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Computer-Automated Structure Evaluation of Antileukemic 9-Anilinoacridines

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SUMMARY

The computer-automated structure evaluation (CASE) program has been applied to the evaluation of antileukemic (L1210) and toxic activities of an extensive series of 9-anilinoacridines. Major molecular fragments relevant to the respective biological endpoints were automatically generated and incorporated within equations used to estimate the degree of activity. Correlations of these activating/inactivating fragments with the biological activities are discussed.

The general class of 9-anilinoacridines is known to possess antineoplastic activity toward murine leukemias. An extensive set of data pertaining to both antitumor activity as well as host toxicity has been gathered by Cain and co-workers (1–16). The biologically significant interaction is believed to involve intercalation of the chromophore between the base pairs of doubly-stranded DNA (15, 17–19). Studies (15, 20) have demonstrated a quantitative correlation between the drugs' binding affinity for DNA and *in vivo* antitumor activity as well as *in vitro* cytotoxic potencies. In addition, it has been observed (21) that long residence times at specific portions of the DNA sequence contribute to increased cytotoxic action. The results of the physical process of intercalation include strand breakage (22–24), inhibition of polymerase progression along the DNA strand (25, 26), and disruption of DNA replication mediated by the topoisomerases (27, 28).

Derivatives of 9-anilinoacridine can be rapidly metabolized within the animal to yield nontoxic as well as tumor-inactive products. Early studies (29–31) had suggested that 9-anilinoacridines undergo nucleophilic attack at the C-9 position by plasma thiols, resulting in the loss of the anilino moiety. A subsequent study (32) has shown, however, that the major metabolic pathway for compounds possessing a secondary amine functionality at the C-1′-position involves microsomal oxidation to the corresponding quinoneimine, which subsequently undergoes glutathione conjugation at the 5′-position. The metabolism of these agents is an important process to be considered since this can become a limiting factor in determining the concentration of tumor-active metabolites *in vivo*.

QSAR studies (12, 16) utilizing the traditional Hansch-Fujita (33) and Free-Wilson (34) methodologies as well as pattern recognition (35) techniques have been performed in hopes of modelling the antineoplastic potency as well as the host toxicity of the 9-anilinoacridine derivatives. It has been established that both biological activities can be successfully correlated with electronic, steric, and lipophilic parameters. No study has been published that can separate, to a high degree of resolution, the toxic properties of the compounds from their therapeutic benefits. In general, toxicity and antitumor potency are intimately linked within the biological action of antineoplastic agents. An encouraging candidate has emerged from the qualitative studies performed by Cain and co-workers (1–16). Amsacrine (NSC 249992) has shown activity against some human leukemias in phase I and phase II clinical trials (36). Minimal activity has been expressed against human solid tumors. Work is being pursued in investigating the antitumor activity of diacridines and triacridines (37). Since the acridine moiety serves as the parent structure, it may be plausible to apply the results obtained in this study concerning substitution patterns to the diacridines and triacridines. Presumably, the mode of interaction of dimeric and trimeric acridines with cellular DNA is similar to that of the monomeric acridines.

We wish to report the results of the application of the CASE program to an extensive series of 9-anilinoacridine derivatives (16) in an attempt to derive a global QSAR modelling both drug potency and host toxicity. The CASE program has been successfully applied (38–41) to a number of biologically active compounds. The CASE methodology differs from traditional QSAR approaches in that the descriptors *automatically* generated by the program are not physicochemical parameters, but represent molecular fragments inherent in a compound's structural composition.

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ABBREVIATIONS: QSAR, quantitative structure-activity relationship; CASE, computer-automated structure evaluation.

Methodology

The outline and philosophy of the CASE methodology have been previously discussed (42). The program requires as input the molecular structures of the compounds to be evaluated together with the experimentally measured values of the biological activity to be studied. The individual structures are coded by use of the Klopman line notation (43). CASE proceeds to "fragment" each molecular structure into units of 3–10 heavy atoms together with their associated hydrogens. Biologically inactive compounds give rise to fragments that are biophobes, whereas biophores are derived from active compounds. Recently, CASE has been revised to accommodate branching at one position along the linear chain of atoms. Furthermore, biologically relevant fragments expanded (differing in one position along the connectivity path) from the parent fragment are also generated. No provisions have been made within the program to account for chirality and *cis/trans* isomerism, although this remains an active area of investigation.

Once all of the fragments are generated, which can easily run into the thousands for a large database consisting of complex molecular structures, that portion of the program devoted to pooling statistically significant fragments is invoked. A binomial distribution is assumed and any considerable deviation from a random distribution of a fragment among the active and inactive molecules is indicative of potential significance to the biological activity being studied. The program is, at this point, capable of qualitatively distinguishing biologically active from inactive compounds based on the presence or absence of statistically relevant fragments. In order to acquire a quantitative estimation of the potency or degree of biological expression, a subset of potential descriptors must be chosen and submitted for a multivariate linear regression analysis. We choose our descriptors by the "family" method. As an initial starting point, a fragment (either biophore or biophobe) is chosen which can classify the greatest number of active and inactive compounds. Subsequent fragments are chosen so as to account for the remaining variance. This procedure culminates in a family of largely uncorrelated fragments which serve as potential variables for the method of linear least squares regression. Fragments are incorporated within a regression equation in a forward stepwise manner until no significant improvement is observed between calculated and actual values. Furthermore, the validity of each variable is established by application of the F partial statistic at the 95% confidence level (44).

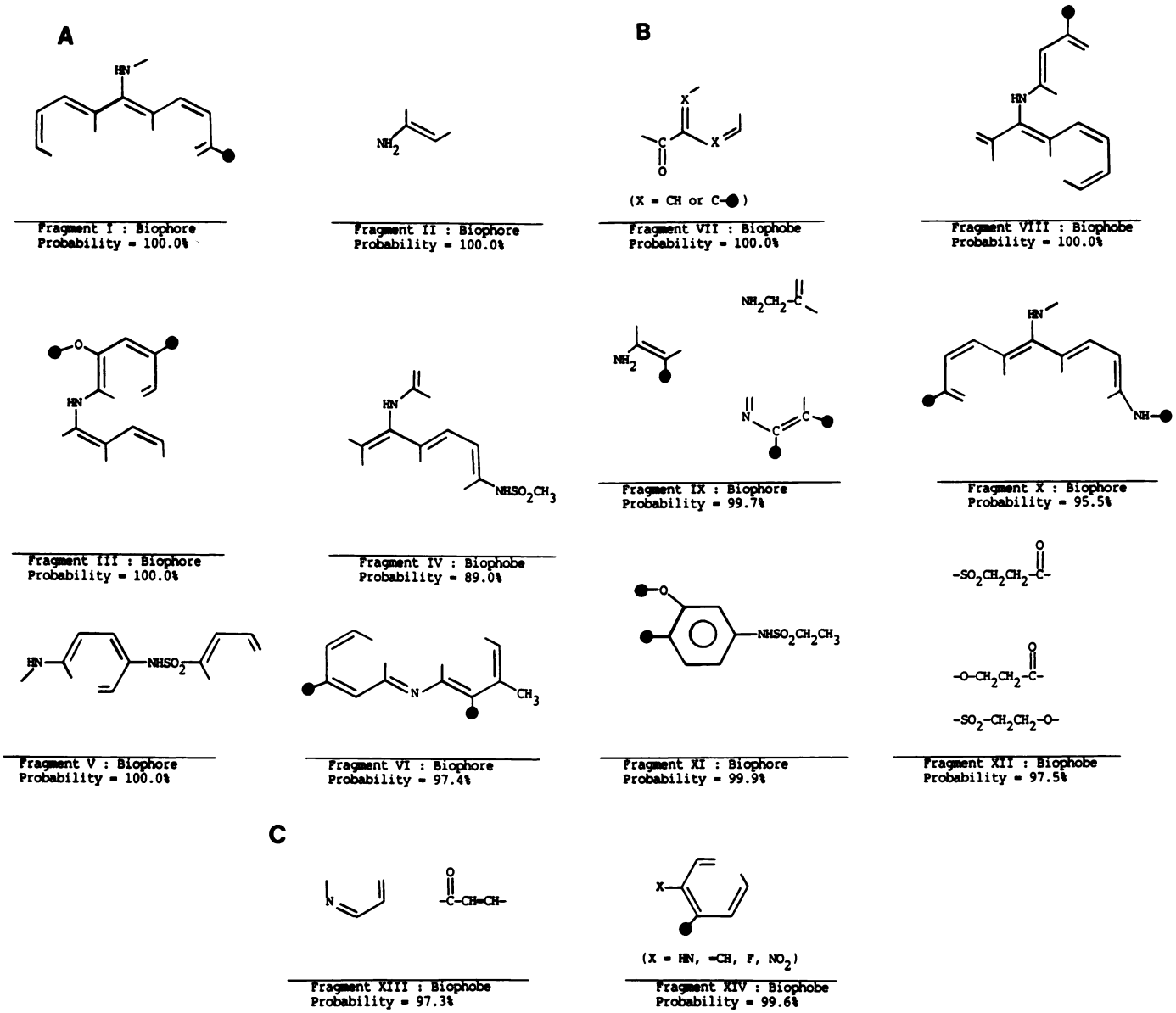
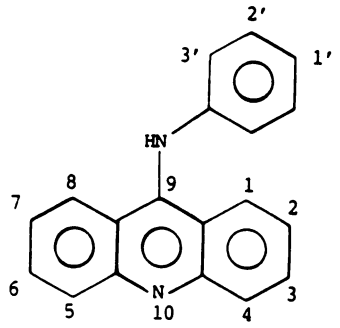


Fig. 1. Fragments used in QSAR equation for estimating $-\text{Log}D_{50}$. ●, a non-hydrogen substituent.

