_3$	6.71	6.66	0.05	0.34	−0.24
225	2-I; 3′-OCH_3; 1′-$NHSO_2CH_3$	6.60	6.63	0.03	0.35	−0.24
226	3-aza; 3′-OCH_3; 1′-$NHSO_2CH_3$	5.53	5.63	0.10	0.78	−0.24
237	3-$NHCOOCH_3$; 3′-OCH_3; 1′-$NHSO_2CH_3$	7.77	7.80	0.03	−0.15	−0.24
229	3-N_3; 3′-OCH_3; 1′-$NHSO_2CH_3$	7.26	7.10	0.16	0.15	−0.24
233	3-$N_3(CH_3)_2$; 3′-OCH_3; 1′-$NHSO_2CH_3$	7.36	7.10	0.26	0.15	−0.24
236	3-$NHCH_3$; 3′-OCH_3; 1′-$NHSO_2CH_3$	9.50	9.41	0.09	−0.84	−0.24
237	3-$NHCOCH_3$; 3′-OCH_3; 1′-$NHSO_2CH_3$	7.40	7.45	0.05	0.00	−0.24
247	3-NO_2; 3′-OCH_3; 1′-$NHSO_2CH_3$	5.72	5.63	0.09	0.78	−0.24
255	3-CH_3; 3′-OCH_3; 1′-$NHSO_2CH_3$	7.70	7.84	0.14	−0.17	−0.24
257	3-Et; 3′-OCH_3; 1′-$NHSO_2CH_3$	7.65	7.80	0.15	−0.15	−0.24
259	3-$CH(CH_3)_2$; 3′-OCH_3; 1′-$NHSO_2CH_3$	7.66	7.80	0.14	−0.15	−0.24
652	3-$C(CH_3)_3$; 3′-OCH_3; 1′-$NHSO_2CH_3$	7.64	7.91	0.27	−0.20	−0.24
258	3-$CH_2CH_2CONH_2$; 3′-OCH_3; 1′-$NHSO_2CH_3$	7.50	7.84	0.34	−0.17	−0.24
260	3-OCH_3; 3′-OCH_3; 1′-$NHSO_2CH_3$	7.81	8.08	0.27	−0.17	−0.24
261	3-CN; 3′-OCH_3; 1′-$NHSO_2CH_3$	5.94	5.91	0.03	0.66	−0.24
262	3-CF_3; 3′-OCH_3; 1′-$NHSO_2CH_3$	6.24	6.19	0.05	0.54	−0.24
263	3-F; 3′-OCH_3; 1′-$NHSO_2CH_3$	7.05	7.31	0.26	0.06	−0.24
264	3-Cl; 3′-OCH_3; 1′-$NHSO_2CH_3$	6.84	6.91	0.07	0.23	−0.24
268	3-Br; 3′-OCH_3; 1′-$NHSO_2CH_3$	6.84	6.91	0.07	0.23	−0.24
270	3-I; 3′-OCH_3; 1′-$NHSO_2CH_3$	6.77	7.03	0.26	0.18	−0.24
768	3-SO_2CH_3; 3′-OCH_3; 1′-$NHSO_2CH_3$	5.87	5.77	0.10	0.72	−0.24
271	4-aza; 3′-OCH_3; 1′-$NHSO_2CH_3$	6.09[f]	5.79	0.30	0.71	−0.24

Table II (*Continued*)

entry no. in table I	group	pK_a[a] obsd	pK_a[a] calcd[d]	$\lvert\Delta pK_a\rvert$	$\Sigma\sigma_{acridine}$[b]	$\Sigma\sigma_{aniline}$[c]
229	4-NO_2; 3′-OCH_3; 1′-$NHSO_2CH_3$	5.05[e]	5.79	0.74	0.71	−0.24
282	4-CH_3; 3′-OCH_3; 1′-$NHSO_2CH_3$	7.39	7.61	0.22	−0.07	−0.24
285	4-$(CH_2)_2CONH_2$; 3′-OCH_3; 1′-$NHSO_2CH_3$	7.15	7.61	0.46	−0.07	−0.24
286	4-Ph; 3′-OCH_3; 1′-$NHSO_2CH_3$	7.02	7.31	0.29	0.06	−0.24
287	4-F; 3′-OCH_3; 1′-$NHSO_2CH_3$	6.33	6.65	0.32	0.34	−0.24
288	4-Cl; 3′-OCH_3; 1′-$NHSO_2CH_3$	6.11	6.58	0.47	0.37	−0.24
289	4-Br; 3′-OCH_3; 1′-$NHSO_2CH_3$	6.09	6.54	0.45	0.39	−0.24
290	4-CN; 3′-OCH_3; 1′-$NHSO_2CH_3$	4.87[e]	6.14	1.27	0.56	−0.24
291	4-OCH_3; 3′-OCH_3; 1′-$NHSO_2CH_3$	7.39	7.17	0.22	0.12	−0.24
295	4-OEt; 3′-OCH_3; 1′-$NHSO_2CH_3$	7.37	7.22	0.15	0.10	−0.24
296	4-OPr; 3′-OCH_3; 1′-$NHSO_2CH_3$	7.36	7.22	0.14	0.10	−0.24
297	4-OBu; 3′-OCH_3; 1′-$NHSO_2CH_3$	7.34	7.22	0.12	0.10	−0.24
301	4-$OCH_2CONHCH_3$; 3′-OCH_3; 1′-$NHSO_2CH_3$	7.35	7.22	0.13	0.10	−0.24
302	4-$O(CH_2)_2OH$; 3′-OCH_3; 1′-$NHSO_2CH_3$	7.36	7.17	0.19	0.12	−0.24
303	4-$OCH_2CH(OH)CH_2OH$; 3′-OCH_3; 1′-$NHSO_2CH_3$	7.00	7.17	0.17	0.12	−0.24
305	4-$O(CH_2)_3CONH_2$; 3′-OCH_3; 1′-$NHSO_2CH_3$	7.36	7.17	0.19	0.12	−0.24
307	4-$CONH_2$; 3′-OCH_3; 1′-$NHSO_2CH_3$	6.37	6.79	0.42	0.28	−0.24
314	4-$CONHCH_3$; 3′-OCH_3; 1′-$NHSO_2CH_3$	6.36	6.63	0.27	0.35	−0.24
315	4-CONHBu; 3′-OCH_3; 1′-$NHSO_2CH_3$	6.36	6.63	0.27	0.35	−0.24
318	4-$CONHCH_2CHOHCH_2OH$; 3′-OCH_3	6.34	6.63	0.29	0.35	−0.24
322	4-CONH-Y;[f] 3′-OCH_3; 1′-$NHSO_2CH_3$	6.35	6.63	0.28	0.35	−0.24
324	4-$CONHCH_2CONH_2$; 3′-OCH_3; 1′-$NHSO_2CH_3$	6.18	6.65	0.47	0.34	−0.24
328	4-$CON(CH_3)_2$; 3′-OCH_3; 1′-$NHSO_2CH_3$	6.16	6.63	0.47	0.35	−0.24
368	2-NH_2; 3-Br; 3′-OCH_3; 1′-$NHSO_2CH_3$	7.01	7.28	0.27	0.07	−0.24
369	2-NH_2; 3-CF_3; 3′-OCH_3; 1′-$NHSO_2CH_3$	6.56	6.56	0.00	0.38	−0.24
663	2-OCH_3; 6-Cl; 3′-OCH_3; 1′-$NHSO_2CH_3$	6.52	6.63	0.11	0.35	−0.24
371	3,4-$(CH_3)_2$; 3′-OCH_3; 1′-$NHSO_2CH_3$	7.65	8.01	0.36	−0.24	−0.24
375	3-Cl; 4-CH_3; 3′-OCH_3; 1′-$NHSO_2CH_3$	6.71	7.07	0.36	0.16	−0.24
377	2-NH_2; 6-I; 3′-OCH_3; 1′-$NHSO_2CH_3$	6.72	7.40	0.68	0.02	−0.24
378	3-NH_2; 5-CH_3; 3′-OCH_3; 1′-$NHSO_2CH_3$	9.88[e]	9.15	0.73	−0.73	−0.24
381	3-N_3; 5-CH_3; 3′-OCH_3; 1′-$NHSO_2CH_3$	7.22	7.26	0.04	0.08	−0.24
387	3,5-$(CH_3)_2$; 3′-OCH_3; 1′-$NHSO_2CH_3$	7.67	8.01	0.34	−0.24	−0.24
383	3-NO_2; 5-OCH_3; 3′-OCH_3; 1′-$NHSO_2CH_3$	5.68	5.35	0.33	0.90	−0.24
391	3-Cl; 5-OCH_3; 3′-OCH_3; 1′-$NHSO_2CH_3$	6.79	6.63	0.16	0.35	−0.24
395	3-I; 5-OCH_3; 3′-OCH_3; 1′-$NHSO_2CH_3$	6.74	6.75	0.01	0.30	−0.24
396	3-I; 5-$OCH_2CHOHCH_2OH$; 3′-OCH_3; 1′-$NHSO_2CH_3$	6.70	6.79	0.09	0.28	−0.24
398	3,6-$(NO_2)_2$; 3′-OCH_3; 1′-$NHSO_2CH_3$	3.82	3.81	0.01	1.56	−0.24
399	3-NO_2; 6-CH_3; 3′-OCH_3; 1′-$NHSO_2CH_3$	6.03	6.03	0.00	0.61	−0.24
401	3,6-$(Cl)_2$; 3′-OCH_3; 1′-$NHSO_2CH_3$	6.18	6.37	0.19	0.46	−0.24
402	3,6-$(Br)_2$; 3′-OCH_3; 1′-$NHSO_2CH_3$	6.17	6.37	0.20	0.46	−0.24
404	4,5-$(CH_3)_2$; 3′-OCH_3; 1′-$NHSO_2CH_3$	6.91[e]	7.77	0.86	−0.14	−0.24
406	4,5-$(OCH_3)_2$; 3′-OCH_3; 1′-$NHSO_2CH_3$	6.90	6.89	0.01	0.24	−0.24

[a] pK_a values determined spectrophotometrically in 20% aqueous DMF as in ref 9; aqueous pK_a values average approximately 0.6 unit higher. [b] Sum of σ values for substituents on the acridine ring; σ_p for 1- and 3-substituents, σ_m for 2- and 4-substituents. [c] Sum of σ values for substituents on the aniline ring; σ_p^- values for 1′- and 2′-substituents, σ_m values ($\simeq\sigma^-_m$ values) for 2-substituents. [d] Calculated using eq 6. [e] Observed value not included in derivation of eq 6. [f] -CONH-Y; amide derived from α-methyl-D-glucosaminide; see ref 8.

values for all of the derivatives, particularly as the 193 examples for which such values have been determined cover a wide range of substituents attached at all carbon positions of the skeleton (i.e., Table II). A better approach was to see whether a reliable relationship could be established between pK_a values and substituent electronic parameters for these compounds. Such a relationship, if established, would be a guide to the types of electronic parameters important for modeling biological activity. It would also allow the determination of electronic parameter values for those substituents for which values are not currently available (e.g., the aza- and alkyltriazene groups) and confirm the suitability of the known values from the benzene system to be used in the anilinoacridine one.

Spectroscopic studies[40] have shown that in acid solution the first proton attaches to the heterocyclic nitrogen of acridines, even when two potentially ionizable centers are present, as in the case of 9-amino or 9-anilinoacridine.

Studies of a series of 9-[[ω-(diethylamino)alkyl]-amino]acridines[41] suggest, however, that the charge is delocalized as a resonance hybrid between the heterocyclic nitrogen and the 9-amino group. Acridines possessing a 9-amino group or a 9-alkylamino group are strong bases, due to the ready formation of a resonant imino cation. In contrast, 9-(dimethylamino)acridine, where effective conjugation of the nitrogen with the ring is sterically prevented, has a pK_a (7.35) more than two units lower than that of 9-(methylamino)acridine. 9-Anilinoacridine is a similarly weak base (pK_a = 7.46), but this is due to the electronic effect of the anilino ring rather than to steric

(40) Orgel, L. E. *Chem. Heterocycl. Compd.* **1956**, *9*, 289–306.

(41) Irvin, J. L.; Irvin, E. M. *J. Am. Chem. Soc.* **1950**, *72*, 2743.

inhibition of conjugation. We have previously shown that for a series of 1′-substituted 9-anilinoacridines there is a close correlation between σ_p values for the 1′-substituents and pK_a values for the acridine, suggesting excellent transmission of electronic effects between the rings. The pK_a values shown in eq 2 were measured in 20% aqueous

$$pK_a = -2.03\ (\pm 0.08)\ \sigma_p + 7.27 \quad (2)$$

$$n = 17;\ r = 0.984;\ s = 0.172$$

DMF and are not corrected for solvent; comparison of values for several compounds determined both in 20% DMF and water suggests an average solvent correction of +0.59 to give the aqueous pK_a.

It is clear from earlier compilations of pK_a values for derivatives of both acridine and 9-aminoacridine that these values are best modeled by using σ_p values for substituents in the 3 position and σ_m values for substituents in the 2 and 4 positions. Equations 3 and 4 can be derived for the

$$pK_a = -3.08\ (\pm 0.43)\ \sum\sigma + 5.19\ (\pm 0.26) \quad (3)$$

$$n = 24;\ r = 0.953;\ s = 0.497 \text{ (substituted acridines)}$$

$$pK_a = -2.65\ (\pm 0.31)\ \sum\sigma + 9.37\ (\pm 0.13) \quad (4)$$

$$n = 26;\ r = 0.963;\ s = 0.297 \text{ (substituted 9-aminoacridines)}$$

pK_a values of a number of substituted acridines and 9-aminoacridines recorded in ref 43. The fit to the data is remarkably good, considering that the bulk of the values were recorded in 50% aqueous EtOH and approximately corrected for solvent by the addition of 0.5 pK_a unit.

pK_a values for 1-substituted derivatives are not well predicted by these equations, for unclear reasons. Acridines with bulky 4-substituents (e.g., 4,5-dimethyl) also proved weaker bases than predicted, due to steric inhibition of proton approach. The different coefficients (ρ values) for the terms of eq 2 compared to eq 3 and 4 suggested that modeling of pK_a values for the 9-anilinoacridines would be best achieved by a two-variable relationship, permitting different ρ values to be computed for the effect of groups in the anilino and acridine rings; this proved to be so (see eq 6 vs eq 5). Residuals were com-

$$pK_a = -1.90\ (\pm 0.13)\ [\sum\sigma_{acridine} + \sum\sigma_{aniline}] + 7.02\ (\pm 0.05) \quad (5)$$

$$n = 176;\ r = 0.904;\ s = 0.315$$

$$pK_a = -2.33\ (\pm 0.14)\ \sum\sigma_{acridine} - 1.44\ (\pm 0.14)\ \sum\sigma_{aniline} + 7.10\ (\pm 0.04) \quad (6)$$

$$n = 176;\ r = 0.939;\ s = 0.259$$

puted using eq 6 and are listed in Table II. The fit is reasonable, considering that the σ parameters used are derived from the benzene system and that σ_p values rather than the difficultly obtainable σ_0 values have been used for the 3′-substituents; steric effects have thus not been allowed for.

Several features of this equation deserve comment. There are six examples of 1-substituted acridines in the data set, and all are very poorly fitted by use of σ_p values (they have been excluded from the calculation). The reason does not appear to be due to steric factors, for the deviations are not systematic, and a similar result was found in the acridine and 9-aminoacridine series. Those compounds with additional heteroatoms in the acridine ring (2-, 3-, and 4-aza derivatives) were not included in the calculation; instead, eq 6 was used to calculate σ values for these groups from the measured pK_as of the corresponding compounds. Thus, for the acridine system, $\sigma_{p(aza)} = 0.78$ and $\sigma_{m(aza)} = 0.55$; these values have been used in the QSAR developments. All compounds with substituents in the 3 position had pK_a values closely modeled by the equation, except for the 3-NH_2 derivatives. These were much more basic than predicted, a phenomenon also true for the acridine and 9-aminoacridine data sets;[43] this is presumably due to the ready formation of a resonant cation stabilizing the charge. In general, 4-substituted compounds were slightly less well fit, due to varying degrees of steric hindrance to protonation of the nitrogen; this was especially noticeable for bulky groups such as 4,5-dimethyl.

Since previous studies had suggested that pK_a values for acridine-substituted *m*-AMSA compounds were an important determinant of activity, possibly because they serve as a measure of drug stability, σ values for acridine ring substituents were determined exactly as for the pK_a calculations, using σ_p values for 1- and 3-groups and σ_m values for 2- and 4-groups. For anilino substituents, sum of σ was similarly calculated using σ_p for 1′- and 3′-groups and using σ_m for 2′ groups. However, the electronic effect of groups in the anilino ring on activity has been less well determined; studies have shown[25] that electron-donating groups in this ring actually decrease drug stability to thiol attack. Thus, a number of other electronic parameters for the anilino groups were considered. In particular, in view of the through resonance possible for 1′- and 3′-groups and the 9-amino group, electronic effects for the anilino substituents were also considered as the sum of σ^- for the 1′- and 3′-groups, together with σ_m values for the 2′-groups ($\sigma_m^- \simeq \sigma_m$).[37]

Values for σ and σ^- were in all cases taken from recent compilations.[37,38] For some substituents, σ^- values have not been derived and have had to be estimated from analogous substituents. σ^- for $-(CH_2)_nCOOH$, where n = 3 or more, is taken to be the same as that for CH_3; σ^- for $O(CH_2)_3COOH$, $OCH(Et)COOH$, OCH_2CH_2OH, and $OCH_2CHOHCH_2OH$ is assumed to be the same as σ^- for OCH_3; σ_m for $CON(CH_3)_2$, $CONHCH_2CHOHCH_2OH$, and $CONHCH_2CONH_2$ is given the same value as that for $CONHCH_3$; σ^- for $CH_2CH_2CONH_2$ is given the same value as σ^- for $-CH_2CH_2COOH$. For the substituents, NHCOR, $NHSO_2R$, $N(SO_2CH_3)CO(CH_2)_nCH_3$, $NHSO_2(CH_2)_nNH_2$, $NHNHCO_2Et$, and $NHCO_2CH_2CHOHCH_2OH$, σ^- is taken to be zero. σ^- is estimated to be 0.28 for $-CH_2SO_2NH_2$ −0.07 for $-CH_2CH_2SO_2NH_2$, and 0.62 for $-CH{=}CHCONH_2$. For $NHCONHCH_3$, σ^- is assumed to be the same as that for $-NHCONH_2$.

Results and Discussion

Biological and physicochemical parameters for a total of 776 9-anilinoacridines are recorded in Table I. The compounds are listed in order of structure in three convenient groups. The first group (compounds **1–541**) are those proving tumor-active, with the exception of a few inactive but toxic congeners (**25**, **61**, **170**, and **277**) which are members of homologous series and thus conveniently placed. Compounds **542–691** proved inactive, but toxic levels could be reached and approximate LD_{10} values recorded. Compounds **692–776** were inactive and nontoxic at dose levels up to the practical limit of 500 (mg/kg)/day.

(42) Albert, A.; Goldacre, R. *J. Chem. Soc.* **1946**, 706.
(43) Gagan, J. M. F. *Chem. Heterocycl. Compd.* **1973**, *9*, 197.

Biological data (LD_{10}, ILS_{max}, D_{50}) were determined in mice bearing ip implanted L1210 leukemia[3,4] and were processed as described under Biological Parameters and in ref 12. For those compounds proving to be tumor inactive but toxic, the numbers recorded under "log $(1/D_{50})$ obsd" in Table I are log $(1/LD_{10})$ values; such compounds are presumed inactive because toxicity intervenes before a dose sufficient for activity can be reached. For the inactive and nontoxic compounds (**692–776**), the value 3.0 is recorded under "log $(1/D_{50})$ obsd" and "log (LD_{10}) obsd"; this is a convenient representation of the top dose tested [usually 500 (mg/kg)/day] in mole per kilogram terms.

For the total data base of 534 tumor-active compounds, the cross correlation matrix of biological parameters was determined, and this is included as Table III. As expected, the results are similar to those obtained for all other groups of antitumor agents examined.[13,21,22] Drug potency and acute toxicity are highly correlated, while tumor cell selectivity (log ILS_{max}) is essentially independent of toxicity. The four parameters examined fall clearly into two groups: tumor potency and acute toxicity on the one hand and tumor cell selectivity and chemotherapeutic index [log (LD_{10}/D_{50})] on the other.

Modeling of Measures of Drug Potency and Toxicity. Equation 7 was derived as a description of the

$$\log (1/D_{10}) = -0.14\ (\pm 0.03)\ \Sigma\pi - 0.01\ (\pm 0.006)\ \Sigma\pi^2 \text{ (hydrophobic terms)} -1.08\ (\pm 0.09)\ \Sigma\sigma - 1.25\ (\pm 0.37)\ R_{BS} \text{ (electronic terms)} -0.32\ (\pm 0.16)\ MR_2 + 1.04\ (\pm 0.13)\ MR_3 - 0.25\ (\pm 0.05)\ MR_3^2 - 0.77\ (\pm 0.13)\ I_{3,6} - 1.68\ (\pm 0.21)\ E_{s(3')} - 1.60\ (\pm 0.22)\ E_{s(3')}^2 \text{ (steric terms)} +0.78\ (\pm 0.13)\ I_{NO_2} + 0.70\ (\pm 0.32)\ I_{DAT} + 0.50\ (\pm 0.18)\ I_{BS} + 3.73\ (\pm 0.07) \text{ (indicator terms)} \quad (7)$$

$n = 509$; $r = 0.878$; $s = 0.323$; ideal $\Sigma\pi$ = −6.04 (−12.0 to 4.22); ideal MR_3 = 2.09 (1.89 to 2.38); ideal $E_{s(3')}$ = −0.53 (−0.56 to −0.50)

antileukemic potency of 509 of the total of 534 tumor-active 9-anilinoacridines in the data base. It is a 13-variable expression with an average of 39 data points per variable. The range of values in the dependent variable is 3300-fold for the included compounds. The stepwise development of the equation is given in Table XI, showing the entry of the variables in decreasing order of significance. While a usual parabolic relationship in drug hydrophobicity ($\Sigma\pi$) could be fitted to the biological data, a better fit resulted from the use of a bilinear expression (eq 8). The bilinear model of quantitative activity/hydrophobicity relationships was derived from the theory of

$$\log (1/D_{50}) = +0.63\ (\pm 0.27)\ \Sigma\pi - 0.75\ (\pm 0.23)\ \log(\beta \cdot 10^{\Sigma\pi} + 1) \text{ (hydrophobic terms)} -1.01\ (\pm 0.09)\ \Sigma\sigma - 1.21\ (\pm 0.36)\ R_{BS} \text{ (electronic terms)} -0.26\ (\pm 0.16)\ MR_2 + 4.95\ (\pm 0.75)\ MR_3 - 5.13\ (\pm 0.86)\ \log(\beta \cdot 10^{MR_3} + 1) - 0.67\ (\pm 0.12)\ I_{3,6} - 1.67\ (\pm 0.20)\ E_{s(3')} - 1.57\ (\pm 0.21)\ E_{s(3')}^2 \text{ (steric terms)} +0.58\ (\pm 0.13)\ I_{NO_2} + 0.87\ (\pm 0.31)\ I_{DAT} + 0.52\ (\pm 0.17)\ I_{BS} + 9.24\ (\pm 1.33) \text{ (indicator terms)} \quad (8)$$

$n = 509$; $r = 0.893$; $s = 0.305$; ideal $\Sigma\pi$ = −4.93 (log β = 5.64); ideal MR_3 = 1.44 (log β = 0.01); ideal $E_{s(3')}$ = −0.53 (−0.56 to −0.50)

Table III. Correlation Matrix for Biological Parameters

	log $(1/LD_{10})$	log (ILS_{max})	log (CI)
log $(1/D_{50})$	0.836	0.356	0.500
log $(1/LD_{10})$		0.056	−0.063
log (ILS_{max})			0.557

countercurrent distribution.[44] It is a theoretically derived model, but more general than other theoretically derived equilibrium[45,46] or probability[47] models. For a large number of data sets which exhibit nonlinear activity/hydrophobicity relationships, the bilinear model often gives a better fit to the experimental data than the parabolic model.[48] Equation 8 was used to calculate the residuals of Table I. The parameters in this equation can be conveniently grouped into four different classes as shown, and these will be discussed separately. The meaning of the equation as a whole will then be considered.

(1) Lipophilicity Parameters. $\Sigma\pi$ is the sum of the π values for all the side chains and is used as a measure of drug hydrophobicity with the implicit assumption that the hydrophobicity of the 9-anilinoacridine framework is always the same; i.e., that the acridine nitrogen is always charged and varying degrees of ionization for compounds of different pK_a can be ignored. We have previously shown for a subset of *m*-AMSA derivatives that this is justified.[13] The few derivatives with carboxylic acid side chains were treated as if COOH groups were in the neutral form for the calculation of π values; such a treatment has often been found appropriate in QSAR studies.[49] There were a larger number of compounds with side chains bearing ionizable nitrogen functions, expected to be fully charged at physiological pH; these were assigned π values, including a term for the nitrogen charge. Alternative calculations were performed where this group of compounds was assigned estimated π values for the uncharged side chains, and an indicator variable for the presence of a potentially charged side chain was included. There is some merit in such an approach, for compounds bearing a second positive charge in the side chain are known to bind more strongly to DNA,[36] and the indicator variable could be said to incorporate such a property. However, it is unreasonable to assume that functions such as alkylguanidines possess any significant percent of uncharged species at physiological pH. The alternative calculations led to significantly poorer fit of the data and were not further considered.

In the present case, the $\Sigma\pi$ coefficients in eq 8 show that activity falls off more rapidly for compounds on the hydrophilic side of the optimum (the coefficient of the $\Sigma\pi$ term is one slope of the activity/$\Sigma\pi$ relationship, while the sum of the coefficients of the $\Sigma\pi$ and bilinear $\Sigma\pi$ terms provides the other slope; 0.63 − 0.75 = −0.12). It may be that in addition to the purely physical phenomena controlling partitioning, the more hydrophilic molecules may be more exposed to plasma thiols; certainly they generally contain relatively reactive functional groups susceptible to biological detoxification mechanisms.

Optimum hydrophobicity occurs at a $\Sigma\pi$ of about −4.9. Since the log *P* of the parent (neutral) 9-anilinoacridine

(44) Kubinyi, H. *Arzneim.-Forsch.* **1976**, *26*, 1991.
(45) Hyde, R. M. *Chem. Ind. (London)* **1977**, 859.
(46) Hyde, R.; Lord, E. *Eur. J. Med. Chem.* **1979**, *14*, 199.
(47) McFarland, J. W. *J. Med. Chem.* **1970**, *13*, 1192.
(48) Kubinyi, H. *J. Med. Chem.* **1977**, *20*, 625.
(49) Panthananickal, A.; Hansch, C.; Leo, A.; Quinn, F. R. *J. Med. Chem.* **1978**, *21*, 16.

can be estimated at 4.8 by fragment constant summation using published[37] values for 9-aminoacridine, log P_0 for the neutral molecule in the series is slightly negative. Alternatively, the measured log P value for *m*-AMSA (compound **162**) at physiological pH (7.41) was determined to be 2.59 (3.07 corrected for ionization). This gives a value for the parent 9-anilinoacridine under similar conditions of about 4.27 (without allowing for the uncoupling effects of the 3-OCH_3 group, which are difficult to estimate but liable to be small). This in turn gives a log P_0 for the series of −0.6. In both cases the values agree quite well with other studies,[49,50] which suggest a negative log P_0 for best activity against the leukemias. However, for the present series of compounds the terms in $\sum\pi$ in eq 8 are not the most significant ones. Drug hydrophobicity is one of the less important determinants of activity, and the data base contains active compounds whose hydrophobicities vary over a wide range. The relatively low significance of the $\sum\pi$ terms in eq 8 could be considered due in part to the fact they were calculated values, rather than experimentally determined ones. However, experimentally measured R_m values were available for a large number of the 9-anilinoacridines.[7-15] Preliminary calculations were performed on 247 derivatives using both calculated $\sum\pi$ and measured R_m values as measures of hydrophobicity, and virtually identical equations emerged. Thus, the use of calculated $\sum\pi$ values seems justified.