TABLE 1
Compounds evaluated by the CASE methodology



Compound	−LogD$_{50}$[a]			−LogLD$_{10}$[b]		
	Exp.	Calc.[c]	Prob.[d]	Exp.	Calc.[e]	Prob.[f]
			%			%
1. 10-CH_3; 2-NH_2	+	+	83.0	++	++	94.5
2. 10-CH_3; 2-$NHCOCH_3$		*g*		+	−	23.0
3. 3-NH_2	+	+++	96.2	−	++	62.9
4. 10-CH_3; 3-$NHCOCH_3$	++	+	84.0	+	+	44.7
5. 1′-$COOCH_3$	−	−	5.0			
6. 1′-COOH	−	+	84.0	+	+	44.7
7. 3′-OCH_3; 1′-COOH	−	−	5.0	−	−	5.9
8. 3-N_3; 1′-COOH	−	+	21.6			
9. 3-NO_2; 1′-COOH	−	−	21.6	−	−	5.9
10. 3-I; 1′-COOH				−	−	5.9
11. 4-CH_3; 1′-COOH	−	−	5.0	+	−	5.9
12. 4-$OCH_2CH(OH)CH_2OH$; 1′-COOH	−	−	5.0	−	−	5.9
13. 4-$CONH_2$; 1′-COOH	−	−	5.0	−	−	5.9
14. 3-NH_2; 1′-CN	−	+++	96.2			
15. 3-NH_2; 1′-$COCH_3$	+	+	57.4	+	−	60.1
16. 3-NH_2; 1′-SO_2NH_2	++	+++	96.2	++	++	85.0
17. 3-NH_2; 1′-SO_2NHCH_3	++	+++	96.2	++	++	85.0
18. 3-NH_2; 1′-SO_2NHEt	++	+++	96.2	++	++	85.0
19. 3-NH_2; 1′-SO_2NHPr				++	+	85.0
20. 3-NH_2; 1′-SO_2NHBu	+	++	96.2	++	+	85.0
21. 3-NH_2; 1′-SO_2NHPe				++	+	85.0
22. 3-NH_2; 1′-SO_2NHHx				++	+	85.0
23. 1′-OH	−	−	NB[h]	−	+	NB
24. 1′-OCH_3; 2′-$NHSO_2CH_3$	+	−	0.6			
25. 3-NH_2; 1′-OCH_3				++	++	85.0
26. 1′-$O(CH_2)_3COOH$	−	−	1.0	−	−	17.0
27. 1′-$O(CH_2)_4COOH$	−	−	1.0	−	−	17.0
28. 1′-CH_3	−	−	NB	−	+	NB
29. 3′-CH_3				−	−	23.0
30. 1′-CH_2SO_3H	−	+	21.0	−	−	6.0
31. 1′-$CH_2SO_2NH_2$	−	+	21.0	+	−	NB
32. 1′-$(CH_2)_2SO_2NH_2$	−	−	21.0			
33. 4-CH_3; 1′-CH_2COOH				+	−	17.0
34. 4-Et; 1′-CH_2COOH	−	−	21.0	−	−	17.0
35. 1′-$(CH_2)_2COOH$	+	−	21.0	+	−	17.0
36. 3′-OCH_3; 1′-$(CH_2)_2COOH$	+	−	21.0	−	−	17.0
37. 4-CH_3; 1′-$(CH_2)_2COOH$	+	−	21.0			
38. 4-Et; 1′-$(CH_2)_2COOH$				−	−	17.0
39. 1′-$(CH_2)_3COOH$	−	−	21.0			
40. 1′-$(CH_2)_4COOH$	−	−	21.0	+	−	17.0
41. 1′-$(CH_2)_5COOH$	+	−	21.0	−	−	17.0
42. 1′-$(CH_2)_6COOH$	−	−	21.0	+	−	17.0
43. 1′-$(CH_2)_7COOH$	−	−	21.0	+	−	17.0
44. 1′-$(CH_2)_8COOH$	−	−	21.0			
45. 1′-$(CH_2)_9COOH$	−	−	21.0	+	−	17.0

[a] −, less than or equal to 3.88; +, 3.89–4.38; ++, 4.39–4.88; +++, 4.89–5.38; ++++, greater than or equal to 5.39.
[b] −, less than or equal to 3.45; +, 3.46–3.95; ++, 3.96–4.45; +++, 4.46–4.95; ++++, greater than or equal to 4.96.
[c] Based on the occurrence of fragments listed in Fig. 1 and Eq. 1.
[d] Overall probability of being an active antitumor agent, based on fragments with probability $p > 70\%$.
[e] Based on the occurrence of fragments listed in Fig. 2 and Eq. 2.
[f] Overall probability of being host toxic, based on fragments with probability $p > 70\%$.
[g] Compound not included in the training set; used within the test set.
[h] NB, no basis found to support activity, compound is presumed to be inactive.
[i] *x*-Ph-*y*, *x* and *y* are *para* to each other unless specified otherwise.

TABLE 1—*Continued*

Compound	$-LogD_{50}$[a]			$-LogLD_{10}$[b]		
	Exp.	Calc.[c]	Prob.[d]	Exp.	Calc.[e]	Prob.[f]
			%			%
46. 1′-CH(Et)COOH	−	−	NB	−	−	0.0
47. 1′-CH_2CONH_2				+	+	NB
48. 1′-$(CH_2)_2CONH_2$	+	−	21.0	+	+	NB
49. 3′-OCH_3; 1′-$(CH_2)_2CONH_2$	+	−	21.0	+	+	NB
50. 1′-$(CH_2)_3CONH_2$				+	+	NB
51. 1′-$(CH_2)_4CONH_2$	+	−	21.0	+	+	NB
52. 1′-$(CH_2)_5CONH_2$	−	−	21.0	+	+	NB
53. 1′-$(CH_2)_7CONH_2$	−	−	21.0	+	+	NB
54. 1′-$(CH_2)_8CONH_2$				+	+	NB
55. 1′-CH═CHCOOH	−	−	11.0			
56. 1′-CH═CHCONH$_2$				−	+	9.0
57. 1′-CH═NNHCONH$_2$	−	+	NB	−	−	9.0
58. 1′-$(CH═CH)_2$COOH				−	−	0.1
59. 1′-CH═CHPhCOOH′				+	−	0.6
60. 1′-CH═C(CN_2)	−	−	NB	−	+	9.0
61. 1′,2′-(CH═NNH)	−	−	NB	−	−	NB
62. 1′-NH_2				+	++	85.0
63. 10-CH_3; 1′-NH_2	−	+	83.0			
64. 2′-NH_2; 1′-NH_2	+	++	100.0	+	+++	91.0
65. 3′-OCH_3; 1′-NH_2				+	++	85.0
66. 3′-CH_3; 1′-NH_2	+	+	83.0	+	++	85.0
67. 3-NH_2; 1′-NH_2	+++	++++	96.2	++	+++	85.0
68. 3-$NHCOCH_3$; 1′-NH_2	+++	+++	96.2			
69. 4-CH_3; 1′-NH_2	+	+	83.0	+	+	85.0
70. 4-CH_3; 3′-OCH_3; 1′-NH_2				+++	+++	95.3
71. 10-CH_3; 2′-NH_2	−	+	23.8			
72. 2′-NH_2; 5′-CH_3	−	−	3.0			
73. 2′-NH_2	−	+	23.8	+	+	50.0
74. 1′-$NHCH_3$	−	−	NB	+	+	NB
75. 1′-NHEt	−	−	NB	+	+	NB
76. 1′-$N(CH_3)_2$	−	−	NB	+	+	NB
77. 1′-$N(CH_3)COCH_3$	−	−	NB	+	+	NB
78. 1′-$N(CH_2CH_2)_2NCOCH_3$	−	−	NB	−	+	NB
79. 1′-$N(CH_2CH_2)_2NSO_2CH_3$	−	−	NB	−	+	NB
80. 1′-$N(CH_2CH_2)_2NCONH_2$	+	−	NB			
81. 1′,2′-(NHCH═N)				+	−	NB
82. 1′-$NHCOCH_3$	+	−	NB	++	+	NB
83. 10-CH_3; 1′-$NHCOCH_3$				+	+	NB
84. 1′-NHCOEt	−	−	NB	+	+	NB
85. 1′-NHCOBu	−	−	NB	−	+	NB
86. 1′-NHCOPe	−	−	NB	+	+	NB
87. 1′-$NHCOCH(CH_3)_2$	−	−	NB			
88. 1′-$NHCOCH_2CH(CH_3)_2$	+	−	NB	+	+	NB
89. 1′-$NHCO(CH_2)_2CH(CH_3)_2$				+	+	21.0
90. 1′-NHCOCHEt				+	+	NB
91. 1′-NHCO-c-C_5H_9	+	−	NB			
92. 1′-$NHCO(CH_2)_3NHCOCH_3$	−	−	NB	−	+	NB
93. 1′-$NHCOPh(CH_2)_5COOH$	−	−	1.4	−	−	5.2
94. 2′-$NHCOCH_3$	−	−	6.0	+	−	15.0
95. 10-CH_3; 2′-$NHCOCH_3$	−	−	6.0	−	−	15.0
96. 1′-NHCOPh	−	−	5.0	+	−	7.4
97. 3-NH_2; 1′-NHCOPh				+	++	31.0
98. 2-NH_2; 1′-$NHCOPhNH_2$	−	−	20.4	+	+	93.8
99. 1′-$NHCOOCH_3$	+	−	NB	+	−	NB
100. 1′-NHCOOEt				+	+	NB
101. 1′-$NHCOOCH_2CH(OH)CH_2OH$	++	+	NB			
102. 1′-NHNHCOOEt	+	+	NB	++	−	NB
103. 1′-$NHCONHCH_3$				+	−	NB
104. 3′-OCH_3; 1′-$NHCONHCH_3$	+	+	NB			
105. 3′-CH_3; 1′-$NHCONHCH_3$				−	+	NB
106. 1′-$NHCONHNHCOOCH_3$	−	+	NB			
107. 1′-$NHCON(CH_2CH_2)_2NCOOEt$	−	+	NB	+	−	NB
108. 1′-NHCONHPh	−	−	NB	−	−	23.0
109. 1′-$NHCONHPhCH_2NH_2$	++	+	43.1	++	++	94.0
110. 3-NO_2; 1′-$NHCONHPhCH_2NH_2$				++	++	94.0
111. 1′-$NHCONHPh(CH_2)_2NH_2$	++	−	21.0	++	++	87.0
112. 1′-$NHCONHPh(CH_2)_3NH_2$				+	++	87.0
113. 1′-$NHCONHPh(CH_2)_4NH_2$	+	−	21.0	++	++	87.0
114. 1′-$NHCONHPh(CH_2)_5NH_2$	+	−	21.0	+	++	87.0
115. 1′-$NHCONHPh(CH_2)_6NH_2$				++	++	87.0