(2) Electronic Parameters. The most significant single term in eq 8 is that ($\sum\sigma$) describing the electronic properties of the substituent groups. A number of different combinations of σ terms were examined. The best fit to the data was provided by using the sum of σ values for the acridine substituents, determined in the same way as for the modeling of pK_a values (i.e., σ_p for the 1- and 3-groups, σ_m for the 2- and 4-groups), and for the sum of electronic parameters for the anilino groups using σ^- values (σ_p^- for 1′- and 3′-, $\sigma_m^- = \sigma_m$ for 3′-groups). This produced the two electronic terms −1.09 (±0.09) $\sum\sigma$ (acridine) − 0.95 (±0.14) $\sum\sigma$ (aniline). Within the accuracy of the equation, these two terms had identical coefficients and thus were combined to provide the single $\sum\sigma$ term in eq 8. The negative coefficient associated with the $\sum\sigma$ (acridine) term indicates that electron-donating substituents in the acridine ring enhance activity. The fact that electron-donating substituents in the acridine ring are known[26] to stabilize 9-anilinoacridine derivatives to thiol attack, the main route of drug breakdown in vivo,[25] provides one possible explanation for the large negative coefficient of the $\sum\sigma$ (acridine) term.

A similarly large negative coefficient for the sum of the σ^- parameters for substituents on the anilino ring indicates that electron-donating substituents here also provide more dose-potent derivatives. The rationale for this is not so clear. Electron-donating groups here are known to *increase* the rate of thiol attack[26] but at the same time contribute to tighter DNA binding.[14] It is not possible to confidently attribute this relationship to any one cause; a combination of effects may produce the observed dependence.

(3) Steric Parameters. When one considers the number of steric terms found significant in eq 8, it becomes apparent why the development of QSAR for the 9-anilinoacridines has proved so difficult. To quantify steric effects, the experimentally determined Taft E_s parameter is to be preferred, but in the present data set there are many substituents for which E_s values are not available. MR values have been used to parameterize steric effects for groups on the acridine ring, where a large number of different types of substituents have been used (MR values have been scaled by 0.1 to provide terms of a similar magnitude to others in the regressions). The interpretation of this term is somewhat ambivalent, but a positive coefficient with MR is usually taken to indicate a role for the binding of the substituent via dispersion forces and/or the production of a favorable conformational change in the receptor induced by the bulk of the substituent. In the present case we consider MR primarily as a measure of the steric properties of groups on the acridine ring and the associated coefficients in eq 8 as a measure of how these steric properties affect binding of the compounds to the critical bioreceptor.

While no coefficient could be computed for MR_1 because none of the nine 1-substituted compounds proved tumor active, it is apparent from the predicted activities of these compounds in Table I that groups in the 1 position have a deleterious effect on activity. It will be seen later that the equation describing the toxicity of these compounds does contain a term in MR_1. All 2-substituents proved dystherapeutic, and the negative coefficient of the MR_2 term suggests that there is also no bulk tolerance about the 2 position. In contrast, small substituents in the 3 position sharply enhance antitumor activity (as seen by the relatively large positive coefficients for the MR_3 term in both eq 7 and 8) up to a maximum size, where activity begins to decline. Again, while the data can be fitted to a parabolic relationship in MR_3 (eq 7), a significant improvement resulted from the use of a bilinear form (eq 8). The coefficient of the bilinear term in MR_3 in eq 8 (−5.13) shows that after the optimum size is reached, larger 3-substituents decrease activity only slowly; the negative slope of the MR_3 relationship is only 4.95 − 5.13 = −0.18. The MR_3 parameter is calculated for groups on both the 3 and equivalent 6 positions; in the vast majority of cases, only one of the positions is substituted. However, there are a small group of active compounds (25 examples) possessing both 3- and 6-substituents and which are considerably depressed in activity over that calculated by use of the bilinear MR_3 term. The indicator variable $I_{3,6}$ (= 1 for 3,6-disubstitution, and 0 otherwise) has a large negative coefficient, indicating that this particular type of substitution pattern is dystherapeutic.

There appears to be no steric hindrance for groups in the 4 position of the acridine; compounds bearing groups as large as phenyl and glucosaminide in this position are well predicted by eq 8.

Derivatives of 9-anilinoacridine (e.g., *m*-AMSA) are known[36,51] to bind tightly to double-stranded DNA by intercalation of the chromophore between the base pairs. The exact mode of binding has been suggested to be with the 9-anilino group lying in the minor groove and the 4 and 5 positions of the acridine toward the major groove, similar to the pseudosymmetrical orientation found by X-ray crystallography for 9-aminoacridine bound to the dinucleotide iodo-CpG.[52] The pattern of steric hindrance relating to in vivo antitumor activity found above for groups on the acridine ring of the 9-anilinoacridines suggests that this mode of binding is the important one for biological activity. X-ray crystallographic studies of AMSA

(50) Panthananickal, A.; Hansch, C.; Leo, A. *J. Med. Chem.* **1979**, *22*, 1267.

(51) Waring, M. J. *Eur. J. Cancer* **1976**, *12*, 995.

(52) Sakore, T. D.; Reddy, B. S.; Sobell, H. M. *J. Mol. Biol.* **1979**, *135*, 763.

(53) Holl, D.; Swann, D. A.; Waters, T. N. *J. Chem. Soc., Perkin Trans. 2*, **1974**, 1334.

show that the ring plane of the aniline is at a considerable angle to that of the acridine,[53] making the complete passage of the drug molecule between the base pairs difficult, and orienting the acridine ring in such a way that the 1 and 2 positions are within 1 Å of the sugar–phosphate chains, with a consequent lack of bulk tolerance for these positions. In such a binding mode there is limited bulk tolerance about the 3 and 6 positions, with small hydrophobic groups expected to enhance binding by extending the area of drug–receptor binding. However, the site is not so large that it can accommodate substituents on both the 3 and 6 positions at once. The 4 and 5 positions of the acridine ring would not be expected to exhibit steric restraints, since groups appended here would project out into the major groove.

In the derivation of eq 8 , no evidence was found for steric hindrance at the 1′ position of the anilino ring; this is in agreement with the supposed environment of this moiety in the minor groove. However, a significant parabolic relationship exists between activity and the size (E_s) of groups in the 3′ position. With only a limited number of different 3′-groups in the data set, it was possible to use E_s values for these substituents, but on the other hand, the small range of substituents limits the applicability of the finding. In fact, a number of other descriptors, such as $\mathcal{F}$ and $\mathcal{R}$ values for the 3′-substituents, were examined in the study, but none achieved the required level of significance. The negative coefficient with the first-order term in E_s indicates that substituents increase antitumor potency up to the point where the E_s^2 term begins to dominate, the ideal substituent being one with an E_s value of −0.53. The meaning of this parameter is not completely clear. It has been shown[26] that substituents at the 3′ position markedly stabilize compounds to thiolytic cleavage of the side chain, presumably by steric hindrance to formation of the transition state. However, a 3′-CH_3 group, which contributes a considerable loss of drug potency, provides very thiol-stable derivatives. It may be that groups much larger than OCH_3 cause severe distortion of the usual geometry of the 9-anilinoacridines, hindering intercalative binding.

(4) Indicator Variables. Also in eq 8 are four discontinuous indicator variables, parameterizing particular groups of compounds which otherwise are poorly predicted by a more or less constant amount. The large positive coefficient for the I_{NO_2} term (I_{NO_2} = 1 for compounds with a 3-NO_2 group) recognizes the established fact that 3-NO_2 derivatives of 9-anilinoacridine show anomalous levels of biological activity, being much more potent (and toxic) than expected.[13,54] It is known[13] that 3-NO_2-*m*-AMSA (**250**) does undergo in vivo reduction to give, in mice, a complex mixture of products. An analogous process has also been shown to occur for the 1-nitroacridine derivative Ledacrin, which undergoes reduction of the 1-NO_2 group in vivo to give a complex mixture of products, including *N*-arylhydroxylamines.[55] Although such reduction is not a prerequisite for antitumor activity, since the isoelectronic 3-aza-*m*-AMSA (**226**) is also active, the anomalously high potency of the 3-NO_2 derivatives is almost certainly due to some degree of in vivo reduction of the nitro group to provide more polar and more strongly basic metabolites.

The positive coefficient for the term I_{DAT} (= 1 for compounds with a 3,3-dialkyltriazene, otherwise = 0), even though only five compounds are involved (**184–186, 230,** and **231**), indicated the strong therapeutic advantage conferred by this alkylating moiety. These compounds were originally made,[7] together with the 3-azido derivatives (**183** and **229**), as potential latentiated forms of the very potent but poorly distributing 3-NH_2 derivative. However, the 3-azido compounds are well predicted by the equation without the need of an additional term; presumably it is the ability of the dialkyltriazene groups to provide alkylating species that is the reason for the almost tenfold increase in antitumor potency of these compounds.

The enhanced potency of a number of benzenesulfonamide derivatives required the use of two further parameters in eq 8. The presence of an unsubstituted benzene ring off the 1′-sulfonamide group in a number of derivatives (**472–495**) provided a useful increment in potency, parameterized by the indicator variable I_{BS} (= 1 for compounds possessing a 1′-$NHSO_2C_6H_5$ group). The high potency of these compounds is unexpected. It might be thought due to increased DNA binding expected for compounds bearing another phenyl ring, but the approximate association constants for binding to poly[d(AT)] for compounds **472** (1′-$NHSO_2C_6H_5$, log K_d = 6.20) and **478** (1′-$NHSO_2C_6H_4$-*p*-NH_2, log K_d = 6.28) are essentially identical with the binding of AMSA itself (compound **148**, 1′-$NHSO_2CH_3$, log K_d = 6.28).[14] Furthermore, other derivatives bearing a benzene ring off the 1′ position but via different link groups (e.g., –NHCO– and –NHCONH–) are well predicted by the equation without the use of the I_{BS} parameter. It should be noted that while the ethidium bromide displacement method of calculating approximate drug–DNA association constants is rapid, convenient, and invaluable for the comparison of the binding strengths of a series of closely related compounds,[14] the contributions made to the overall association constant by different possible modes of binding cannot be distinguished.

It is possible that the particular geometry of the sulfonamide linkage, as in benzenesulfonanilide,[56] prevents the extra aromatic ring from making further binding contact with the DNA, instead protruding out of the minor groove. In such a position, a variety of different types of interaction, such as charge-transfer and ion-dipole, are possible with a second macromolecule; these interactions may be important for bioactivity.[57] It is clear from the experimental data that the electronic nature of the groups on the benzenesulfonamide ring has a further sizeable effect on activity. Although the range of substituents in this position is not as wide as desirable, it is still sufficient to explore the utility of several different types of electronic parameters. The one clearly fitting best is R, which describes purely the resonance effects of substituent groups, separate from their field and inductive effects.[37] Substituents possessing large resonance effects, such as $-NH_2$, provide a group of derivatives among the most potent of the several hundred tested for in vivo activity against L1210 leukemia, as demonstrated by the magnitude of the coefficient for R_{BS} in eq 8.

Equation 8 thus provides a detailed picture of the features necessary for antitumor activity in the 9-anilinoacridines; together, these features account for over 80% of the variance in the biological data for 509 of the 534 active compounds. Most of the 25 compounds not well predicted by eq 8 (and not used in its derivation) fall into one of four different categories: (1) compounds which

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(55) Pawlak, J. W.; Konopa, J. *Biochem. Pharmacol.* **1979**, *28*, 3391.
(56) Rerat, C. *Acta Crystallogr.* **1967**, *23*, 856; Rerat, B. *Acta Crystallogr., Sect. B* **1969**, *25*, 1392.
(57) Robertson, I. G. C.; Denny, W. A.; Baguley, B. C. *Eur. J. Cancer*, in press.
(58) Ferguson, L. R.; Denny, W. A. *J. Med. Chem.* **1979**, *22*, 251.

Table IV. ω-(4-Nitrophenyl)alkylamine Benzenesulfonate Salts

compd	mp, °C	formula[a]	yield, %
2-(4-nitrophenyl)-ethanamine	225-227	$C_{15}H_{18}N_2O_5S$[b]	85
3-(4-nitrophenyl)-propanamine	218-220	$C_{15}H_{20}N_2O_5S$	87
4-(4-nitrophenyl)-butanamine	174-178	$C_{16}H_{20}N_2O_5S$	93
5-(4-nitrophenyl)-pentanamine	186-187	$C_{17}H_{22}N_2O_5S$	94
6-(4-nitrophenyl)-hexanamine	156-160	$C_{18}H_{24}N_2O_5S$	97

[a] All compounds analyzed satisfactorily for C, H, and N. [b] Tosylate salt.

Table V. *N*-[ω-(4-Nitrophenyl)alkyl]phthalimides

compd	mp, °C	formula[a]	yield, %
N-[4-(4-nitrophenyl)-butyl]phthalimide	136-138	$C_{18}H_{16}N_2O_4$	77
N-[5-(4-nitrophenyl)-pentyl]phthalimide	88-89	$C_{19}H_{18}N_2O_4$	81
N-[6-(4-nitrophenyl)-hexyl]phthalimide	134-135	$C_{10}H_{10}N_2O_4$	85

[a] All compounds analyzed satisfactorily for C, H, and N.