TABLE 1—*Continued*

Compound	−LogD$_{50}$[a]			−LogLD$_{10}$[b]		
	Exp.	Calc.[c]	Prob.[d]	Exp.	Calc.[c]	Prob.[f]
			%			%
116. 1′-NHCONHPhCH$_2$CH(NH$_2$)COOH	−	−	21.0	−	−	0.0
117. 3-NO$_2$; 1′-NHCONHPhCH$_2$ CH(NH$_2$)COOH				−	−	0.0
118. 1′-NHCONHPhCOOH				+	−	5.9
119. 1′-NHCONHPhCH$_2$COOH	−	−	21.0			
120. 1′-NHCONHPh(CH$_2$)$_2$COOH	+	−	21.0	−	−	17.0
121. 1′-NHCONHPh(CH$_2$)$_3$COOH	−	−	21.0	−	−	17.0
122. 1′-NHCONHPh(CH$_2$)$_4$COOH				+	−	17.0
123. 1′-NHCONHPh(CH$_2$)$_5$COOH	−	−	21.0			
124. 1′-NHCONHPhNHSO$_2$CH$_3$				−	−	NB
125. 1′-NHCONHPhNHC(NH)NH$_2$	++	+	100.0			
126. 3-NO$_2$; 1′-NHCONHPhNHC(NH)NH$_2$	+++	++	84.0	−	−	NB
127. 1′-NHCONHPhNHC(NH)NHC(NH)NH$_2$				++	−	NB
128. 3-NO$_2$; 1′-NHCONHPhNHC(NH)NHC(NH)NH$_2$	+++	++	84.0	+	−	NB
129. 10-CH$_3$; 3-NH$_2$; 1′-NHCONHPhNHC(NH)NHC(NH)NH$_2$	++++	+++	96.2	−	++	85.0
130. 1′-NHCONHPhC(CH$_3$)NNHC(NH)NH$_2$				+	−	50.0
131. 10-CH$_3$; 3-NH$_2$; 1′-NHCONHPhC(CH$_3$)NNHC(NH)NH$_2$	++++	++++	98.6			
132. 1′-N(COCH$_2$CH$_2$SO$_2$)	−	−	1.0	−	+	14.1
133. 1′-N(COOCH$_3$)SO$_2$CH$_3$	−	+	NB	−	−	NB
134. 3-NH$_2$; 1′-N(COOCH$_3$)SO$_2$CH$_3$	++	+++	96.2	+	+++	93.6
135. 1′-N(CH$_3$)SO$_2$CH$_3$	−	−	NB	−	−	NB
136. 1′-NHSO$_2$CH$_2$Cl	−	−	NB	−	+	NB
137. 2′-NHSO$_2$CH$_3$	−	−	6.0			
138. 3′-CH$_3$; 2′-NHSO$_2$CH$_3$				+	−	NB
139. 1′-NHSO$_2$CH$_3$	+	+	NB	+	−	NB
140. 10-CH$_3$; 1-NHSO$_2$CH$_3$				+	−	23.0
141. 1′-NHSO$_2$Et	+	−	NB	−	−	NB
142. 1′-NHSO$_2$Pr	−	−	NB	−	+	NB
143. 1′-NHSO$_2$Bu				−	+	NB
144. 1′-NHSO$_2$Pe	−	−	NB	+	+	NB
145. 1′-NHSO$_2$Hx	−	−	NB	+	+	NB
146. 2′-Aza; 1′-NHSO$_2$CH$_3$	−	+	NB	−	−	NB
147. 2′-NH$_2$; 1′-NHSO$_2$CH$_3$				+	+	91.0
148. 1′,2′-(NHSO$_2$CH$_3$)$_2$	−	−	0.6	−	−	15.0
149. 3′-NH$_2$; 1′-NHSO$_2$CH$_3$	++	++	100.0	++	++	98.3
150. 3′-CH$_3$; 1′-NHSO$_2$CH$_3$	+	−	NB	+	−	NB
151. 3′-OH; 1′-NHSO$_2$CH$_3$				++	−	NB
152. 3′-OCH$_3$; 1′-NHSO$_2$CH$_3$	+++	+	NB	+++	−	NB
153. 10-CH$_3$; 3′-OCH$_3$; 1′-NHSO$_2$CH$_3$	++	+	81.0	++	−	NB
154. 3′-OCH$_3$; 1′-NHSO$_2$Et	+++	+	100.0			
155. 3′-OCH$_3$; 1′-NHSO$_2$Pr				++	+	75.0
156. 3′-OCH$_3$; 1′-NHSO$_2$Bu	+	−	NB	+	+	75.0
157. 3′-OCH$_3$; 1′-NHSO$_2$Pe	+	−	NB	++	+	75.0
158. 3′-OCH$_3$; 1′-NHSO$_2$Hx	+	−	NB	++	+	75.0
159. 3′-OCH$_3$; 1′-NHSO$_2$Hp				+	+	75.0
160. 3′-OCH$_3$; 1′-NHSO$_2$Oct				++	+	75.0
161. 3′-OEt; 1′-NHSO$_2$CH$_3$	+	+	NB			
162. 3′-OCH$_2$CH$_2$OH; 1′-NHSO$_2$CH$_3$	−	+	NB	−	−	NB
163. 2-NH$_2$; 1′-NHSO$_2$CH$_3$	+	++	83.0	++	++	98.3
164. 10-CH$_3$; 2-NH$_2$; 1′-NHSO$_2$CH$_3$	+++	++	83.0	+++	++	98.3
165. 2-NHCOCH$_3$; 1′-NHSO$_2$CH$_3$				−	−	NB
166. 10-CH$_3$; 2-NHCOCH$_3$; 1′-NHSO$_2$CH$_3$				+	−	NB
167. 2-N$_3$; 1′-NHSO$_2$CH$_3$	−	+	NB			
168. 2-N(CH$_3$)$_2$; 1′-NHSO$_2$CH$_3$	−	+	NB	−	−	NB
169. 3-NH$_2$; 1′-NHSO$_2$CH$_3$	++++	+++	96.2			
170. 10-CH$_3$; 3-NH$_2$; 1′-NHSO$_2$CH$_3$				++++	++	85.0
171. 3-NHCH$_3$; 1′-NHSO$_2$CH$_3$	++++	++	84.0	+++	+	73.0
172. 3-NHCOOCH$_3$; 1′-NHSO$_2$CH$_3$	++	++	84.0			
173. 3-N$_3$; 1′-NHSO$_2$CH$_3$	++	++	84.0	++	++	100.0
174. 3-N$_3$(CH$_3$)$_2$; 1′-NHSO$_2$CH$_3$	++++	++	84.0	+++	++	100.0
175. 3-N$_3$(Et)$_2$; 1′-NHSO$_2$CH$_3$	+++	++	84.0	+	++	100.0
176. 3-NHCOCH$_3$; 1′-NHSO$_2$CH$_3$	+++	++	84.0	++	+	73.0
177. 10-CH$_3$; 3-NHCOCH$_3$; 1′-NHSO$_2$CH$_3$	+++	++	84.0	+++	+	73.0
178. 3-NHCOCH$_3$; 1′-NHSO$_2$Et	+++	++	84.0	++	+	73.0
179. 3-NHCOCH$_3$; 1′-NHSO$_2$Pr	+++	++	84.0	++	+	73.0
180. 3-NHCOCH$_3$; 1′-NHSO$_2$Bu				++	+	73.0
181. 3-NHCOCH$_3$; 1′-NHSO$_2$Pe	++	++	84.0			
182. 3-NHCOCH$_3$; 1′-NHSO$_2$Hx	+	++	84.0	++	+	73.0
183. 3-N(CH$_3$)COCH$_3$; 1′-NHSO$_2$CH$_3$	++	++	84.0	++	−	NB
184. 3-NHCOEt; 1′-NHSO$_2$CH$_3$				++	+	73.0
185. 3-NHCOPr; 1′-NHSO$_2$CH$_3$	+	++	84.0	+	+	73.0