Table VI. *N*-[ω-(4-Aminophenyl)alkyl]phthalimides

compd	mp, °C	formula[a]	yield, %
N-[3-(4-aminophenyl)-propyl]phthalimide	117-118	$C_{17}H_{16}N_2O_2$	65
N-[4-(4-aminophenyl)-butyl]phthalimide	125-126	$C_{18}H_{18}N_2O_2$	73
N-[5-(4-aminophenyl)-pentyl]phthalimide	87-88	$C_{19}H_{20}N_2O_2$	74
N-[6-(4-aminophenyl)-hexyl]phthalimide	99-100	$C_{20}H_{22}N_2O_2$	71

[a] All compounds analyzed satisfactorily for C, H, and N.

proved very insoluble at the doses predicted to be needed for activity and which are less active than expected, possibly due to a lack of bioavailability (e.g., **67**, **218**, **252**, **253**, **338**, **419**); (2) compounds possessing ionizable groups conjugated with the aromatic skeleton, whose electronic effects are liable to be poorly parameterized by the usual σ terms (e.g., **132** and **228**); (3) compounds with depressed activity possessing moieties prone to biotransformation (e.g., the amino acid groups of **124** and 125); (4) a number of 3-substituted and 3,6-disubstituted compounds still not well parameterized by the steric terms MR_3 and $I_{3,6}$ (e.g., **258**, **259**, **358**, **359**, **461**, and **465**). While very bulky groups in the 3 position are compatible with activity (e.g., compounds **245**, and **246**), MR is not the best available measure of such bulk. The 3-groups on the latter compounds are capable of lying essentially in the plane of the acridine ring, whereas those such as *i*-Pr and *t*-Bu, with out-of-plane steric bulk close to the ring, provide weakly active agents (**259** and **652**; compound **652** has an ILS_{max} of 27%).

There remain nine compounds (less than 2% of the data base) whose activities are poorly predicted by eq 8, although it is to be realized their omission from the calculation is a rather arbitrary decision in some cases. (In fact, inclusion of all of the tumor-active compounds in the calculation did not alter the form of the equation but slightly lowered its overall significance; see eq 9.) Compounds **3**, **437**, **456**, **459**, and **538** have activities considerably depressed over those expected; these compounds possess a variety of side chains that are also present in other, well-predicted agents. Of the derivatives proving more active than predicted, **511** and **512** belong to the class of "latentiated" compounds (see below). In all of these series there is a tendency for the higher members to be more active than predicted, possibly due to varying rates of liberation of the core molecule. The potency of compound **342** is close to that predicted (and observed) for the more potent 3-NH_2 analogue (**339**), suggesting that some hydrolysis of the $-NHCOCH_3$ group may have occurred during preparation. The large increment in potency of **319** over that expected (and over that observed for compounds of very similar structure such as **318** and **320**) may constitute a useful lead for future work.

It should be noted that 41 of the compounds in eq 8 contain the 1′-N(CO-alkyl)SO_2CH_3 group. These analogues were made[7] to act as prodrugs, undergoing ready deacylation in vivo to liberate the core molecule. It was found that for several different homologous series of acyl groups, the lower homologues provided enhanced activity, measured as ILS_{max}, over that achieved by the unacylated core molecule.[7] Since such compounds are known to be unstable in vivo, their inclusion in eq 8 can be questioned. The fact is that although significant variations in ILS_{max} within series is seen,[7] the potency of these compounds is fairly well predicted by eq 8 and they have been included in its derivation (their omission does not alter the quality of the equation or the conclusions to be drawn from it). It may well be that in vivo both the latentiated form and the core agent, in varying amounts, are contributing to the observed activity. The reason why eq 8 predicts these compounds well is that the added acyl group has been placed in a position of proven bulk tolerance and does not markedly alter the electronic properties of the molecule; the only effect is on $\sum\pi$, upon which activity is not very highly dependent.

Inclusion of all the 534 tumor-active compounds in the data base provided eq 9, of slightly poorer overall fit than eq 7, fit in which all of the individual terms retained significance at the 5% level.

$$\log (1/D_{50}) = -0.13\ (\pm 0.03) \sum\pi - 0.09\ (\pm 0.08) \sum\pi^2 - 1.01\ (\pm 0.12) \sum\sigma - 0.28\ (\pm 0.21)\ MR_2 + 0.96\ (\pm 0.18)\ MR_3 - 0.24\ (\pm 0.07)\ MR_3^2 - 0.59\ (\pm 0.17)\ I_{3,6} - 1.42\ (\pm 0.27)\ E_{s(3')} - 1.38\ (\pm 0.29)\ E_{s(3')}^2 + 0.68\ (\pm 0.16)\ I_{NO_2} + 0.81\ (\pm 0.42)\ I_{DAT} + 0.51\ (\pm 0.24)\ I_{BS} - 1.24\ (\pm 0.50)\ R_{BS} + 3.76\ (\pm 0.10) \quad (9)$$

$n = 534$; $r = 0.791$; $s = 0.428$; ideal $\sum\pi$ = −7.68 (−69.9 to −4.50); ideal MR_3 = 2.03 (1.78 to 2.46); ideal $E_{s(3')}$ = −0.51 (−0.56 to −0.47)

There exist an additional 157 compounds (**25**, **61**, **277**, **502**, **503**, and **542–691**) that are tumor-inactive but for which toxic dose levels [below 500 (mg/kg)/day] were reached in testing. If we presume that this group of compounds acts in a similar way in the test system, the reason for their inactivity must be that toxic levels are reached before therapeutic ones. Thus, a crucial test of eq 8 is whether it correctly predicts D_{50} values for these compounds that are higher than the observed LD_{10} values.

Before looking at this in detail, however, it is instructive to attempt the derivation of an equation modeling acute drug toxicity (log LD_{10}). If the inactive but toxic compounds do act in a similar way to the active ones, then all of the compounds for which toxicity data are available (**1–691**) must be considered as a data set for modeling toxicity. Two points need to be noted. First, toxicity data are generally even more difficult to determine accurately.

While it can be assumed that all members of a class act in some broadly similar way to express some specific therapeutic activity, observed levels of toxicity may depend on several competing modes of drug breakdown. Even when one is likely to be dominant, such as thiolytic cleavage of the side chain for the 9-anilinoacridines, the presence of certain drug substituents may activate alternative pathways. At a practical level, higher doses need to be employed than for determinations of activity parameters such as D_{50}, and drug insolubility is more of a problem; the toxicity of a drug can be markedly altered just by a change of counterion, which alters solubility. Furthermore, there is little incentive to offset these problems by more careful and extended testing, for the inactive compounds are perforce of limited interest. The "noise" in toxicity data militates against their use to draw very detailed pictures from the results of regression analyses. The second point is that for antitumor compounds in general and for the present data set in particular (Table III), drug potency and acute toxicity for tumor-active compounds are highly correlated. Thus, modeling of drug toxicity data might be expected to lead to an equation similar to eq 8 but of lower accuracy. Such is indeed the case. Equation 10 can be derived for the tox-

$$\log (1/LD_{10}) = -0.07\ (\pm 0.02)\ \sum\pi \text{ (hydrophobic term)}$$
$$-0.76\ (\pm 0.09)\ \sum\sigma - 1.13\ (\pm 0.33)\ R_{BS} \text{ (electronic terms)}$$
$$-0.56(\pm 0.48)\ MR_1 - 0.24\ (\pm 0.13)\ MR_2 - 0.59\ (\pm 0.12)$$
$$MR_3 - 0.12\ (\pm 0.04)\ MR_3^2 - 0.89\ (\pm 0.16)\ E_{s(3')} - 0.61$$
$$(\pm 0.11)\ E_{s(3')}^2 - 0.51\ (\pm 0.14)\ I_{3,6} \text{ (steric terms)}$$
$$+0.43\ (\pm 0.12)\ I_{NO_2} + 0.50\ (\pm 0.13)\ I_{NH_2} +$$
$$3.57\ (\pm 0.12) \text{ (indicator terms)} \quad (10)$$

$n = 643$; $r = 0.771$; $s = 0.362$; ideal $MR_3 = 2.51$ (2.12 to 3.30); ideal $E_{s(3')} = -0.73$ (−0.80 to −0.67)

icity (log LD_{10}) for 643 of the examples in Table I for which such data were available, a data set containing both tumor-active and inactive examples. The toxicity data cover a range of nearly 700-fold. Equation 10 is of lower significance than eq 8 but of a similar general form. One omission is the lack of a term in $\sum\pi^2$, either in a parabolic or bilinear form. Although the implication is thus that even more polar compounds than those tested would be more toxic, with no minimum in sight, it should be remembered that the $\sum\pi$ terms in eq 8 were among the less significant in that equation. The lower accuracy of the toxicity data may be the reason for the lack of significance of a parabolic term in eq 10, rather than a lack of sufficiently polar compounds in the data set. Clearly, though, there will be little of value to be gained by pursuing 9-anilinoacridine derivatives much more polar than the optimum value found in eq 8. The coefficient of the $\sum\sigma$ parameter is similar to that in eq 8 and is again the single most significant term. Again, a variety of electronic parameters were tested, with this being the most effective. All of the steric parameters found in eq 8 occur again and with broadly similar coefficients; however, there is an additional term in MR_1 with a coefficient twice as large as that for MR_2. The significance of this term is not high, for there were only six examples of 1-substituted derivatives. Also, there is some doubt about how to deal with the electronic contribution of such substituents; σ_p has been used, but it can be noted from the residuals of eq 6 that this proved inadequate for modeling of the pK_a values of such compounds. It seems clear, though, that 1-substituents are very dystherapeutic; inclusion of a similar coefficient for MR_1 in eq 8 would allow the successful prediction of the inactivity of all the 1-substituted 9-anilinoacridines.

Table VII. *N*-[ω-[4-[(4-Nitrophenyl)carbamido]phenyl]-alkyl]phthalimides

alkyl	mp, °C	formula[a]	yield, %
methyl	247-251	$C_{22}H_{16}N_4O_5$	85
ethyl	287-288	$C_{23}H_{18}N_4O_5$	87
propyl	228-229	$C_{24}H_{20}N_4O_5$	84
butyl	242-243	$C_{25}H_{22}N_4O_5$	93
pentyl	218-219	$C_{26}H_{24}N_4O_5$	94
hexyl	226-227	$C_{27}H_{26}N_4O_5$	94

[a] All compounds analyzed satisfactorily for C, H, and N.

Table VIII. ω-[4-[(4-Nitrophenyl)carbamido]-phenyl]alkylamines

alkyl	mp, °C	formula[a]	yield, %
methyl	187-188	$C_{14}H_{14}N_4O_3$	71
ethyl	161-162	$C_{15}H_{16}N_4O_3$	74
propyl	166-167	$C_{16}H_{18}N_4O_3$	79
butyl	146-147	$C_{17}H_{20}N_4O_3$	73
pentyl	162-163	$C_{18}H_{22}N_4O_3$	82
hexyl	148-149	$C_{19}H_{24}N_4O_3 \cdot 0.5H_2O$	81

[a] All compounds analyzed satisfactorily for C, H, and N.

No significant coefficients were seen for the indicator variables I_{DAT} and I_{BS} used in eq 8; the compounds parameterized by these variables had toxicities well predicted by eq 10. The only new indicator variable found useful for the modeling of toxicity data was I_{NH_2} (= 1 for compounds with a 3-NH_2 group on an unquaternized acridine, otherwise = 0). No clear reason can be seen as to why this feature should contribute so heavily to toxicity, but the implication for drug design is clear, since inclusion of this parameter in eq 8 modeling activity gave a coefficient of no statistical significance.

Again, the latentiated compounds bearing 1′-N(CO-alkyl)SO_2CH_3 groups were well accommodated by the equation. Of the 48 compounds not included in the derivation of eq 11, 14 were also outliers in the derivation of eq 8 (compounds **3**, **124**, **125**, **132**, **228**, **254**, **258**, **338**, **358**, **419**, **437**, **456**, and **538**). A further group of 25 of the tumor-active 9-anilinoacridines with activities well predicted by eq 8 had poorly predicted toxicities. Of the 11 derivatives that proved more toxic than expected (**174**, **180**, **197**, **198**, **247**, **335**, **406**, and **531–534**), seven contained the 3-NO_2 moiety. Although there are a number of other 3-NO_2 compounds in the data base well predicted by eq 10, the fact that bioreduction of this group is needed to provide the toxic species in vivo must add to the variability of the measurements. Another member of this group (**335**) contains the labile 3-NHCHO group, which in vivo would rapidly provide the more toxic 3-NH_2 species. No common feature is apparent for the 14 compounds proving less toxic than predicted (**28**, **105**, **114**, **134**, **137**, **220**, **244**, **301**, **343**, **356**, **383**, **440**, **460**, and **464**). Only compounds **134** and **356** are really insoluble at toxic levels, thus reducing bioavailability. Compound **220** contains a 2′-OCH_3 group; although there are too few examples of toxic compounds bearing 2′-substituents to parameterize this position, such substitution does seem to lower bioactivity generally. For 12 derivatives whose toxicities are well predicted by eq 10 but which possess poorly predicted antitumor activity (**67**, **218**, **252**, **253**, **319**, **342**, **359**, **459**, **461**, **465**, **511**, and **512**), no common factor emerges. The less demanding statistics of eq 11 naturally permit the inclusion of more outlying points; where the line should be drawn is of course somewhat arbitrary. Thus again, inclusion of values for

all of the 9-anilinoacridines for which toxic doses could be calculated gave eq 11, of lower overall significance but of identical form.

Only nine of the tumor-inactive but toxic compounds had log ($1/LD_{10}$) values poorly predicted by eq 10. Compound **559** contains the most bulky 3′-group of all the compounds in the data set; although it is relatively nontoxic, the influence of the 3′-*t*-Bu group is overstated by eq 10. Compounds **586**, **611**, **654**, and **671** are also more toxic than predicted, for unclear reasons. Of the four derivatives found less toxic than expected (**568**, **604**, **607**, and **652**), **604** and **607** contain strongly basic acridine nuclei together with carboxylic acid side chains. It has been noted before[11] that many members of this class deviate from the broad structure–activity relationship (SAR) of the 9-anilinoacridines.

The similar forms of eq 8 and 10 clearly suggest that the tumor-inactive derivatives act by similar mechanisms and are inactive primarily due to supervening toxicity. For this reason, "log ($1/D_{50}$) obsd" values for these compounds recorded in Table I are, in fact, log ($1/LD_{10}$) values, which can thus be compared with the "log ($1/D_{50}$) calcd" values determined by eq 8. Thus, positive deviations constitute a correct prediction that these compounds are tumor-inactive because therapeutic levels cannot be reached before toxicity intervenes. More realistically, in view of the inherent inaccuracy in the determination of both LD_{10} and D_{50} values, a deviation of no greater than −0.5 can be regarded as a reasonable prediction. To this criterion, eq 11 is successful in accounting for the inactivity of about two-thirds of the inactive but toxic derivatives (101 of 155 examples). Of those most poorly predicted, some contain the same structural features possessed by compounds which are active but poorly predicted by eq 8, e.g., the amino acid moiety of **609** and **610**. Five compounds (**642–645** and **661**) possess 1-substituted acridines. However, it has been noted that inclusion of an MR_1 parameter with a coefficient similar to that found in eq 8 would successfully predict these compounds. The largest group of poorly predicted compounds is that containing acid groups (**603–610** and **615–617**). It has been noted above that members of this class of compounds deviate from the broad SAR of the 9-anilinoacridines. However, some acid derivatives possess antitumor activity which is well predicted by eq 8.