TABLE 1—*Continued*

Compound	−LogD$_{50}$[a]			−LogLD$_{10}$[b]		
	Exp.	Calc.[c]	Prob.[d]	Exp.	Calc.[e]	Prob.[f]
			%			%
186. 3-NO_2; 1′-$NHSO_2CH_3$	+++	++	84.0	+++	−	NB
187. 3-NO_2; 1′-$NHSO_2Pr$	++	++	84.0			
188. 3-NO_2; 1′-$NHSO_2Bu$	+	++	84.0	+	+	NB
189. 3-NO_2; 1′-$NHSO_2Hx$	−	+	84.0	+	+	NB
190. 3-OH; 1′-$NHSO_2CH_3$	++	++	84.0	++	−	NB
191. 3-OCH_3; 1′-$NHSO_2CH_3$	+++	++	84.0	++	++	98.0
192. 3-CH_3; 1′-$NHSO_2CH_3$	++	++	84.0	++	++	92.0
193. 3-CH_3; 1′-$NHSO_2Et$				++	++	92.0
194. 3-Cl; 1′-$NHSO_2CH_3$	+	++	84.0	+	+	NB
195. 3-Br; 1′-$NHSO_2CH_3$	+	++	84.0	++	+	99.0
196. 10-CH_3; 3-Br; 1′-$NHSO_2CH_3$	+	++	84.0	+	+	99.0
197. 3-I; 1′-$NHSO_2CH_3$	+	++	84.0	+	+	NB
198. 4-NH_2; 1′-$NHSO_2CH_3$	+	+	83.0			
199. 4-CH_3; 1′-$NHSO_2CH_3$	+	−	NB			
200. 4-CH_2OH; 1′-$NHSO_2CH_3$				+	−	NB
201. 4-Et; 1′-$NHSO_2CH_3$				−	+	NB
202. 4-OCH_3; 1′-$NHSO_2CH_3$	+	+	NB	+	−	NB
203. 4-OEt; 1′-$NHSO_2CH_3$				−	−	NB
204. 4-OPr; 1′-$NHSO_2CH_3$	−	−	NB			
205. 4-$CONH_2$; 1′-$NHSO_2CH_3$	−	+	NB	−	−	NB
206. 3-NO_2; 2′-Aza; 1′-$NHSO_2CH_3$	+	++	84.0	+	−	NB
207. 3-NH_2; 2′-OCH_3; 1′-$NHSO_2CH_3$				−	++	50.0
208. 2-NH_2; 3′-OCH_3; 1′-$NHSO_2CH_3$	+++	++	95.4	+++	++	98.3
209. 2-CH_3; 3′-OCH_3; 1′-$NHSO_2CH_3$	−	+	81.0	−	−	NB
210. 2-$CH(CH_3)_2$; 3′-OCH_3; 1′-$NHSO_2CH_3$				−	+	6.0
211. 2-F; 3′-OCH_3; 1′-$NHSO_2CH_3$	+	+	81.0	+	−	NB
212. 2-I; 3′-OCH_3; 1′-$NHSO_2CH_3$	−	+	81.0	+	+	NB
213. 3-Aza; 3′-OCH_3; 1′-$NHSO_2CH_3$				+	−	NB
214. 3-$NHCOOCH_3$; 3′-OCH_3; 1′-$NHSO_2CH_3$	+++	+++	95.7			
215. 3-$NHSO_2CH_3$; 3′-OCH_3; 1′-$NHSO_2CH_3$	−	−	54.1	−	++	92.0
216. 3-N_3; 3′-OCH_3; 1′-$NHSO_2CH_3$	+++	+++	95.7	+++	++	100.0
217. 3-$N_3(CH_3)_2$; 3′-OCH_3; 1′-$NHSO_2CH_3$	++++	+++	95.7	+++	++	100.0
218. 3-$N_3(CH_3)Pr$; 3′-OCH_3; 1′-$NHSO_2CH_3$	++++	+++	95.7			
219. 3-NH_2; 1′-$N(CH_3)SO_2CH_3$	+++	+++	96.2	++	+++	93.6
220. 3-NH_2; 3′-OCH_3; 1′-$NHSO_2CH_3$	++++	++++	99.1	+++	+++	96.0
221. 3-NH_2; 3′-OCH_3; 1′-$NHSO_2Et$	++++	++++	100.0	++++	+++	98.6
222. 3-NH_2; 3′-CH_3; 1′-$NHSO_2CH_3$				++	++	85.0
223. 3-$NHCH_3$; 3′-OCH_3; 1′-$NHSO_2CH_3$				++++	++	92.0
224. 3-$NHCOCH_3$; 3′-OCH_3; 1′-$NHSO_2CH_3$	++++	+++	95.7	++	++	92.0
225. 3-$NHCOCH_3$; 3′-OCH_3; 1′-$NHSO_2Et$	++++	+++	100.0	+++	++	97.2
226. 3-$NHCOCH_3$; 3′-OCH_3; 1′-$NHSO_2Pr$	+++	+++	95.7	+++	++	97.2
227. 3-$NHCOCH_3$; 3′-OCH_3; 1′-$NHSO_2Bu$	++	+++	95.7			
228. 3-$NHCOCH_3$; 3′-OCH_3; 1′-$NHSO_2Hx$	++	++	95.7	++	++	97.2
229. 3-$NHCOCH_3$; 3′-OCH_3; 1′-$NHSO_2Hp$	++	++	95.7	++	++	97.2
230. 3-$NHCOCH_3$; 3′-CH_3; 1′-$NHSO_2CH_3$	++	++	84.0			
231. 3-$NHCOH_2N$(-$CONHCH_2CO$-); 3′-OCH_3; 1′-$NHSO_2CH_3$	++++	+++	84.0	+++	+	81.0
232. 3-N(-$COCH_2NHCO$-); 3′-OCH_3; 1′-$NHSO_2CH_3$	+++	++	84.0			
233. 3-NO_2; 3′-OCH_3; 1′-$NHSO_2CH_3$	++++	+++	95.7	++++	+	81.0
234. 3-NO_2; 3′-OCH_3; 1′-$NHSO_2Et$				+++	++	92.7
235. 3-NO_2; 3′-OCH_3; 1′-$NHSO_2Pr$	++	++	95.7	+	++	92.7
236. 3-NO_2; 3′-OCH_3; 1′-$NHSO_2Bu$	++	++	95.7	++	++	92.7
237. 3-NO_2; 3′-OCH_3; 1′-$NHSO_2Pe$				++	++	92.7
238. 3-NO_2; 3′-OCH_3; 1′-$NHSO_2Hx$	−	++	95.7	+	++	92.7
239. 3-NO_2; 3′-OCH_3; 1′-$NHSO_2Hp$				−	++	92.7
240. 3-NO_2; 3′-CH_3; 1′-$NHSO_2CH_3$	+	++	84.0			
241. 3-CH_3; 3′-OCH_3; 1′-$NHSO_2CH_3$	++++	+++	95.7	+++	++	98.0
242. 3,3′-$(CH_3)_2$; 1′-$NHSO_2CH_3$	++	++	84.0	+	+	92.0
243. 3-$CH_2CH_2CONH_2$; 3′-OCH_3; 1′-$NHSO_2CH_3$	−	+++	85.6	−	+	81.0
244. 3-$CH(CH_3)_2$; 3′-OCH_3; 1′-$NHSO_2CH_3$	−	++	95.7	−	+	21.4
245. 3,3′-$(OCH_3)_2$; 1′-$NHSO_2CH_3$	+++	+++	95.7	+++	+++	99.5
246. 3-CN; 3′-OCH_3; 1′-$NHSO_2CH_3$				+	+	75.5
247. 3-CF_3; 3′-OCH_3; 1′-$NHSO_2CH_3$	+	+++	95.7			
248. 3-F; 3′-OCH_3; 1′-$NHSO_2CH_3$	++	+++	95.7	++	+	81.0
249. 3-Cl; 3′-OCH_3; 1′-$NHSO_2CH_3$				+++	+	81.0
250. 10-CH_3; 3-C1; 3′-OCH_3; 1′-$NHSO_2CH_3$	++	++	95.7	++	+	81.0
251. 3-Cl; 3′-OCH_3; 1′-$NHSO_2CH_3$	++	+++	100.0	++	++	92.7
252. 10-CH_3; 3-C1; 3′-OCH_3; 1′-$NHSO_2CH_3$	++	++	95.7	+	+	81.0
253. 3-Br; 3′-OCH_3; 1′-$NHSO_2CH_3$	+++	+++	95.7	+++	++	99.8
254. 10-CH_3; 3-Br; 3′-OCH_3; 1′-$NHSO_2CH_3$				+++	++	99.8
255. 3-I; 3′-OCH_3; 1′-$NHSO_2CH_3$	+++	++	95.7	+++	+	81.0

TABLE 1—*Continued*

Compound	−LogD$_{50}$[a]			−LogLD$_{10}$[b]		
	Exp.	Calc.[c]	Prob.[d]	Exp.	Calc.[c]	Prob.[f]
			%			%
256. 4-Aza; 3′-OCH_3; 1′-$NHSO_2CH_3$	+	−	14.0	+	−	NB
257. 4-Aza; 3′-OCH_3; 1′-$NHSO_2Et$				+	+	75.0
258. 4-Aza; 3′-OCH_3; 1′-$NHSO_2Pr$	+	−	14.0			
259. 4-Aza; 3′-OCH_3; 1′-$NHSO_2Bu$	−	−	14.0	+	+	75.0
260. 4-Aza; 3′-OCH_3; 1′-$NHSO_2Pe$				+	+	75.0
261. 4-Aza; 3′-OCH_3; 1′-$NHSO_2Hx$	−	−	14.0	−	+	75.0
262. 4-$NHCOCH_3$; 3′-OCH_3; 1′-$NHSO_2Pr$	+	+	81.0	+	++	91.4
263. 4-NO_2; 3′-OCH_3; 1′-$NHSO_2CH_3$				+	+	78.0
264. 4-CH_3; 3′-OCH_3; 1′-$NHSO_2CH_3$	+++	+	81.0	+++	+	78.0
265. 4-CH_3; 3′-OCH_3; 1′-$NHSO_2Et$	++	++	100.0			
266. 4,3′-$(CH_3)_2$; 1′-$NHSO_2CH_3$				++	+	78.0
267. 4-CH_2OH; 3′-OCH_3; 1′-$NHSO_2CH_3$	+	+	81.0	+	+	78.0
268. 4-CH_2OH; 3′-OCH_3; 1′-$NHSO_2Et$	++	+	81.0	++	+	78.0
269. 4-$(CH_2)_2CONH_2$; 3′-OCH_3; 1′-$NHSO_2CH_3$	+++	++	81.0	+++	+	78.0
270. 4-Ph; 3′-OCH_3; 1′-$NHSO_2CH_3$	−	−	24.0			
271. 4-F; 3′-OCH_3; 1′-$NHSO_2CH_3$				++	+	78.0
272. 4-Cl; 3′-OCH_3; 1′-$NHSO_2CH_3$	+	+	81.0	++	+	78.0
273. 4-Br; 3′-OCH_3; 1′-$NHSO_2CH_3$	+	+	81.0	+	+	78.0
274. 4-CN; 3′-OCH_3; 1′-$NHSO_2CH_3$	+	++	81.0	+	+	78.0
275. 4-OCH_3; 3′-OCH_3; 1′-$NHSO_2CH_3$	+++	+	81.0	+++	+	78.0
276. 4-OCH_3; 3′-OCH_3; 1′-$NHSO_2Et$	++	++	100.0	+++	++	91.4
277. 4-OCH_3; 3′-OCH_3; 1′-$NHSO_2Pr$	++	+	81.0	++	++	91.4
278. 4-OCH_3; 3′-OCH_3; 1′-$NHSO_2Bu$	++	+	81.0			
279. 4-OEt; 3′-OCH_3; 1′-$NHSO_2CH_3$				++	+	78.0
280. 4-OPr; 3′-OCH_3; 1′-$NHSO_2CH_3$	++	+	81.0	++	+	78.0
281. 4-OBu; 3′-OCH_3; 1′-$NHSO_2CH_3$	++	+	81.0	++	+	78.0
282. 4-OBu; 3′-OCH_3; 1′-$NHSO_2Pr$	+	+	81.0	++	++	91.4
283. 4-OCH_2COOH; 3′-OCH_3; 1′-$NHSO_2CH_3$	+	++	81.0	−	+	42.1
284. 4-$OCH_2CONHCH_3$; 3′-OCH_3; 1′-$NHSO_2CH_3$	++	++	81.0			
285. 4-OCH_2CH_2OH; 3′-OCH_3; 1′-$NHSO_2CH_3$	+++	++	81.0			
286. 4-$OCH_2CH(OH)CH_2OH$; 3′-OCH_3; 1′-$NHSO_2CH_3$				++	+	78.0
287. 4-$OCH_2CH(OH)CH_2OH$; 3′-OCH_3; 1′-$NHSO_2Et$	++	++	81.0	+	+	78.0
288. 4-$O(CH_2)_3CONH_2$; 3′-OCH_3; 1′-$NHSO_2CH_3$	+++	++	81.0	++	+	78.0
289. 4-$CONH_2$; 3′-CH_3; 1′-$NHSO_2CH_3$				−	+	78.0
290. 4-$CONH_2$; 3′-OCH_3; 1′-$NHSO_2Et$	++	++	100.0	++	++	91.4
291. 4-$CONH_2$; 3′-OCH_3; 1′-$NHSO_2Pr$	++	+	81.0	++	++	91.4
292. 4-$CONH_2$; 3′-OCH_3; 1′-$NHSO_2Bu$	+	+	81.0	+	++	91.4
293. 4-$CONH_2$; 3′-OCH_3; 1′-$NHSO_2Pe$				+	++	91.4
294. 4-$CONH_2$; 3′-OCH_3; 1′-$NHSO_2Hx$	+	+	81.0	+	++	91.4
295. 4-$CONH_2$; 3′-OCH_3; 1′-$NHSO_2Hp$	−	+	81.0	−	++	91.4
296. 4-$CONHCH_3$; 3′-OCH_3; 1′-$NHSO_2CH_3$	++	++	81.0			
297. 4-CONHBu; 3′-OCH_3; 1′-$NHSO_2CH_3$				+	+	78.0
298. 4-CONHBu; 3′-OCH_3; 1′-$NHSO_2Pr$	−	+	81.0	+	++	91.4
299. 4-$CONH(CH_2)_2OH$; 3′-OCH_3; l′-$NHSO_2CH_3$				++	+	78.0
300. 4-$CONHCH_2CH(OH)CH_3$; 3′-OCH_3; 1′-$NHSO_2CH_3$	+++	++	81.0	+	+	78.0
301. 4-$CONH(CH_2)_3OH$; 3′-OCH_3; l′-$NHSO_2CH_3$	++	++	81.0	+	+	78.0
302. 4-$CONHCH_2CH(OH)CH_2OH$; 3′-OCH_3; 1′-$NHSO_2CH_3$	+	++	81.0			
303. 4-$CONHCH_2CONH_2$; 3′-OCH_3; 1′-$NHSO_2CH_3$				+	+	78.0
304. 4-$CONHCH_2CONHCH_3$; 3′-OCH_3; 1′-$NHSO_2CH_3$	++	++	81.0	+	+	78.0
305. 4-$CONH(CH_2)_6OSO_2CH_3$; 3′-OCH_3; l′-$NHSO_2CH_3$	+	++	81.0	−	+	78.0
306. 4-$CONHCH_2CONH(CH_2)_2NH$-$(CH_2)_2OH$; 3′-OCH_3; 1′-$NHSO_2CH_3$				+	+	78.0
307. 4-$CON(CH_3)_2$; 3′-OCH_3; 1′-$NHSO_2CH_3$	++	+	81.0			
308. 4-$CON(CH_2CH_2)_2O$; 3′-OCH_3; 1′-$NHSO_2CH_3$	−	+	NB	−	−	NB
309. 2,6-$(NH_2)_2$; 1′-$NHSO_2CH_3$	+++	+++	83.0	+++	+++	98.3
310. 2-NH_2; 6-Cl; 1′-$NHSO_2CH_3$	+	++	83.0	+	++	98.3
311. 3-NH_2; 4-CH_3; 1′-$NHSO_2CH_3$	++++	+++	100.0	+++	++	98.3
312. 3-$NHCOCH_3$; 4-CH_3; 1′-$NHSO_2CH_3$	++	++	84.0	++	+	73.0
313. 3-NHCHO; 4-CH_3; 1′-$NHSO_2CH_3$				++++	+	73.0
314. 3-NO_2; 4-CH_3; 1′-$NHSO_2CH_3$				+	−	NB
315. 3,4-$(CH_3)_2$; 1′-$NHSO_2CH_3$	++	++	84.0	+	+	NB
316. 3,4-$(OCH_3)_2$; 1′-$NHSO_2CH_3$				−	−	NB
317. 3-NH_2; 5-CH_3; 1′-$NHSO_2CH_3$	++++	+++	96.2			
318. 3-NH_2; 5-OCH_3; 1′-$NHSO_2CH_3$	++++	+++	96.2	++++	++	85.0
319. 3-$NHCH_3$; 5-CH_3; 1′-$NHSO_2CH_3$	++++	++	84.0	++++	+++	99.6
320. 3-$NHCOCH_3$; 5-CH_3; 1′-$NHSO_2CH_3$	++++	++	84.0	+++	+++	99.6
321. 3-$NHCOCH_3$; 5-OCH_3; 1′-$NHSO_2CH_3$	+++	++	84.0			
322. 3-NO_2; 5-CH_3; 1′-$NHSO_2CH_3$	+	++	84.0			
323. 3-NO_2; 5-CH_3; 1′-$NHSO_2Et$				+	+	NB
324. 3-NO_2; 5-OCH_3; 1′-$NHSO_2CH_3$	+	++	84.0	−	−	NB

TABLE 1—*Continued*

Compound	$-\text{Log}D_{50}$[a]			$-\text{Log}LD_{10}$[b]		
	Exp.	Calc.[c]	Prob.[d]	Exp.	Calc.[c]	Prob.[f]
			%			%
325. 3,5-$(CH_3)_2$; 1′-$NHSO_2CH_3$	+++	++	84.0	+++	++	92.0
326. 3,5-$(CH_3)_2$; 1′-$NHSO_2Et$	++	++	84.0	+++	++	92.0
327. 3-OCH_3; 5-CH_3; 1′-$NHSO_2CH_3$	+++	++	84.0	++	++	98.0
328. 3-Cl; 5-CH_3; 1′-$NHSO_2CH_3$				+	+	NB
329. 3-Cl; 5-OCH_3; 1′-$NHSO_2CH_3$	+	++	84.0	−	−	NB
330. 3-I; 5-OCH_3; 1′-$NHSO_2CH_3$	++	++	84.0	+	+	NB
331. 3,6-$(NH_2)_2$; 1′-$NHSO_2CH_3$	++++	+++	83.0	++++	+++	85.0
332. 3-NH_2; 6-NO_2; 1′-$NHSO_2CH_3$	++	++	83.0	+++	+++	98.9
333. 3-NH_2; 6-OCH_3; 1′-$NHSO_2CH_3$	+++	++	83.0			
334. 3,6-$(NHCOCH_3)_2$;1′-$NHSO_2CH_3$	++	++	86.0	−	−	NB
335. 3-$NHCOCH_3$; 6-NO_2; 1′-$NHSO_2CH_3$	++++	+	86.0			
336. 3-$NHCOCH_3$; 6-OCH_3; 1′-$NHSO_2CH_3$				−	−	NB
337. 3-$NHCOCH_3$; 6-Cl; 1′-$NHSO_2CH_3$	−	+	86.0	−	−	NB
338. 3-NO_2; 6-OCH_3; 1′-$NHSO_2CH_3$	+	+	NB	−	−	NB
339. 3,6-$(N_3)_2$; 1′-$NHSO_2CH_3$	+	++	NB	++	+++	100.0
340. 3,6-$(OCH_3)_2$; 1′-$NHSO_2CH_3$				+	−	NB
341. 3-Cl; 6-OCH_3; 1′-$NHSO_2CH_3$	−	−	NB	−	−	NB
342. 3,6-$(Br)_2$; 1′-$NHSO_2CH_3$	−	−	NB			
343. 4,5-$(CH_3)_2$; 1′-$NHSO_2CH_3$	−	−	NB	+	+	NB
344. 2-NH_2; 3-Br; 3′-OCH_3; 1′-$NHSO_2CH_3$				++	++	98.3
345. 2-NH_2; 3-CF_3; 3′-OCH_3; 1′-$NHSO_2CH_3$	++	+++	100.0	++	++	98.3
346. 3,4,3′-$(CH_3)_3$; 1′-$NHSO_2CH_3$	++	++	84.0			
347. 3,4-$(CH_3)_2$; 3′-OCH_3; 1′-$NHSO_2CH_3$	+++	+++	95.7	+++	+	81.0
348. 3,4-Benz; 3′-OCH_3; 1′-$NHSO_2CH_3$	++	−	NB			
349. 3,4-(CH═CHCH═N); 3′-OCH_3; 1′-$NHSO_2CH_3$				+++	−	NB
350. 3-Cl; 4-CH_3; 3′-OCH_3; 1′-$NHSO_2CH_3$	++	++	95.7	+++	+	81.0
351. 2-NH_2; 6-NO_2; 3′-OCH_3; 1′-$NHSO_2CH_3$	+++	++	95.4	++	++	99.6
352. 2-NH_2; 6-I; 3′-OCH_3; 1′-$NHSO_2CH_3$	++++	++	95.4	++	++	99.6
353. 3-NH_2; 5-CH_3; 3′-OCH_3; 1′-$NHSO_2CH_3$	++++	++++	99.1	++++	++++	98.8
354. 3-$NHCH_3$; 5-CH_3; 3′-OCH_3; 1′-$NHSO_2CH_3$	++++	+++	95.7	++++	++++	100.0
355. 3-N_3; 5-CH_3; 3′-OCH_3; 1′-$NHSO_2CH_3$	+++	+++	95.7	+++	+++	100.0
356. 3-NO_2; 5,3′-$(CH_3)_2$; 1′-$NHSO_2CH_3$	+	++	84.0			
357. 3-NO_2; 5,3′-$(OCH_3)_2$; 1′-$NHSO_2CH_3$	+++	+++	95.7	++	++	93.8
358. 3-NO_2; 5-CH_3; 3′-OCH_3; 1′-$NHSO_2Et$	+++	+++	100.0	+++	++	97.8
359. 3-NO_2; 5-CH_3; 3′-OCH_3; 1′-$NHSO_2CH_3$	+++	+++	95.7	+++	++	93.8
360. 3,5,3′-$(CH_3)_3$; 1′-$NHSO_2CH_3$	++	++	84.0	++	++	97.6
361. 3,5-$(CH_3)_2$; 3′-OCH_3; 1′-$NHSO_2CH_3$	+++	+++	95.7	++++	+++	99.4
362. 3-CH_3; 5-OCH_3; 3′-OCH_3; 1′-$NHSO_2CH_3$	+++	+++	95.7	+++	+++	99.4
363. 3-OCH_3; 5-CH_3; 3′-OCH_3; 2′-$NHSO_2CH_3$	++++	++	84.0	++++	+++	99.9
364. 3-Cl; 5-CH_3; 3′-OCH_3; 1′-$NHSO_2CH_3$	+++	++	95.7			
365. 3-Cl; 5,3′-$(OCH_3)_2$; 1′-$NHSO_2CH_3$	++	+++	95.7	+++	++	93.8
366. 3-Br; 5-CH_3; 3′-OCH_3; 1′-$NHSO_2CH_3$	+++	+++	95.7	+++	+++	99.9
367. 3-Br; 5-OCH_3; 3′-OCH_3; 1′-$NHSO_2CH_3$				+++	+++	99.9
368. 3-I; 5-CH_3; 3′-OCH_3; 1′-$NHSO_2CH_3$	+++	++	95.7	+++	++	93.8
369. 3-I; 5,3′-$(OCH_3)_2$; 1′-$NHSO_2CH_3$	+++	++	95.7			
370. 3-I; 5-$OCH_2CH(OH)CH_2OH$; 3′-OCH_3; 1′-$NHSO_2CH_3$	+++	+++	95.7	+	++	93.8
371. 3,6-$(NHCOCH_3)_2$; 3′-OCH_3; 1′-$NHSO_2CH_3$	+	+++	96.3	++	++	81.0
372. 3-NO_2; 6-CH_3; 3′-OCH_3 1′-$NHSO_2CH_3$	+++	+	81.0	++	+++	98.0
373. 3-Cl; 6-OCH_3; 3′-OCH_3; 1′-$NHSO_2CH_3$				++	++	81.0
374. 3,6-Cl_2; 3′-OCH_3; 1′-$NHSO_2CH_3$	+	+	81.0	+	++	81.0
375. 3,6-Br_2; 3′-OCH_3; 1′-$NHSO_2CH_3$	−	+	81.0	−	++	81.0
376. 4,5,3′-$(CH_3)_3$; 1′-$NHSO_2CH_3$	−	−	NB			
377. 4,5-$(CH_3)_2$; 3′-OCH_3; 1′-$NHSO_2CH_3$	++	+	81.0	+	++	78.0
378. 4,5-$(CH_3)_2$; 3′-OCH_3; 1′-$NHSO_2Et$	++	++	100.0	++	++	91.4
379. 4,5-$(OCH_3)_2$; 3′-OCH_3; 1′-$NHSO_2CH_3$	++	++	81.0	+++	++	78.0
380. 2-NH_2; 3-Br; 5-CH_3; 1′-$NHSO_2CH_3$	++	++	100.0			
381. 3-NH_2; 4,5-$(CH_3)_2$; 1′-$NHSO_2CH_3$				++++	++	98.3
382. 3-$NHCOCH_3$; 4,5-$(CH_3)_2$; 1′-$NHSO_2CH_3$	++	++	84.0	++	+	73.0
383. 3-NO_2; 4,6-$(CH_3)_2$; 1′-$NHSO_2CH_3$	−	−	NB			
384. 3-NH_2; 5,6-$(CH_3)_2$; 1′-$NHSO_2CH_3$	++++	+++	97.3	+++	++	85.0
385. 3-$NHCH_3$; 5,6-$(CH_3)_2$; 1′-$NHSO_2CH_3$	+++	++	97.8	+++	++	99.0
386. 3-NO_2; 5,6-$(CH_3)_2$; 1′-$NHSO_2CH_3$	++	+	88.0	−	+	NB
387. 3,4,5-$(CH_3)_3$; 1′-$NHSO_2CH_3$	++	++	84.0	−	+	NB
388. 3,4,6-$(CH_3)_3$; 1′-$NHSO_2CH_3$	+	+	88.0			
389. 2-NH_2; 3-Br; 5-CH_3; 3′-OCH_3; 1′-$NHSO_2CH_3$	+++	++	100.0	++	+++	99.5
390. 3-NH_2; 4,5-$(CH_3)_2$; 3′-OCH_3; 1′-$NHSO_2CH_3$	++++	++++	100.0	++++	++++	99.9
391. 3,4,5-$(CH_3)_3$; 3′-OCH_3; 1′-$NHSO_2CH_3$	++	++	95.7	++	++	93.8
392. 3-NO_2; 5,6-$(CH_3)_2$; 3′-OCH_3; 1′-$NHSO_2Et$	++	+++	100.0			
393. 3-NH_2; 5,6-$(CH_3)_2$; 3′-OCH_3; 1′-$NHSO_2Et$	++++	++++	100.0	++++	+++	98.6
394. 3-$NHCH_3$; 5,6-$(CH_3)_2$; 3′-OCH_3; 1′-$NHSO_2CH_3$	++++	+++	99.5			