Inclusion of values for all of the toxic 9-anilinoacridines (compounds **1–691** in Table I) gave eq 11, of lower overall

$$\log (1/LD_{10}) = -0.05\ (\pm 0.02)\ \Sigma\pi - 0.62\ (\pm 0.11)\ \Sigma\sigma + 0.56\ (\pm 0.61)\ MR_1 - 0.19\ (\pm 0.16)\ MR_2 + 0.48\ (\pm 0.15)\ MR_3 + 0.10\ (\pm 0.05)\ MR_3^2 - 0.64\ (\pm 0.18)\ E_{s(3')} + 0.43\ (\pm 0.12)\ E_{s(3')}^2 - 0.34\ (\pm 0.54)\ I_{3,6} + 0.39\ (\pm 0.14)\ I_{NO_2} - 1.15\ (\pm 0.41)\ I_{BS} + 0.37\ (\pm 0.15)\ I_{NH_2} + 363\ (\pm 0.15) \quad (11)$$

$n = 691$; $r = 0.629$; $s = 0.451$; ideal MR_3 = 2.49 (1.97 to 4.20); ideal $E_{s(3')}$ = −0.74 (−0.87 to −0.63)

significance but retaining as significant all of the terms in eq 9 with the exception of MR_1, which is determined by only six data points out of 691.

The third class of compounds to be considered are those (**692–776**) for which no accurate biological data are available. All of these compounds are inactive against the L1210 leukemia in vivo and do not show acute toxicity up to a dose of 500 (mg/kg)/day, which is a practical upper limit for the protocol chosen. For ease of identification

Table IX. ω-[4-[(4-Nitrophenyl)carbamido]-phenyl]alkanoic Acids

alkanoic acid	mp, °C	formula[a]	yield, %
ethanoic	221–223	$C_{15}H_{13}N_3O_5$	81
propanoic	234–236	$C_{16}H_{15}N_3O_5$	87
butanoic	187–189	$C_{17}H_{17}N_3O_5 \cdot 0.5H_2O$	88
pentanoic	196–198	$C_{18}H_{19}N_3O_5$	90
hexanoic	183–185	$C_{19}H_{21}N_3O_5 \cdot H_2O$	87

[a] All compounds analyzed satisfactorily for C, H, and N.

in Table I, "log ($1/D_{50}$) obsd" and "log ($1/LD_{10}$) obsd" values for these compounds are given as 3.00, which corresponds approximately with a dose of 500 (mg/kg)/day in molar terms. As before, a correct prediction by eq 8 for the inactivity of these compounds would be a positive deviation, indicating that the dose required for therapeutic activity is greater than the highest dose tested [500 (mg/kg)/day]. Similarly, a correct prediction by eq 10 for the toxicity of these compounds would be a positive deviation, indicating that the predicted log ($1/LD_{10}$) values lie above the highest dose tested at 500 (mg/kg)/day. Equation 10 in fact does perform reasonably well, with about half of the compounds possessing predicted log ($1/LD_{10}$) values within 1 standard deviation of those actually observed. In fact, 56/85 (66%) of this last group of compounds have predicted log ($1/LD_{10}$) values above 2.50, compared with only 56/691 (8%) of those in the data set of eq 9.

This last series of compounds is made up largely of four different types of 9-anilinoacridines. The first is a group of 2′- and 3′-substituted derivatives (**694–710**). The 3′-substituted compounds are reasonably well predicted by both eq 8 and 10; bulky 3′-substituents are very dystherapeutic. The 2′-substituted compounds are less well predicted. This is the only position in the 9-anilinoacridine skeleton that was not able to be parameterized, for there are few active or even toxic examples. It seems clear that the majority of groups in this position also prove disadvantageous. The second group (**715–725**) is that with acid substituents which are very poorly predicted by both eq 8 and 10; the apparently different SAR of these compounds has been commented upon. A third group (**726–736**) is that possessing electron-withdrawing groups at the 1′position. By and large, these are well predicted by both equations; electron-withdrawing groups at this position have large σ_p^- values, detrimental to activity and toxicity. The last main group (**740–773**) comprises AMSA and *m*-AMSA derivatives with a variety of electron-withdrawing groups in the 2, 3, and 4 positions of the acridine. With some exceptions (e.g., **767–769**), the lack of toxicity of this group is reasonably well predicted; however, eq 8 deems that most of them should show antitumor activity well below a dose of 500 (mg/kg)/day. It may be that the stability of these weakly basic compounds is not well parameterized by $\Sigma\sigma$; certainly the aza derivatives (**746**, **747**, **754**, and **757**) are very unstable, even to hydrolytic cleavage.

Modeling of Measures of Selectivity. Two measures of the selectivity of the 9-anilinoacridines were available. ILS_{max}, the percentage increase in life span achieved by a drug when given at a constant toxic level to the host (the LD_{10}), is a measure of in vivo tumor cell selectivity. A related parameter is the chemotherapeutic index, determined as log (LD_{10}/D_{50}). It can be seen from Table III that these two measures are quite unrelated to acute toxicity, whereas drug potency (log $1/D_{50}$) is highly correlated. Such parameters thus potentially contain complementary information, and it is instructive to attempt

Table X. Physical and Analytical Data for Previously Unreported 9-Anilinoacridines

no.[a]	formula	mp, °C	anal.[b]	no.[a]	formula	mp, °C	anal.[b]
13	$C_{23}H_{20}N_2O_5 \cdot HCl \cdot 0.5H_2O$	171-174	C, H, N, Cl	349	$C_{22}H_{21}N_3O_3S \cdot HCl$	284-285	C, H, N, Cl
15	$C_{20}H_{14}N_3 \cdot HCl$	335-337	C, H, N, Cl	359	$C_{23}H_{22}N_4O_4S \cdot HCl$	238-240	C, H, N, Cl
16	$C_{21}H_{17}N_3O \cdot HCl \cdot H_2O$	217-220	C, H, N, Cl	360	$C_{22}H_{19}ClN_4O_3S \cdot HCl$	244-246	C, H, N; Cl[i]
17	$C_{19}H_{16}N_4O_2S \cdot HCl \cdot 0.5H_2O$	324-325	C, H, N, Cl	363	$C_{20}H_{14}N_9O_2S \cdot HCl$	>340	C, H, N
18	$C_{20}H_{18}N_4O_2S \cdot HCl$	319-322	C, H, N, Cl	372	$C_{25}H_{21}N_3O_3S \cdot HCl$	266-268	C, H, N, Cl
19	$C_{19}H_{19}N_5O_2S \cdot HCl$	243-246	C, H, N	373	$C_{24}H_{20}N_4O_3S \cdot HCl \cdot 1.5H_2O$	210-212	C, H, N, Cl
20	$C_{20}H_{18}N_4O_2S \cdot HCl$	210 dec	C, H, N, Cl	374	$C_{24}H_{23}N_3O_3S \cdot CH_3SO_3H \cdot H_2O$	182-183	C, H, N, S
21	$C_{21}H_{20}N_4O_2S \cdot HCl \cdot 2H_2O$	204-209	C, H, N, Cl	375	$C_{22}H_{20}ClN_3O_3S \cdot HCl \cdot H_2O$	208-210	C, H, N, Cl
22	$C_{22}H_{22}N_4O_2S \cdot HCl$	314-315	C, H, N, Cl	377	$C_{21}H_{19}IN_4O_3S \cdot HCl \cdot 0.5H_2O$	250-255	C, H, N
23	$C_{23}H_{24}N_4O_2S \cdot HCl$	294-296	C, H, N, Cl	380	$C_{24}H_{24}N_4O_5S \cdot HCl$	293-294	C, H, N, Cl
24	$C_{24}H_{26}N_4O_2S \cdot HCl \cdot 0.5H_2O$	178-180	C, H, N, Cl	381	$C_{22}H_{21}N_6O_3S \cdot HCl$	225-229	C, H, Cl
25	$C_{25}H_{28}N_4O_2S \cdot HCl \cdot H_2O$	278-280	C, H, N, Cl	384	$C_{23}H_{22}N_4O_5S$	220-221	C, H, S
27	$C_{21}H_{19}N_3O_3S \cdot C_7H_8SO_3H$	124-126	C, H, N, S	388	$C_{23}H_{23}N_3O_4S \cdot HCl \cdot H_2O$	213-214	C, H, N, Cl
31	$C_{25}H_{24}N_2O_6 \cdot HCl$	160-165	H, N; C[c]	389	$C_{23}H_{23}N_3O_4S \cdot HCl$	209 dec	C, H, N, Cl
32	$C_{25}H_{23}N_3O_8 \cdot HCl$	219-220	C, H, N, Cl	392	$C_{22}H_{20}BrN_3O_3S \cdot HBr \cdot H_2O$	296 dec	C, H, N, Br
64	$C_{21}H_{17}N_5O \cdot HCl \cdot 0.5H_2O$	240-245	C, H, Cl; N[d]	393	$C_{22}H_{20}BrN_3O_4S \cdot HCl$	245-246	C, H, N, Br
66	$C_{28}H_{20}N_2O_2 \cdot HCl$	>360	C, H, N, Cl	397	$C_{25}H_{25}N_5O_4S \cdot CH_3SO_3H \cdot 0.5H_2O$	240-244	C, H, N
67	$C_{22}H_{14}N_4$	134-138	C, H, N	400	$C_{21}H_{18}ClN_3O_3S \cdot HCl$	271-272	C, H, N
68	$C_{20}H_{14}N_4 \cdot HCl$	320 dec	C, H, N, Cl	406	$C_{23}H_{23}N_3O_5S \cdot HCl$	263-265	C, H, N, Cl
72	$C_{20}H_{17}N_3O \cdot HCl \cdot H_2O$	277 dec	C, H, N, Cl	418	$C_{23}H_{24}N_4O_3S \cdot HBr$	319-321	C, H, N, Br
73	$C_{20}H_{17}N_3O \cdot 2HCl \cdot 0.5H_2O$	312-313	C, H, N, Cl	427	$C_{22}H_{19}N_5O_5S \cdot HCl$	284-286	C, H, N, Cl
75	$C_{21}H_{18}N_4O \cdot HCl$	300-301	C, H, N, Cl	430	$C_{24}H_{24}N_6O_5S \cdot 2HCl \cdot 1.5H_2O$	247 dec	C, H, N
76	$C_{20}H_{17}N_3 \cdot HBr$	347-348	C, H, N, Br	433	$C_{24}H_{25}N_5O_3S \cdot HCl \cdot H_2O$	185-205	C, H, N, Cl
77	$C_{21}H_{19}N_3O \cdot 2HCl$	291-293	C, H, N, Cl	439	$C_{23}H_{23}N_3O_2S$	179-180	C, H, N, S
79	$C_{20}H_{17}N_3 \cdot 2HCl \cdot H_2O$	241-243	C, H, N, Cl	440	$C_{23}H_{21}N_5O_5S \cdot HCl$	263-265	C, H, N, Cl
88	$C_{20}H_{14}N_4 \cdot HCl \cdot 0.5H_2O$	231-233	C, N, Cl; H[e]	451	$C_{26}H_{30}N_6O_2S \cdot 2HCl \cdot 1.5H_2O$	207-209	C, H, N, Cl
90	$C_{22}H_{20}BrN_3O$	343 dec	C, H, N, Br	459	$C_{23}H_{23}N_7O_5S \cdot 2HCl \cdot 0.5H_2O$	214-219	C, H, N, Cl
99	$C_{25}H_{23}N_3O \cdot HCl$	313-314	C, H, N, Cl	460	$C_{22}H_{24}N_8O_2S \cdot 2HCl \cdot 2H_2O$	270-275	C, H
100	$C_{24}H_{24}N_4O_3S \cdot HCl$	265-266	C, H, N, Cl	464[j]	$C_{23}H_{26}N_8O_2S \cdot 2HCl$	205-210	C, H; N[j]
106	$C_{26}H_{21}N_5O \cdot HBr$	228-230	C, H, N; Br[f]	473	$C_{25}H_{20}N_4O_2S \cdot HCl$	300-301	C, H, N, Cl
113	$C_{22}H_{20}N_4O \cdot HCl \cdot 0.5H_2O$	210-215	C, H, N, Cl	474	$C_{25}H_{20}N_4O_2S \cdot HCl$	>360	C, H, N, Cl
117	$C_{27}H_{23}N_5O \cdot 2HCl$	324-326	C, H, N, Cl	475	$C_{26}H_{18}N_4O_3 \cdot HCl \cdot 0.5H_2O$	323-324	C, H, N
118	$C_{27}H_{22}N_6O_3 \cdot 2HCl$	>360	C, H, N, Cl	476	$C_{20}H_{17}N_3O_2S \cdot C_7H_8SO_3H$	324-325	C, H, N, S
119	$C_{28}H_{25}N_5O \cdot 2HCl \cdot H_2O$	256-258	C, H, N, Cl	477	$C_{28}H_{24}N_4O_3S \cdot HCl$	>360	C, H, N, Cl
120	$C_{29}H_{27}N_5O \cdot 2HCl$	239-242	C, H, N, Cl	479	$C_{24}H_{19}N_5O_2S \cdot HCl \cdot 0.5H_2O$	290-291	C, H, N, Cl
121	$C_{30}H_{29}N_5O \cdot 2HBr \cdot 2H_2O$	218-222	C, H, N	480	$C_{26}H_{22}N_4O_2S \cdot HCl$	312 dec	C, H, N, Cl
122	$C_{31}H_{31}N_5O \cdot 2HCl$	229-234	C, H, N, Cl	481	$C_{26}H_{22}N_4O_3S \cdot HCl$	255-257	C, H, N, Cl
123	$C_{32}H_{33}N_5O \cdot 2HCl$	273-274	C, H, N, Cl	482	$C_{25}H_{21}N_5O_2S \cdot HBr$	242-243	C, H, N, Br
124	$C_{29}H_{25}N_5O_3 \cdot HCl$	251-254	C, H, N, Cl	483	$C_{25}H_{19}ClN_4O_2S \cdot HCl$	>360	C, H, N, Cl
125	$C_{29}H_{24}N_6O_5 \cdot HCl$	>360	C, H, N	484	$C_{27}H_{24}N_4O_2S \cdot HCl$	300-301	C, H, N, Cl
126	$C_{27}H_{20}N_4O_3 \cdot HCl \cdot H_2O$	225-229	C, H, N, Cl	485	$C_{27}H_{24}N_4O_3S \cdot HCl$	226-228	C, H, N, Cl
127	$C_{28}H_{22}N_4O_3 \cdot HCl$	254-255	C, H, N, Cl	486	$C_{26}H_{21}ClN_4O_2S \cdot HCl$	>360	C, H, N, Cl
128	$C_{29}H_{24}N_4O_3 \cdot HCl$	248-250	C, H, N, Cl	487	$C_{27}H_{24}N_4O_2S \cdot HCl \cdot H_2O$	265-267	C, H, N, Cl
129	$C_{30}H_{26}N_4O_3$	295-297	C, H, N	489	$C_{24}H_{25}N_7O_4S \cdot 2HCl \cdot 0.5H_2O$	>360	C, H, N, Cl
130	$C_{31}H_{28}N_4O_3 \cdot HCl$	222-223	C, H, N, Cl	490	$C_{25}H_{17}N_5O_6 \cdot HCl$	312-313	H, N; C[k]
131	$C_{32}H_{30}N_4O_3$	288-292	C, H, N	491	$C_{29}H_{26}N_4O_3S \cdot HCl \cdot 0.5H_2O$	330-331	C, H, N, Cl
132	$C_{27}H_{23}N_5O_3S \cdot HCl$	299-301	C, H, N, Cl	492	$C_{26}H_{19}N_3O_4S \cdot HCl$	328 dec	C, H, N, Cl
133	$C_{27}H_{23}N_7O \cdot 2HCl$	253-256	C, H, N, Cl	493	$C_{27}H_{21}N_4O_4S \cdot HCl$	334 dec	C, H, N, Cl
134	$C_{27}H_{22}N_8O_3 \cdot 2HCl \cdot 0.5H_2O$	260 dec	C, H, N, Cl	494	$C_{28}H_{24}N_6O_5S \cdot 2HCl$	281 dec	C, H, N, Cl
135	$C_{28}H_{25}N_9O \cdot 2HCl$	255-260	C, H, N, Cl	495	$C_{26}H_{21}N_3O_4S_2 \cdot CH_3SO_3H$	326-327	C, H, N, S
136	$C_{28}H_{24}N_{10}O_3 \cdot 2HCl \cdot 1.5H_2O$	263-265	C, H, N	536	$C_{24}H_{24}N_4O_3S \cdot HCl \cdot 0.5H_2O$	232-234	C, H, N, S
137	$C_{29}H_{28}N_{10}O \cdot 2HCl$	305-309	C, H, N, Cl	537	$C_{24}H_{22}N_4O_5S$	244-245	C, H, N, S
138	$C_{29}H_{26}N_8O \cdot 2HCl$	276-277	C, H, N, Cl	540	$C_{26}H_{26}N_4O_6S$	236-238	C, H, N, S
139	$C_{30}H_{29}N_9O \cdot 2HCl$	269 dec	C, H, Cl; N[g]	544	$C_{22}H_{19}N_3O \cdot HBr$	248-249	C, H, N, Br
142	$C_{22}H_{20}N_4O_4S \cdot HCl \cdot 0.5H_2O$	209-211	C, H, N, Cl	547	$C_{22}H_{21}N_3 \cdot 2HCl$	288-290	C, H, N, Cl
143	$C_{24}H_{22}N_4O_5S \cdot HCl \cdot 2H_2O$	202-203	C, H, N, Cl	567	$C_{21}H_{18}N_2 \cdot HCl$	281-283	C, H, N, Cl
147	$C_{21}H_{19}N_3O_2S \cdot HCl$	230-231	C, H, N, Cl	568	$C_{19}H_{14}N_2O_2 \cdot HCl$	>360	C, H, Cl
177	$C_{20}H_{16}N_6O_2S \cdot HCl$	195-200	C, H, N	569	$C_{21}H_{18}N_2O_2 \cdot HCl \cdot 2H_2O$	128-129	C, H, N
201	$C_{24}H_{24}N_4O_4S \cdot HCl$	290-291	C, H, N, Cl	570	$C_{20}H_{17}N_3 \cdot 2HCl$	319-320	C, H, N, Cl
202	$C_{25}H_{26}N_4O_4S \cdot HCl$	268-269	C, H, N, Cl	571	$C_{20}H_{17}N_3O \cdot 2HCl$	273-275	C, H, N, Cl
216	$C_{22}H_{21}N_3O_3S \cdot HCl$	196-198	C, H, N, Cl	572	$C_{20}H_{17}N_3 \cdot 2HCl$	>360	C, H, N, Cl
219	$C_{19}H_{15}N_5O_4S \cdot 2HCl \cdot H_2O$	222-229	C, H, N, Cl	573	$C_{20}H_{17}N_3O \cdot 2HCl$	334-336	C, H, N, Cl
220	$C_{21}H_{20}N_4O_3S \cdot HCl$	264-265	C, H, N, Cl	574	$C_{19}H_{14}N_4O_2 \cdot HCl$	>360	C, H, N, Cl
228	$C_{22}H_{22}N_4O_3S_2 \cdot HCl$	246-248	C, H, N, S	575	$C_{20}H_{17}N_3O \cdot 2HCl$	285-286	C, H, N, Cl
232	$C_{21}H_{20}N_4O_2S \cdot HCl \cdot 2H_2O$	197-200	C, H, N, Cl	579	$C_{23}H_{23}N_3 \cdot HBr$	269-271	C, H, N, Br
234	$C_{22}H_{22}N_5O_4S \cdot HCl$	256-257	C, H, N, Cl	584	$C_{27}H_{21}N_3O \cdot HCl$	309-319	C, H, N, Cl
245	$C_{26}H_{24}N_6O_6S \cdot HCl \cdot 1.5H_2O$	261-262	C, H, N	585	$C_{24}H_{20}N_4O_2 \cdot 2HCl$	>320	C, H, N
246	$C_{24}H_{21}N_3O_5S \cdot HBr$	271-273	C, H, N	586	$C_{25}H_{24}N_4O_5 \cdot HCl \cdot 2H_2O$	283 dec	C, H, N
278	$C_{25}H_{26}N_4O_4S \cdot HCl$	268-269	C, H, N, Cl	588	$C_{21}H_{19}N_3O \cdot HCl$	264-265	C, H, N, Cl
283	$C_{22}H_{21}N_3O_4S \cdot HCl$	212 dec	C, H, Cl; N[h]	589	$C_{20}H_{17}N_3 \cdot 2HCl \cdot H_2O$	>360	C, H, N, Cl
284	$C_{24}H_{26}N_4O_3S \cdot HCl$	298-300	C, H, N, Cl	590	$C_{20}H_{16}N_4O_2 \cdot 2HCl$	300 dec	C, H, N, Cl
300	$C_{23}H_{21}N_3O_6S \cdot HCl$	98-99	C, H, N, Cl	591	$C_{22}H_{21}N_3 \cdot 2HCl$	258-260	C, H, N, Cl
306	$C_{22}H_{20}N_4O_3S \cdot HCl$	303-303	C, H, N, Cl	592	$C_{21}H_{19}N_3 \cdot 2HCl$	328-330	C, H, N, Cl
327	$C_{28}H_{32}N_4O_6S \cdot 2HCl$	200-201	C, H, N, Cl	593	$C_{21}H_{18}N_4O_2 \cdot 2HCl$	318-319	C, H, N, Cl
335	$C_{22}H_{20}N_4O_3S \cdot HCl \cdot 0.5H_2O$	246-248	C, H, S, Cl	594	$C_{21}H_{18}N_2O$	188-190	C, H, N
343	$C_{23}H_{22}N_4O_4S \cdot HCl$	290-291	C, H, N, Cl	595	$C_{22}H_{21}N_3 \cdot 2HCl$	302-303	C, H, N, Cl
345	$C_{22}H_{20}N_4O_4S$	267-268	C, H, N, S	596	$C_{22}H_{20}N_4O_2 \cdot 2HCl$	273-274	C, H, N, Cl

Table X (*Continued*)

no.[a]	formula	mp, °C	anal.[b]	no.[a]	formula	mp, °C	anal.[b]
597	$C_{23}H_{23}N_3 \cdot 2HCl$	281-283	C, H, N, Cl	655	$C_{20}H_{14}N_9O_2S \cdot HCl$	>360	C, H, N, Cl
598	$C_{23}H_{22}N_4O_2 \cdot 2HCl$	276-278	C, H, N, Cl	657	$C_{23}H_{22}N_4O_4S \cdot HCl$	303-304	C, H, N, Cl
599	$C_{24}H_{25}N_3 \cdot 2HCl \cdot 1.5H_2O$	272-274	C, H, N, Cl	659	$C_{22}H_{20}ClN_3O_4S \cdot HCl$	300-303	C, H, N, Cl
600	$C_{24}H_{24}N_4O_2 \cdot 2HCl$	215-216	C, H, N	661	$C_{22}H_{19}ClN_4O_4S \cdot HCl$	271-274	C, H, N, Cl
601	$C_{25}H_{27}N_3 \cdot 2HCl$	258-260	C, H, N; Cl[l]	662	$C_{25}H_{21}N_3O_3S \cdot CH_3SO_3H \cdot 0.5H_2O$	276-277	C, H, N, S
602	$C_{25}H_{26}N_4O_2 \cdot 2HCl$	212-214	C, H, N, Cl	674	$C_{27}H_{24}N_4O_2S \cdot 2HCl \cdot H_2O$	216-220	C, H, N, Cl
605	$C_{24}H_{21}N_3O_3 \cdot HCl$	313-315	C, H, N, Cl	678	$C_{24}H_{25}N_5O_4S \cdot 2HCl \cdot 2H_2O$	198-202	C, H
611	$C_{27}H_{20}N_2 \cdot HCl$	328-332	C, H, N, Cl	679	$C_{25}H_{27}N_5O_4S \cdot 2HCl$	205-207	C, H, N, Cl
620	$C_{19}H_{14}BrN_3 \cdot HCl$	235-245	C, H, N, Br	684	$C_{24}H_{25}N_7O_2S \cdot 2HCl \cdot 1.5H_2O$	211-222	C, H
622	$C_{23}H_{21}N_3O \cdot HBr$	268-270	C, H, N, Br	688	$C_{29}H_{33}N_5O_2S_2 \cdot 2HCl$	190-230	C, H, N, S
623	$C_{25}H_{28}N_4O_2S \cdot 2HCl \cdot 0.5H_2O$	203-205	C, H, N	689	$C_{28}H_{33}N_7O_4S \cdot 2HCl \cdot 1.5H_2O$	187-189	C, H
627	$C_{23}H_{23}N_3O_3S \cdot HCl$	291 dec	C, H, N, Cl	693	$C_{20}H_{17}N_3O_2S \cdot HCl \cdot H_2O$	197-199	C, H, N, Cl
632	$C_{21}H_{20}N_4O_4S_2 \cdot HCl$	319-320	C, H, N, Cl	695	$C_{25}H_{19}N_3O_2S \cdot HCl$	317-320	C, H, N, Cl
635	$C_{20}H_{16}IN_3O_2S \cdot HCl$	310-311	C, H, N, I	711	$C_{20}H_{18}N_4O_2S \cdot HCl \cdot H_2O$	211-213	C, H, N
637	$C_{21}H_{18}N_4O_3S \cdot C_7H_7SO_3H$	314-315	C, H, N, S	712	$C_{21}H_{15}N_5O_2 \cdot HCl$	277-278	C, H, N, Cl
638	$C_{23}H_{20}N_4O_3S \cdot C_7H_7SO_3H$	304-305	C, H, N, S	734	$C_{21}H_{20}N_4O_2S \cdot HCl$	300-301	C, H, N, Cl
641	$C_{22}H_{20}N_4O_4S \cdot HCl$	260-261	C, H, N, Cl	737	$C_{21}H_{20}N_4O_4S_2 \cdot HCl$	315-317	C, H, N, Cl
644	$C_{22}H_{21}N_3O_3S \cdot HCl$	276-277	C, H, N, Cl	738	$C_{21}H_{19}N_3O_2S \cdot HCl$	324-325	C, H, N
645	$C_{22}H_{21}N_3O_4S \cdot HCl$	217-219	C, H, N, Cl	739	$C_{21}H_{20}N_4O_4S_2 \cdot HCl$	294-295	C, H, N, Cl
647	$C_{25}H_{27}N_3O_3S \cdot HCl$	291-292	C, H, N, Cl	748	$C_{27}H_{22}N_4O_3S \cdot CH_3SO_3H \cdot 0.5H_2O$	264-265	C, H, N, S
648	$C_{22}H_{21}N_3O_4S \cdot HCl$	277-280	C, H, N, Cl	763	$C_{22}H_{21}N_3O_2S \cdot HCl$	>360	C, H, N, Cl
649	$C_{21}H_{18}ClN_3O_3S \cdot HCl$	290-293	C, H, N, Cl	764	$C_{22}H_{21}N_3O_4S \cdot HCl$	261-263	C, H, N, Cl
650	$C_{22}H_{20}N_4O_4S \cdot HCl \cdot 0.5H_2O$	304-306	C, H, N, Cl	765	$C_{20}H_{18}ClN_3O_2S \cdot HCl$	210-214	C, H, N, Cl
651	$C_{23}H_{24}N_4O_4S_2 \cdot CH_3SO_3H$	245-246	C, H, N, S	767	$C_{23}H_{23}N_3O_2S \cdot HCl$	221-224	C, H, N
653	$C_{27}H_{31}N_3O_5S_2 \cdot HCl \cdot H_2O$	165-168	C, H, N, Cl	768	$C_{22}H_{21}N_3O_5S_2 \cdot HCl \cdot 0.5H_2O$	235-237	C, H, N, Cl

[a] Entry number in Table I. [b] Analyses were within ±0.4% of the theoretical value for the elements quoted, unless otherwise indicated. [c] C out by 0.6. [d] N out by 0.7. [e] H out by 0.8. [f] Br out by 0.7. [g] N out by 0.9. [h] N out by 0.9. [i] Cl out by 0.7. [j] N out by 0.5. [k] C out by 0.8. [l] Cl out by 0.7.

modeling of them in terms of drug structural features. However, unlike measures of drug therapeutic potency and acute toxicity, measures of selectivity vary over a much narrower range. Thus, for the 9-anilinoacridines, ILS_{max} values vary only about tenfold.