TABLE 1—*Continued*

Compound	−LogD$_{50}$[a]			−LogLD$_{10}$[b]		
	Exp.	Calc.[c]	Prob.[d]	Exp.	Calc.[c]	Prob.[f]
			%			%
395. 3-NO_2; 5,6-$(CH_3)_2$; 3′-CH_3; 1′-$NHSO_2CH_3$	−	+	88.0	−	+	NB
396. 3-NO_2; 5,6-$(CH_3)_2$; 3′-OCH_3; 1′-$NHSO_2CH_3$				++	++	81.0
397. 3,4,6-$(CH_3)_3$; 3′-OCH_3; 1′-$NHSO_2CH_3$	+++	++	96.9	+++	+++	98.0
398. 3-NO_2; 1′-$NHSO_2(CH_2)_2NHCHO$	+	++	84.0	−	−	NB
399. 1′-$NHSO_2(CH_2)_2NHCOCH_3$				+	−	NB
400. 1′-$NHSO_2(CH_2)_2N(CH_3)COCH_3$				−	−	13.0
401. 3-NO_2; 1′-$NHSO_2(CH_2)_2NHCOCH(CH_3)NH_2$	+	++	84.0			
402. 1′-$NHSO_2(CH_2)_2NHCOOCH_3$				−	−	NB
403. 1′-$NHSO_2(CH_2)_2NHCONH_2$	−	+	NB	−	−	NB
404. 3,5-$(CH_3)_2$; 1′-$NHSO_2(CH_2)_2NHCONH_2$				+	++	92.0
405. 1′-$NHSO_2(CH_2)_2NHSO_2CH_3$	−	+	NB	+	−	NB
406. 1′-$NHSO_2(CH_2)_2N(CONHCH_2CO)$				−	−	13.0
407. 1′-$NHSO_2(CH_2)_2OCH_3$	−	−	24.0	−	−	25.0
408. 1′-$NHSO_2(CH_2)_2CONH_2$	−	−	1.0			
409. 1′-$NHSO_2(CH_2)_2CON(CH_3)_2$	−	−	1.0	−	−	6.0
410. 1′-$(CH_2)_3NHSO_2CH_3$				+	+	NB
411. 3-NO_2; 1′-$NHSO_2(CH_2)_2NHCHO$	+	++	84.0	−	−	NB
412. 1′-$NHSO_2(CH_2)_2NHCOCH_2NH_2$	−	+	NB			
413. 3-NO_2; 1′-$NHSO_2(CH_2)_2NHCOCH_2NH_2$	+	++	84.0	−	−	NB
414. 3-NO_2; 1′-$NHSO_2(CH_2)_2NHCO(CH_2)_2NH_2$	++	++	84.0	+	+	87.0
415. 3-NO_2; 1′-$NHSO_2(CH_2)_2NH_2$	+	++	84.0	++	++	87.0
416. 10-CH_3; 3-NH_2; 1′-$NHSO_2(CH_2)_2NH_2$	+++	+++	96.2			
417. 3-NO_2; 1′-$NHSO_2(CH_2)_3NH_2$				++	++	87.0
418. 10-CH_3; 1′-$NHSO_2(CH_2)_4NH_2$	+	−	99.0	++	++	87.0
419. 10-CH_3; 3-NH_2; 1′-$NHSO_2(CH_2)_4NH_2$	++++	+++	100.0	++	+++	97.4
420. 3-$NHCOCH_3$; 1′-$NHSO_2(CH_2)_4NH_2$	++	++	99.8	++	++	94.8
421. 3-NO_2; 1′-$NHSO_2(CH_2)_4NH_2$	++	++	99.8	+	++	87.0
422. 4,5-$(CH_3)_2$; 1′-$NHSO_2(CH_2)_4NH_2$	++	−	99.0	++	++	87.0
423. 3-NO_2; 3′-OCH_3; 1′-$NHSO_2(CH_2)_4NH_2$	+++	+++	100.0	++++	+++	98.8
424. 3-NO_2; 5,6-$(CH_3)_2$; 1′-$NHSO_2(CH_2)_4NH_2$				++	++	87.0
425. 3-NO_2; 1′-$NHSO_2(CH_2)_4N(CH_3)_2$	++	++	84.0			
426. 3-NO_2; 1′-$NHSO_2(CH_2)_5NH_2$	++	++	84.0			
427. 3-NO_2; 1′-$NHSO_2(CH_2)_6NH_2$	++++	++	84.0	++++	++	87.0
428. 3-NO_2; 1′-$NHSO_2(CH_2)_7NH_2$	+	+	84.0	++	++	87.0
429. 3-NO_2; 1′-$NHSO_2(CH_2)_2NHC(NH)NH_2$	++	++	84.0	++	−	NB
430. 3-NO_2; 3′-OCH_3; 1′-$NHSO_2(CH_2)_2NHC(NH)NH_2$	+	+++	95.7	+	++	92.7
431. 3-$NHCOCH_3$; 6-NO_2;1′-$NHSO_2(CH_2)_2NHC(NH)NH_2$	++++	++	86.0	++	++	94.0
432. 10-CH_3; 3-NH_2; 1′-$NHSO_2(CH_2)_3NHC(NH)NH_2$	+++	+++	96.2	++	++	85.0
433. 3-NO_2; 1′-$NHSO_2(CH_2)_3NHC(NH)NH_2$	++	++	84.0	+	−	NB
434. 2,6-$(NH_2)_2$; 1′-$NHSO_2(CH_2)_3NHC(NH)NH_2$				++	++	98.3
435. 3-$NHCOCH_3$; 6-NO_2; 1′-$NHSO_2(CH_2)_3NHC(NH)NH_2$	+++	++	86.0	++	++	94.0
436. 10-CH_3; 3-NH_2; 1′-$NHSO_2(CH_2)_4NHC(NH)NH_2$	++++	+++	96.2	+++	++	85.0
437. 3-NO_2; 1′-$NHSO_2(CH_2)_4NHC(NH)NH_2$	++	++	84.0	+	−	NB
438. 4,5-$(CH_3)_2$; 1′-$NHSO_2(CH_2)_4NHC(NH)NH_2$	−	+	NB	+	−	NB
439. 3-NO_2; 1′-$NHSO_2(CH_2)_5NHC(NH)NH_2$	++	++	84.0			
440. 3-NO_2; 1′-$NHSO_2(CH_2)_6NHC(NH)NH_2$				+	−	NB
441. 1′-$NHSO_2Ph$	++	++	94.0	+	−	23.0
442. 2-NH_2; 1′-$NHSO_2Ph$	++	+++	98.7	−	++	62.9
443. 3-NO_2; 1′-$NHSO_2Ph$				−	−	23.0
444. 4-CH_3; 1′-$NHSO_2Ph$	+	+	94.0	++	−	23.0
445. 3-$NHCOCH_3$; 5-CH_3; 1′-$NHSO_2Ph$	+++	+++	98.8	++	++	98.8
446. 1′-$NHSO_2PhNH_2$	++++	++	98.7	+++	+	85.0
447. 2′-Aza; 1′-$NHSO_2PhNH_2$	++	++	83.0	++	++	85.0
448. 3′-CH_3; 1′-$NHSO_2PhNH_2$	++++	++	98.7	++	++	85.0
449. 3′-OCH_3; 1′-$NHSO_2PhNH_2$	++++	++	98.7	++++	+	85.0
450. 3-NH_2; 1′-$NHSO_2PhNH_2$	++++	++++	99.8	++++	+++	85.0
451. 3-Cl; 1′-$NHSO_2PhNH_2$	++++	++++	99.8	+++	++	85.0
452. 4-CH_3; 3′-OCH_3; 1′-$NHSO_2PhNH_2$	+++	++	98.7	++	+++	95.3
453. 4-CH_3; 3′-OCH_3; 1′-$NHSO_2PhNH_2$	++++	+++	99.7	++++	+++	95.3
454. 3-Cl; 5-CH_3; 1′-$NHSO_2PhNH_2$	++	++++	99.8	++	++	85.0
455. 4,5-$(CH_3)_2$; 1′-$NHSO_2PhNH_2$	++	+++	98.7	++	++	85.0
456. 1′-$NHSO_2PhNHCOCH_3$				−	+	NB
457. 3-NO_2; 1′-$NHSO_2Ph$-*m*-$NHC(NH)NH_2$	++	+++	98.8			
458. 3-NO_2; 1′-$NHSO_2PhNO_2$	++	+++	98.8	−	+	NB
459. 3-$NHCOCH_3$; 5-CH_3; 1′-$NHSO_2PhCH_3$	+++	+++	98.8	+	+++	99.6
460. 1′-$NHSO_2PhCOOH$	+	−	45.2	−	−	5.9
461. 3-NO_2; 1′-$NHSO_2PhCONHCH_3$				++	+	21.0
462. 1′-$NHSO_2PhSO_2CH_3$	+	++	94.0			
463. 1′-$N(COCH_3)SO_2CH_3$	+	+	99.0	−	−	NB
464. 1′-$N(COEt)SO_2CH_3$	−	−	NB	−	−	NB

TABLE 1—*Continued*

Compound	$-\text{Log}D_{50}$[a]			$-\text{Log}LD_{10}$[b]		
	Exp.	Calc.[c]	Prob.[d]	Exp.	Calc.[e]	Prob.[f]
			%			%
465. 1′-N(COPr)SO_2CH_3	−	−	NB			
466. 1′-N(COBu)SO_2CH_3				−	+	NB
467. 1′-N(COPe)SO_2CH_3	−	−	NB	−	+	NB
468. 1′-N(COHx)SO_2CH_3	−	−	NB	−	+	NB
469. 1′-N(COHp)SO_2CH_3				−	+	NB
470. 1′-N(CO-Oct)SO_2CH_3				−	−	NB
471. 3′-OCH_3; 1′-N($COCH_3$)SO_2CH_3	+++	+	99.0	+++	+	72.0
472. 3-NH_2; 1′-N($COCH_3$)SO_2CH_3	++++	+++	100.0	++++	+++	93.6
473. 3-NH_2; 1′-N(COEt)SO_2CH_3	+++	+++	96.2			
474. 3-NH_2; 1′-N(COPr)SO_2CH_3	++++	+++	96.2	++++	+++	93.6
475. 3-NH_2; 1′-N(COBu)SO_2CH_3	++++	+++	96.2	++++	+++	93.6
476. 3-NH_2; 1′-N(COPe)SO_2CH_3	+++	+++	96.2	++++	+++	93.6
477. 3-NH_2; 1′-N(COHx)SO_2CH_3	+++	+++	96.2	++++	+++	93.6
478. 3-NH_2; 1′-N(COHp)SO_2CH_3	++++	+++	96.2	++++	+++	93.6
479. 3-NH_2; 1′-N(CO-Oct)SO_2CH_3	++++	+++	96.2	++++	+++	93.6
480. 3-$NHCOCH_3$; 1′-N($COCH_3$)SO_2CH_3	++	++	99.8	++	++	87.4
481. 3-$NHCOCH_3$; 1′-N(COEt)SO_2CH_3	+++	++	84.0	++	++	87.4
482. 3-$NHCOCH_3$; 1′-N(COPr)SO_2CH_3	++	++	84.0			
483. 3-$NHCOCH_3$; 1′-N(COBu)SO_2CH_3	+++	++	84.0	+	++	87.4
484. 3-$NHCOCH_3$; 1′-N(COPe)SO_2CH_3	++	++	84.0	+	++	87.4
485. 3-$NHCOCH_3$; 1′-N(COHx)SO_2CH_3	++	++	84.0	++	++	87.4
486. 3-$NHCOCH_3$; 1′-N(COHp)SO_2CH_3				+	++	87.4
487. 3-$NHCOCH_3$; 1′-N(CO-Oct)SO_2CH_3	+++	+	84.0	+	++	87.4
488. 3-$NHCOCH_3$; 1′-N(COC_9H_{19})SO_2CH_3	++	+	84.0	+	++	87.4
489. 3-$NHCOCH_3$; 1′-N($COC_{10}H_{21}$)SO_2CH_3	++	+	84.0			
490. 3-$NHCOCH_3$; 1′-N($COC_{11}H_{23}$)SO_2CH_3	++	+	84.0	++	++	87.4
491. 3-$NHCOCH_3$; 1′-N[$COCH(CH_3)_2$]SO_2CH_3	++	++	84.0	+	++	87.4
492. 3-$NHCOCH_3$; 1′-N[$COCH(CH_3)$Et]SO_2CH_3				+	++	87.4
493. 3-NO_2; 1′-N($COCH_3$)SO_2CH_3	+++	++	99.8			
494. 3-NO_2; 1′-N(COEt)SO_2CH_3	++	++	84.0	+	+	72.0
495. 3-NO_2; 1′-N(COPr)SO_2CH_3	+	++	84.0	−	+	72.0
496. 3-NO_2; 1′-N(COBu)SO_2CH_3	++	++	84.0	++	+	72.0
497. 3-NO_2; 1′-N(COPe)SO_2CH_3	++	+	84.0			
498. 3-NO_2; 1′-N(COHx)SO_2CH_3	++	+	84.0	++	+	72.0
499. 3-NO_2; 1′-N(COHp)SO_2CH_3	++	+	84.0	+++	+	72.0
500. 3-NO_2; 1′-N(CO-Oct)SO_2CH_3				+	+	72.0
501. 3-NO_2; 5-CH_3; 1′-N($COCH_3$)SO_2CH_3				−	+	72.0
502. 3-NO_2; 5-CH_3; 1′-N(COEt)SO_2CH_3	+	++	84.0			
503. 3-NO_2; 5-CH_3; 1′-N(COPr)SO_2CH_3	++	++	84.0	+	+	72.0
504. 3-NO_2; 5-CH_3; 3′-OCH_3; 1′-N(COPr)SO_2CH_3	+++	++	95.7	++	+++	97.5
505. 3-NH_2; 4,5-$(CH_3)_2$; 1′-N($COCH_3$)SO_2CH_3	++++	+++	100.0	+++	+++	99.3
506. 10-CH_3	−	−	NB	−	−	23.0
507. 3-$NHSO_2CH_3$	−	−	21.6	−	+	44.7
508. 2′-Aza	−	−	14.0			
509. 2′-$NHSO_2Ph$	−	−	6.0	−	−	0.5
510. 2-NO_2				−	−	23.0
511. 2′-CH_2CH_2COOH	−	−	1.7	−	−	3.5
512. 2′-CH═CHCOOH	−	−	0.8	−	−	0.0
513. 2′-$(CH═CH)_2COOH$				−	−	0.0
514. 2′-Cl	−	−	6.0	−	−	15.0
515. 2′-COOH	−	−	0.3	−	−	1.1
516. 3′-$NHCOOCH_3$	−	−	9.0	−	−	23.0
517. 3′-$CH_2NHSO_2CH_3$	−	−	1.0			
518. 3′-OH				−	−	23.0
519. 3′-Cl	−	−	9.0	−	−	23.0
520. 3′-Br				−	−	23.0
521. 3′-I	−	−	9.0	−	−	23.0
522. 3′-$CONH_2$	−	−	1.0	−	−	13.5
523. 3′-$COOCH_3$				−	−	13.5
524. 3′-SO_2NH_2	−	−	9.0	−	−	23.0
525. 3-$NHSO_3CH_3$; 1′-NH_2	−	−	57.4			
526. 1′-N(CONHNHCO)	−	+	NB	−	+	72.0
527. 1′-N$(SO_2CH_3)_2$	−	+	NB	−	−	NB
528. 1′-NO_2				−	+	NB
529. 4-$OCH_2CH(OH)CH_2OH$; 1′-COOH	−	−	5.0	−	−	5.9
530. 1′-$(CH_2)_2SO_3H$	−	−	21.0	−	−	6.0
531. 3-NO_2; 1′-$(CH_2)_2SO_3H$	−	++	58.3	−	−	6.0
532. 3-$NHCOCH_3$; 1′-$(CH_2)_5COOH$				−	+	35.6
533. 1′-$OCH(CH_3)COOH$	−	−	1.0	−	−	0.0
534. 1′-$O(CH_2)_2COOH$	−	−	0.3	−	−	6.4