Furthermore, although the parameter is reproducible in replicate tests for a particular compound,[12] much of the data are gathered at high doses close to the LD_{10}. For insoluble compounds, factors difficult to parameterize, such as the particle size of the suspension, may play a large role in determining activity by influencing drug bioavailability. Even though ILS_{max} values are determined from the totality of the data gathered from over the whole dose range, these effects may mask relationships with the more usual physicochemical properties. Thus, ILS_{max} values have proved quite amenable to QSAR determination in the past for classes of compounds that are very water soluble and thus pose no problems of administration[16,21] but have not been as useful in studies of the more insoluble *m*-AMSA compounds[13,27] where the higher drug doses must often be administered as suspensions.

In the present studies using regression techniques, no satisfactory or useful relationship that extended to the whole data base of 9-anilinoacridines could be discerned between ILS_{max} values and drug structural parameters. The chemotherapeutic index varies over a somewhat greater range (approximately 60-fold), and modeling of this parameter can of course be achieved initially by a simple subtraction of eq 8 from eq 10. The essential similarity of these equations ensures that only a few terms are liable to be of significance: those that do not occur in both or those that do but with greatly differing coefficients. Examination of a number of other structural descriptors was also made, but no equation modeling chemotherapeutic index for the whole data base was found that could account for more than about 25% of the variance in the biological data.

Despite this, a comparison of eq 8 and 10 shows some differences that need to be kept in mind when formulating future synthetic programs. For example, the coefficient of the I_{NH_2} term in eq 10 indicates that addition of a 3-NH_2 group to the molecule provides an average increase in toxicity of about threefold, whereas the coefficient of this term in eq 9 was found to be vanishingly small, signifying that a comparable increase in therapeutic potency was not obtained. Conversely, while addition of a 3-alkyltriazene group increases potency an average of 7.5-fold, no corresponding increase in toxicity was evident. Again, the coefficient for the I_{BS} term in eq 9 indicates the favorable contribution of the 1′-benzenesulfonamide moiety to therapeutic potency without a corresponding increase in toxicity.

Conclusions

A large number of examples of the 9-anilinoacridine class of antitumor drugs have been prepared and tested for in vivo activity. As with any extensive drug development and testing program, the resultant biological data represent a considerable amount of work, and the maximum amount of useful information should be extracted from them. We have attempted to do this by formulating QSAR for the activity of these compounds. Careful in vivo testing procedures allow a number of different biological parameters to be determined for each compound. Together with acute toxicity data, two broad types of measurement of therapeutic activity can be made. One type, drug potency, has been successfully modeled by eq 8. Acute toxicity data have also been modeled for the tumor-active compounds and for additional inactive but toxic variants in eq 10. It is most satisfying that such a large body of biological data can thus be essentially reduced to two equations. Not unexpectedly, these are of broadly similar form, thus exemplifying the close relationship between potency and

Table XI. Development of Equations 7 and 10

							Equation 7									
intercept	MR_3	$\Sigma\sigma$	I_{NO_2}	$I_{3,6}$	R_{BS}	$\Sigma\pi$	$E_{s(3')}$	$E_{s(3')}^2$	MR_3^2	I_{BS}	I_{DAT}	MR_2	$\Sigma\pi^2$	r	s	$F_{1,X}$
4.14	0.46													0.400	0.611	97.0
4.14	0.48	−0.62												0.553	0.552	116.1
4.09	0.40	−1.08	0.86											0.662	0.501	95.7
4.05	0.51	−1.17	0.99	−0.79										0.701	0.477	66.2
4.01	0.53	−1.17	1.02	−0.79	−1.67									0.742	0.449	65.4
3.93	0.52	−1.11	0.90	−0.77	−1.76	−0.09								0.772	0.426	56.8
3.90	0.51	−1.21	1.12	−0.82	−1.85		−1.66	−1.63						0.813	0.391	
3.82	0.50	−1.15	1.00	−0.80	−1.92	−0.09	−1.65	−1.59						0.840	0.364	75.6
3.67	1.01	−1.07	0.80	−0.82	−1.92	−0.10	−1.67	−1.58	−0.22					0.858	0.345	58.2
3.64	1.02	−1.07	0.77	−0.80	−1.27	−0.10	−1.71	−1.61	−0.22	0.50				0.866	0.336	27.8
3.64	1.06	−1.07	0.76	−0.76	−1.27	−0.10	−1.71	−1.61	−0.25	0.50	0.71			0.871	0.331	17.9
3.72	1.05	−1.07	0.75	−0.76	−1.25	−0.11	−1.72	−1.62	−0.25	0.51	0.72	−0.32		0.875	0.326	14.1
3.63	1.04	−1.09	0.78	−0.77	−1.25	−0.14	−1.68	−1.60	−0.25	0.50	0.70	−0.32	−0.01	0.879	0.323	12.6

							Equation 10								
intercept	$\Sigma\sigma$	I_{NO_2}	MR_3	I_{NH_2}	R_{BS}	$E_{s(3')}$	$E_{s(3')}^2$	$I_{3,6}$	$\Sigma\pi$	MR_3^2	MR_2	MR_1	r	s	$F_{1,X}$
3.89	−0.58												0.421	0.512	138.0
3.81	−0.95	0.71											0.537	0.476	100.4
3.68	−0.91	0.78	0.25										0.597	0.453	67.2
3.65	−0.78	0.52	0.24	0.54									0.635	0.437	50.4
3.64	−0.77	0.53	0.25	0.53	−1.10								0.657	0.427	31.5
3.57	−0.74	0.52	0.23	0.61		−0.85	−0.60						0.692	0.408	
3.55	−0.77	0.59	0.29	0.63		−0.87	−0.60	−0.48					0.712	0.398	37.2
3.50	−0.75	0.47	0.23	0.54	−1.15	−0.87	−0.60		−0.07				0.732	0.386	
3.48	−0.78	0.54	0.29	0.54	−1.15	−0.89	−0.61	−0.48	−0.07				0.751	0.374	42.0
3.39	−0.76	0.43	0.60	0.51	−1.15	−0.87	−0.59	−0.50	−0.07	−0.12			0.763	0.367	27.2
3.45	−0.75	0.41	0.60	0.50	−1.13	−0.88	−0.60	−0.51	−0.07	−0.12	−0.24		0.769	0.363	13.2
3.53	−0.76	0.43	0.59	0.50	−1.13	−0.89	−0.61	−0.51	−0.07	−0.12	−0.24	−0.56	0.771	0.362	5.24

toxicity seen in Table III. Structuring the data in this way and comparison of the two equations enable one to see the best way of altering drug structure in order to best separate toxicity and therapeutic potency. Inferences can also be drawn from the form of the equations concerning the possible mode of action of this class of compounds.

Hydrophobicity is a determinant of both potency and toxicity but not a dominant one. For maximum separation of these bioactivities, derivatives should have a $\sum\pi$ of around −4.5 or higher; below this value, increasing toxicity will tend to negate possible therapeutic gains. The most important properties contributing to both types of activity are those suggested as being important for drug stability, being parameterized by $\sum\sigma$ and $E_{s(3')}$. Not unexpectedly, they contribute in a similar fashion to both bioactivities, and there is little prospect of divorcing potency and toxicity by manipulation of these factors. Many of the positions around the 9-anilinoacridine molecule are subject to steric restraint; the pattern of restraint is entirely consistent with the biologically important receptor being DNA and the drugs binding intercalatively with the side chain protruding into the minor groove. Only positions 1′ and 4 seem totally free of steric restraint, while small groups at the 3′ position enhance activity. Again, the pattern is similar for both toxicity and potency. However, inspection of the indicator variables used in eq 8 and 10 suggests that there are specific substitution patterns that can be manipulated to provide some separation of toxicity and therapeutic potency. Increased toxicity with no corresponding increase in potency is seen for 3-NH_2 compounds; thus, even though 3-NH_2 substitution is an excellent way of increasing drug stability, use of this substituent should be avoided. An improvement in drug potency but not toxicity is seen with the 3-alkyltriazenes. Although such alkylating moieties are often associated with increased mutagenic potential, 3-$N_3(CH_3)_2$-AMSA (compound **184**) is less mutagenic in the Ames test than the parent AMSA.[54] The benzenesulfonamide derivatives constitute a series of remarkably potent compounds whose toxicities do not follow suit.

More generally, eq 8 and 10 provide an essential base of knowledge about how the physicochemical properties of the 9-anilinoacridines affect their toxicity and therapeutic activities in an animal tumor system. They are a base line against which to compare any future QSAR obtained for this class of agent acting in other in vivo or in vitro tumor systems.

They also serve to illuminate the areas of the chemistry of the 9-anilinoacridines which have been well explored and those which have not. Thus, patterns of acridine substitution have been fairly well covered and seem limited to small groups in the 3 position, with only the 5 position then available for the attachment of hydrophobic groups with which to adjust overall hydrophobicity to desired levels. Fairly definite conclusions can also be reached about the nature of substitution at the 3′ position of the anilino ring. Although a number of different small groups would be predicted to be protherapeutic (e.g., NH_2, OH, OCH_3, SCH_3), for reasons of stability to oxidative processes the best choice of group for this position is OCH_3. However, even in the huge data base considered, there remain potentially interesting areas of 9-anilinoacridine chemistry that have been less well explored; an example is the benzenesulfonamides. QSAR techniques, by structuring the enormous amounts of biological data available, allow such areas to be identified.

Finally, this study demonstrates again the more analytic approach to drug design made possible by the advent and application of QSAR techniques. Given the natural desire to uncover more active and potent derivatives and the time and expense of adequate in vivo tumor testing, inactive or weakly active congeners often do not receive thorough testing at the high dose levels that might be needed. However, the employment of sets of substituents carefully chosen to possess mutually orthogonal physicochemical properties, together with thorough testing of all these congeners (to extend the spread of the dependent variable as far as possible), would have permitted relationships similar to those of eq 8 and 10 to have been established for the 9-anilinoacridines using far fewer examples and is an approach generally applicable to other sets of antitumor agents.

Table XII. Squared Correlation Matrices for Variables in Equations 7 and 10

Equation 7

	$\Sigma\sigma$	MR_3	$E_{s(3')}$	I_{NO_2}	I_{NH_2}	$I_{3,6}$	R_{BS}	MR_2	I_{DAT}
$\Sigma\pi$	0.00	0.00	0.00	0.03	0.00	0.00	0.01	0.00	0.00
$\Sigma\sigma$		0.00	0.01	0.45	0.00	0.00	0.00	0.00	0.00
MR_3			0.00	0.04	0.14	0.00	0.00	0.01	0.11
$E_{s(3')}$				0.01	0.00	0.00	0.00	0.00	0.00
I_{NO_2}					0.03	0.00	0.01	0.00	0.00
$I_{3,6}$						0.00	0.00	0.00	0.00
I_{BS}							0.38	0.00	0.00
R_{BS}								0.00	0.00
MR_2									0.00

Equation 10

	$\Sigma\sigma$	MR_1	MR_2	MR_3	$E_{s(3')}$	I_{NO_2}	I_{NH_2}	$I_{3,6}$	R_{BS}
$\Sigma\pi$	0.02	0.00	0.00	0.00	0.01	0.06	0.01	0.01	0.00
$\Sigma\sigma$		0.00	0.00	0.00	0.01	0.39	0.09	0.00	0.00
MR_1			0.00	0.00	0.00	0.00	0.00	0.00	0.00
MR_2				0.00	0.00	0.00	0.00	0.00	0.00
MR_3					0.01	0.05	0.00	0.14	0.00
$E_{s(3')}$						0.01	0.01	0.00	0.00
I_{NO_2}							0.01	0.04	0.00
I_{NH_2}								0.01	0.00
$I_{3,6}$									0.00

Experimental Section

For analyses indicated by symbols of the elements, analytical results obtained for these compounds 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.

Preparation of 9(10*H*)-Acridanones. 3-(Hydantoinylacetamido)-9(10*H*)-acridanone. A stirred mixture of 3-amino-9(10*H*)-acridanone (4.2 g, 0.02 mol) and hydantoin-3-acetic acid (3.8 g, 0.024 mol) in pyridine (50 mL) was treated dropwise at 0 °C with PCl_3 (1.74 mL; 0.02 mol). The mixture was stirred for 3 h at 20 °C, followed by 1 h at 100 °C, and the volatiles were removed in vacuo. The residue was shaken with water, acidified with 2 N HCl, and collected. Crystallization from DMF/EtOH/water gave needles: mp >320 °C; 89% yield. Anal. ($C_{18}H_{14}N_4O_4 \cdot 1.5H_2O$) C, H, N. Activation with $SOCl_2$/DMF gave the 9-chloroacridine for preparation of compound **245**.

3-[*N*-(Ethoxycarbonyl)glycinamido]-9(10*H*)-acridanone. A mixture of 3-amino-9(10*H*)-acridanone (5.2 g, 0.025 mol) and *N*-(ethoxycarbonyl)glycine (7.3 g, 0.05 mol) was treated with PCl_3 (2.4 mL; 0.027 mol) as above. The product was crystallized from aqueous EtOH and then from DMF/EtOH/water to give needles: mp 293–295 °C; 84% yield. Anal. ($C_{18}H_{17}N_3O_4$) C, H, N. A suspension of this acridanone (10.3 g, 0.3 mol) in 4 N aqueous KOH (200 mL) was stirred at 100 °C until homogeneous and then for an additional 1 h. The cooled solution was acidified with 12 N HCl (75 mL), and the resulting solid was collected and washed

thoroughly with boiling 0.1 N HCl to remove a quantity of 3-aminoacridanone. Crystallization from DMF/1 N HCl, followed by aqueous DMF, gave needles of 3-hydantoinyl-9(10*H*)-acridanone for the preparation of compound **246**: mp >320 °C; 55% yield. Anal. ($C_{16}H_{11}N_3O_3 \cdot 1.5H_2O$) C, H, N.

4-(Dimethylamino)-9-chloroacridine. This was prepared by vigorously stirring a solution of 4-(bromomethyl)-9-chloroacridine[28] (3.06 g, 0.01 mol) in $CHCl_3$ (50 mL) and 4 N aqueous dimethylamine (100 mL) for 24 h at 20 °C. The organic layer was separated, washed well with water, and concentrated to give the crude product (2.5 g, 93%), suitable for direct preparation of compound **284**. A sample of the acridine was refluxed for 1 h with 2 N HCl and neutralized with Na_2CO_3, and the resultant solid was recrystallized from EtOH to give 4-[(dimethylamino)-methyl]-9(10*H*)-acridanone: mp 193–195 °C; 91% yield. Anal. ($C_{16}H_{16}N_2O$) C, H, N.

1-Chloro-4-carboxy-9(10*H*)-acridanone. 5-Chloro-2′-carboxydiphenylamine-2-carboxylic acid (29.1 g, 0.1 mol) was dissolved in concentrated H_2SO_4 (200 mL) and heated at 100 °C for 4 h. The hot mixture was poured very slowly into well-stirred boiling water (2 L), and when cool the precipitated product was collected and washed well with water. Repeated recrystallization from large volumes of EtOH gave the acridanone: mp 300 °C; 66% yield. Anal. ($C_{14}H_8ClNO_3$) C, H, N, Cl.

Preparation of Side Chains. *N*-(4-Acetamidophenyl)-sulfamoylbutane was prepared from equimolar quantities of 4-aminoacetanilide and butanesulfonyl chloride in pyridine, the product crystallizing from EtOH as needles: mp 121–123 °C; 75% yield. Anal. ($C_{12}H_{18}N_2O_3S$) C, H, N, S. The corresponding sulfamoylpentane [mp 131–132 °C; 81% yield. Anal. ($C_{13}H_2O$-N_2O_3S) C, H, N, S] and sulfamoylhexane [mp 109–111 °C; 83% yield. Anal. ($C_{14}H_{22}N_2O_3S$) C, H, N, S] were similarly prepared.

***N*-(4-Aminophenyl)sulfamoylbutane** for the preparation of compound **23** was synthesized by 2 N HCl hydrolysis of the above acetamido compound and was crystallized from EtOH as needles: mp 111–112 °C; 70% yield. Anal. ($C_{10}H_{16}N_2O_2S$) C, H, N. The corresponding sulfamoylpentane [mp 120–121 °C; 75% yield. Anal. ($C_{11}H_{18}N_2O_2S$) C, H, N] for the preparation of compound **24** and sulfamoyl hexane [mp 126–128 °C; 80% yield. Anal. ($C_{12}H_{20}N_2O_2S$) C, H, N] for the preparation of compound **25** were similarly made.

2-Methoxy-5-nitromethanesulfonanilide was prepared by treatment of the appropriate nitromethoxyaniline in pyridine with methanesulfonyl chloride, followed by dilution with water and crystallization of the product from aqueous EtOH to give prisms: mp 164–165 °C; 88% yield. Anal. ($C_8H_{10}N_2O_5S$) C, H, N, S. Similar treatment of appropriate nitroanilines gave 2-methyl-3-nitromethanesulfonanilide [mp 170–171 °C; 83% yield. Anal. ($C_8H_{10}N_2O_4S$) C, H, N, S], 3-methanesulfonamido-5-nitromethanesulfonanilide [mp 222–224 °C; 83% yield. Anal. (C_8-$H_{11}N_2O_6S_1$) C, H, N, S], 3-nitro-4-methylmethanesulfonanilide [mp 157–159 °C; 81% yield. Anal. ($C_8H_{10}N_2O_4S$)], and 2-nitro-4-methanesulfonamidomethanesulfonanilide [mp 189–190 °C; 79% yield. Anal. ($C_8H_{11}N_3O_6S_2$) C, H, N, S]. Reduction of these compounds with Pd/C, H_2 gave the corresponding amino compounds, which were used directly for the preparation of derivatives **27**, **147**, **737**, **738**, and **739**, respectively.

ω-[4-[(4-Aminophenyl)carbamido]phenyl]alkylamines for the preparation of compounds **117–123** were synthesized by the following general procedures.

ω-(4-Nitrophenyl)alkylamine benzenesulfonate salts were prepared by Curtius reaction of the appropriate ω-(4-nitrophenyl)alkanoic acids[8] using $CHCl_3/HN_3$ at 50 °C for 4 h. Addition of 2 equiv of benzenesulfonic acid to the aqueous layer afforded the amine salts, which were recrystallized from water and which had the characteristics shown in Table IV. A mixture of the requisite ω-(4-nitrophenyl)alkylamine (0.02 mol, prepared from the benzenesulfonate salt by partition between 2 N aqueous NaOH and ether) and phthalic anhydride (0.025 mol) in pyridine (12 mL) was stirred at 100 °C until homogeneous and for a further 0.5 h. The solvent was removed in vacuo, AcOH (20 mL) and Ac_2O (2.5 mL) were added, and the mixture was heated under reflux for 1 h. Slow addition of water to the boiling solution gave the crude phthalimides, which were recrystallized from aqueous AcOH. New examples are recorded in Table V.

The above nitro compounds of Table V were hydrogenated over 10% Pd/C in EtOAc–MeOH (1:1). After evaporation of the solvents, the residue was extracted with hot 0.05 N aqueous methanesulfonic acid, and the filtered solutions were treated with excess 4 N aqueous NaOAc to provide the free amines. Crystallization from aqueous AcOH (benzene–petroleum ether for the higher homologues) gave pure material; data for new compounds are recorded in Table VI.

The amines in Table VI (0.02 mol) were dissolved in dry *N*-methylpyrrolidinone–benzene (1:1; 20 mL), and a warm solution of 4-nitrophenyl isocyanate (0.02 mol) in benzene (60 mL) was added through a filter. The resulting solid was stirred at 50 °C for 10 min, and precipitation was completed by dilution with petroleum ether. The products were crystallized from DMF, and the analytical data are given in Table VII.

The preceding phthalimide derivatives (0.02 mol) were suspended in pyridine (30 mL), treated with hydrazine hydrate (98%, 0.04 mol) at 20 °C, and then stirred at 60 °C for 3 h. Solvents were removed in vacuo, and the solid residue was triturated with 4 N NH_4OH, collected, and washed well with water. The residue was then extracted with excess boiling 0.5 N AcOH, and the hot solution was clarified, diluted with half its volume of EtOH, and neutralized with NH_4OH to give the free amine. Recrystallization from aqueous EtOH gave yellow needles: analytical details are given in Table VIII.

Reduction of the nitro compounds in Table VIII with Fe/HCl, filtration of the mixture, evaporation of the filtrate, and extraction of the residue with EtOH gave the requisite side chains for the preparation of compounds **117–123**.

ω-[4-[(4-Aminophenyl)carbamido]phenyl]alkanoic acids for the preparation of compounds **127–131** were elaborated by reaction of 4-nitrophenyl isocyanate with the appropriate ω-(4-aminophenyl)alkanoic acid by the procedure described above. The crude products were dissolved in hot 10% aqueous Na_2CO_3, filtered, and acidified to return the free acid. Crystallization from aqueous EtOH gave the desired products, which had the physical properties listed in Table IX. The potassium salts of the compounds in this table in 40% aqueous CH_3OH were hydrogenated over Pd/C to provide the side chains for the preparation of compounds **127–131**.

4-[(4-Nitrophenyl)carbamido]methanesulfonanilide was prepared from 4-aminomethanesulfonanilide and 4-nitrophenyl isocyanate using procedures described above. The product was recrystallized from hot aqueous DMF as prisms: mp 257–260 °C; 76% yield. Anal. ($C_{14}H_{14}N_4O_5S$) C, H, N, S. Reduction with Fe/HCl gave the side chain for the preparation of compound **132**.

***N′*-[4-[(4-Nitrophenyl)carbamido]phenyl]guanidine hydrochloride** was prepared from 4-[(4-nitrophenyl)carbamido]-aniline and cyanamide by published procedures. Crystallization of the product from aqueous NH_4Cl and then EtOH–H_2O–NH_4Cl gave pale yellow prisms: mp 309–310 °C; 71% yield. Anal. ($C_{14}H_{15}ClN_6O_3$) C, H, N, Cl. Reduction with Fe/HCl gave the side chain for the preparation of compound **133**.

2-Isopropoxy-4-nitroacetanilide. A mixture of sodium 2-acetamido-5-nitrophenate (0.02 mol) and isopropyl iodide (0.03 mol) in DMF (6 mL) was stirred under reflux until the red coloration was discharged. The cooled mixture was shaken well with 2 N aqueous KOH (25 mL), and the collected solid was washed well with water, dissolved in EtOAc, and washed again with 2 N aqueous KOH and water. Solvent removal gave an oil, which solidified on trituration with petroleum ether. Repeated recrystallization from aqueous EtOH gave yellow plates: mp 101–103 °C; yield 52%. Anal. ($C_{11}H_{14}N_2O_4$) C, H, N.

The above compound was hydrogenated in EtOH over Pd/C, the solvent was removed in vacuo, and the air-sensitive product was treated with methanesulfonyl chloride in pyridine to give 4-acetamido-3-isopropoxymethanesulfonanilide. Multiple crystallization from water gave prisms: mp 131–133 °C; 67% yield. Anal. ($C_{16}H_{17}N_3O_5S$) C, H, N, S. Hydrolysis of this product in 2 N HCl–EtOH gave the side chain for compound **627**.

2-(4-Nitrophenyl)-4′-acetamidoethanesulfonanilide was prepared by the reactions of 4-aminoacetanilide (0.05 mol) with 2-(4-nitrophenyl)ethanesulfonyl chloride (0.06 mol) in pyridine (50 mL) at 0 °C for 30 min, followed by dilution with water and crystallization from aqueous EtOH to give needles: mp 211–212 °C; 81% yield. Anal. ($C_{16}H_{17}N_3O_5S$) C, H, N, S. Hydrolysis of the above compound in 2 N HCl gave 2-(4-nitrophenyl)-4′-

aminoethanesulfonanilide as needles from aqueous EtOH: mp 148–149 °C; 70% yield. Anal. ($C_{14}H_{15}N_3O_4S$) C, H, N, S. This side chain was coupled with 9-chloroacridine, and the resultant product was reduced with Fe/HCl to provide compound 674.

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Supplementary Material Available: Calculation of π values for representative side chains by the fragment constant method (15 pages). Ordering information is given on any current masthead page.

Quantitative Structure–Inhibitory Activity Relationships of Phenols and Fatty Acids for *Bacillus subtilis* Spore Germination

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Phenols and fatty acids were found to inhibit L-alanine-initiated germination of *Bacillus subtilis* spores without altering their heat resistance. Inhibitory effect was defined as the concentration necessary to cause 50% inhibition of the germination rate. The quantitative structure–inhibitory activity relationships for 39 phenols and 7 fatty acids were analyzed. The pH dependency of inhibition showed that the nonionized form of the molecule was responsible for inhibition. Hydrophobicity, which was expressed by the partition coefficient or the distribution coefficient of the compounds, was important for inhibition. In addition to hydrophobicity, the electronic effect, which was expressed by the dissociation constant, played a partial role in phenols. The correlation equation of the fatty acids was similar to those of the alcohols and other hydrophobic compounds, which had been reported earlier. That of the phenols, however, appeared to be different, indicating a different and more complex mechanism of inhibition. The type of inhibition by both compounds was mixed rather than competitive or noncompetitive.

Germination of bacterial spores is a sequential process, from a dormant state to a metabolically active vegetative form, in which a number of events take place shortly after exposure of spores to specific germinants. The spore sequentially loses its heat resistance as the earliest event, releases dipicolinic acid, acquires permeability to dyes, releases calcium ions, loses refractility, and shows a decrease in absorbance.[1]

To characterize the nature of the trigger reaction, several kinds of inhibitors of germination have been reported.[2] Our previous studies[3,4] had shown that alcohols and various kinds of hydrophobic compounds inhibited L-alanine-initiated germination of *B. subtilis* spores. The inhibitory activity of these compounds correlated quantitatively with their hydrophobicity, and the hydrophobic character near the L-alanine receptor site was demonstrated.

The present article describes the inhibition of germination of *B. subtilis* spores by some compounds, including phenols and fatty acids, which have an ionizable character in the molecule. Relationships between the chemical structure and inhibitory activity could contribute to a further understanding of the L-alanine receptor site and the mechanism of the trigger reaction of spore germination.

Results

Inhibition of Germination by Phenols at pH 7.2. The inhibitory effect of various concentrations of phenols on the germination rate in 0.1 mM L-alanine is shown in Figure 1. The molar concentration of a phenol necessary to cause 50% inhibition of the germination rate (I_{50}) was determined. The I_{50} values in Table I represent means of three determinations. For hydrophobic parameters, the partition coefficient (log P) according to Hansch and Leo[5] and the distribution coefficient (log D) according to Scherrer and Howard[6] are shown. For the electronic parameter the dissociation constant (pK_a) is shown. The regression analysis for 39 phenols in Table I, except salicylic acid, p-hydroxybenzoic acid, p-aminophenol, and L-tyrosine, is described below, where the figures in parentheses are the Student's t test values, n is the number of compounds submitted to the regression, r is the correlation coefficient, s is the standard deviation, and F is the overall statistical significance of the equation. Log P^0 and log D^0 are the ideal values of log P and log D, respectively, for parabolic dependence with the 95% confidence intervals in parentheses. The relationship between the inhi-

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