TABLE 1—*Continued*

Compound	$-\text{Log}D_{50}$[a]			$-\text{Log}LD_{10}$[b]		
	Exp.	Calc.[c]	Prob.[d]	Exp.	Calc.[c]	Prob.[f]
			%			%
535. 1′-OCH(Pr)COOH	−	−	1.0	−	−	0.0
536. 3-$NHCH_3$; 1′-$O(CH_2)_3COOH$	−	+	5.0			
537. 3′-OH; 1′-COOH				−	−	5.9
538. 3′-CH_3; 1′-COOH	−	−	5.0	−	−	5.9
539. 3-$NHCOCH_3$; 1′-COOH	−	−	21.6	−	+	14.4
540. 1′-$COCH_3$	−	−	5.0	−	−	21.0
541. 10-CH_3; 1′-$CONH_2$	−	−	5.0	−	+	21.0
542. 1′-SO_2CH_3	−	−	NB	−	−	2.0
543. 1′-SO_2NH_2	−	+	NB	−	−	NB
544. 10-CH_3; 1′-SO_2CH_3	−	−	NB	−	−	2.0
545. 1′-SO_2NHCH_3	−	+	NB	−	−	NB
546. 1′-$SO_2NH(CH_2)_2NH_2$				−	++	87.0
547. 1′-Cl	−	−	NB	−	+	NB
548. 1′-Br	−	−	NB	−	+	NB
549. 2′-6′-$(NHSO_2CH_3)_2$	−	−	6.0			
550. 5′-CH_3; 2′-$NHSO_2CH_3$	−	−	0.6	−	−	15.0
551. 2′-5′-$(NHSO_2CH_3)_2$				−	−	15.0
552. 2′-NO_2; 1′-$NHSO_2CH_3$	−	−	0.8	−	−	15.0
553. 2′-F; 1′-$NHSO_2CH_3$	−	−	0.8	−	−	15.0
554. 1′,3′-$(NHSO_2CH_3)_2$	−	−	9.0	−	−	NB
555. 3′-NO_2; 1′-$NHSO_2CH_3$	−	−	11.0	−	−	NB
556. 3′-F; 1′-$NHSO_2CH_3$	−	−	11.0	−	−	NB
557. 1-Aza; 1′-$NHSO_2CH_3$	−	−	14.0			
558. 2-Aza; 1′-$NHSO_2CH_3$				−	−	NB
559. 2-NHCOPh; 1′-$NHSO_2CH_3$	−	−	5.0	−	−	7.4
560. 2-NO_2; 1′-$NHSO_2CH_3$	−	+	NB	−	−	NB
561. 10-CH_3; 2-NO_2; 1′-$NHSO_2CH_3$	−	−	NB	−	+	NB
562. 2-OCH_3; 1′-$NHSO_2CH_3$	−	+	NB			
563. 2-F; 1′-$NHSO_2CH_3$	−	+	NB	−	−	NB
564. 2-$CONH_2$; 1′-$NHSO_2CH_3$				−	−	21.0
565. 3-Aza; 1′-$NHSO_2CH_3$	−	−	14.0	−	−	NB
566. 3-CF_3; 1′-$NHSO_2CH_3$	−	++	84.0	−	−	2.0
567. 3-SO_2CH_3; 1′-$NHSO_2CH_3$	−	++	84.0	−	−	2.0
568. 4-Aza; 1′-$NHSO_2CH_3$	−	−	14.0	−	−	NB
569. 4-$NHCOCH_3$; 1′-$NHSO_2CH_3$				−	−	NB
570. 4-NO_2; 1′-$NHSO_2CH_3$	−	+	NB	−	−	NB
571. 4-F; 1′-$NHSO_2CH_3$	−	+	NB	−	−	NB
572. 4-Cl; 1′-$NHSO_2CH_3$	−	−	NB	−	+	NB
573. 4-COOEt; 1′-$NHSO_2CH_3$	−	−	NB			
574. 3′-5′-$(CH_3)_2$; 1′-$NHSO_2CH_3$	−	−	NB	−	+	NB
575. 3′,5′-$(OCH_3)_2$; 1′-$NHSO_2CH_3$				−	−	NB
576. 1-Cl; 3′-OCH_3; 1′-$NHSO_2CH_3$	−	+	81.0	−	−	NB
577. 2-NO_2; 3′-OCH_3; 1′-$NHSO_2CH_3$				−	−	NB
578. 2-Et; 3′-OCH_3; 1′-$NHSO_2CH_3$	−	+	53.1	−	−	NB
579. 3-SO_2CH_3; 3′-OCH_3; 1′-$NHSO_2CH_3$	−	+++	95.7	−	−	8.0
580. 2,6-$(NHCOCH_3)_2$; 1′-$NHSO_2CH_3$	−	+	NB			
581. 2,7-$(NHCOCH_3)_2$; 1′-$NHSO_2CH_3$				−	−	NB
582. 3-Cl; 6-CF_3; 1′-$NHSO_2CH_3$	−	−	NB	−	−	2.0
583. 3,6-$(Cl)_2$; 1′-$NHSO_2CH_3$	−	−	NB	−	+	NB
584. 3-Cl; 6-CF_3; 3′-OCH_3; 1′-$NHSO_2CH_3$				−	−	8.0
585. 1′-$NHSO_2(CH_2)_2COOCH_3$	−	−	1.0			
586. 1′-$NHSO_2(CH_2)_2COOH$	−	−	1.0	−	−	1.3
587. 1′-$NHSO_2(CH_2)_3NHCOCH_3$	−	+	NB	−	−	NB
588. H				−	−	23.0
589. 10-CH_3; 2-NO_2				−	−	23.0
590. 2′-$NHCH_3$				−	−	15.0
591. 2′-$CH_2N(CH_3)_2$				+	−	15.0
592. 2′-CH_2COOH				+	−	3.5
593. 2′-OH				−	−	15.0
594. 2′-OCH_3				−	−	15.0
595. 3′-Aza				−	−	23.0
596. 3′-$NHCOCH_3$				−	−	23.0
597. 3′-NO_2				−	−	23.0
598. 3′-$N(CH_3)SO_2CH_3$				−	−	23.0
599. 3′-Et				−	−	23.0
600. 3′-$CH(CH_3)_2$				−	−	9.1
601. 3′-CH_2COOH				−	−	5.8
602. 3′-CH═CHCOOH				−	−	0.2
603. 3′-$(CH_2)_2COOH$				−	−	5.8
604. 3′-OCH_3				+	−	23.0

TABLE 1—*Continued*

Compound	$-LogD_{50}$[a]			$-LogLD_{10}$[b]		
	Exp.	Calc.[c]	Prob.[d]	Exp.	Calc.[e]	Prob.[f]
			%			%
605. 3′-COOH				+	−	3.5
606. 3′-F				−	−	23.0
607. 3′,5′-$(CH_3)_2$				−	−	NB
608. 3′,5′-$(OH)_2$				−	+	NB
609. 1′-NH_2; 2′-CH_3				+	+	91.0
610. 2-CH_3; 1′-NH_2				+	+	85.0
611. 2-OCH_3; 1′-NH_2				−	++	85.0
612. 3-OCH_3; 1′-NH_2				++	+++	99.6
613. 1′-NHBu				+	+	NB
614. 1′-NHPr				+	+	NB
615. 1′-NH-Hx				+	+	NB
616. 1′-NEt_2				++	+	NB
617. 1′-$N(CH_2CH_2)_2NH$				++	+	72.0
618. 3-NO_2; 1′-$N(CH_2CH_2)_2NH$				++	+	72.0
619. 1′-$N(CH_2CH_2)_2NCH_3$				+	+	NB
620. 1′-$NHCOCH_2Ph$				++	−	23.0
621. 1′,2′-(N═C[(CHOH)$_4$CHOH]NH)				++	−	NB
622. 4-$CONH_2$; 1′-CH_3				−	+	NB
623. 1′-CH_2NH_2				+	++	94.0
624. 1′-$CH_2N(CH_3)_2$				+	+	NB
625. 1′-$(CH_2)_2NH_2$				++	++	87.0
626. 3-NO_2; 1′-$(CH_2)_2NH_2$				+++	++	87.0
627. 1′-$(CH_2)_3NH_2$				++	++	87.0
628. 3-NO_2; 1′-$(CH_2)_3NH_2$				++	++	87.0
629. 1′-$(CH_2)_4NH_2$				++	++	87.0
630. 3-NO_2; 1′-$(CH_2)_4NH_2$				++	++	87.0
631. 1′-$(CH_2)_5NH_2$				++	++	87.0
632. 3-NO_2; 1′-$(CH_2)_5NH_2$				++	++	87.0
633. 1′-$(CH_2)_6NH_2$				++	++	87.0
634. 3-NO_2; 1′-$(CH_2)_6NH_2$				++	++	87.0
635. 1′-CH_2COOH				−	−	17.0
636. 3-$NHCH_3$; 1′-CH_2COOH				−	+	35.6
637. 3-$NHCOCH_3$; 1′-$(CH_2)_2COOH$				+	+	35.6
638. 3-$NHCH_3$; 1′-$(CH_2)_3COOH$				−	+	35.6
639. 3′-OCH_3; 1′-CH═$CHCONH_2$				−	+	9.0
640. 1′-$CH_2CH(NH_2COOH$				−	−	0.0
641. 3-NO_2; 1′-$CH_2CH(NH_2)COOH$				−	−	0.0
642. 1′-CH═CHPh				+	−	2.9
643. 3′-OCH_3; 1′-CH═CHCOOH				−	−	0.2
644. 1′-OCH_3				+	+	NB
645. 1′-OCH(Et)COOH				−	−	0.0
646. 1′-OCH_2COOH				−	−	17.0
647. 3-NH_2; 1′-COOH				+	+	26.1
648. 1′-CN				−	+	42.0
649. 1′-F				−	+	NB
650. 3-NH_2; 1′-Br				++	++	85.0
651. 1′-I				+	+	NB
652. 1′-CONHPr				−	+	21.0
653. 1′-$SO_2NH(CH_2)_6NH_2$				−	++	87.0
654. 2′-CH_3; 1′-$NHSO_2CH_3$				−	−	15.0
655. 2′-Cl; 1′-$NHSO_2CH_3$				−	−	15.0
656. 3′-$OCH(CH_3)_2$; 1′-$NHSO_2CH_3$				−	+	NB
657. 3′-Cl; 1′-$NHSO_2CH_3$				−	+	NB
658. 1-NO_2; 1′-$NHSO_2CH_3$				+	−	NB
659. 1-CH_3; 1′-$NHSO_2CH_3$				−	−	NB
660. 2-$NHSO_2CH_3$; 1′-$NHSO_2CH_3$				+	−	NB
661. 2-CH_3; 1′-$NHSO_2CH_3$				−	−	NB
662. 2-Cl; 1′-$NHSO_2CH_3$				−	+	NB
663. 2-I; 1′-$NHSO_2CH_3$				−	+	NB
664. 3-F; 1′-$NHSO_2CH_3$				−	−	NB
665. 3-NHCOPh; 1′-$NHSO_2CH_3$				++	−	23.0
666. 3-NHCOCH═CHPh; 1′-$NHSO_2CH_3$				+	−	26.7
667. 3-CN; 1′-$NHSO_2CH_3$				−	−	42.0
668. 4-$CONH_2$; 2′-OCH_3; 1′-$NHSO_2CH_3$				−	−	15.0
669. 1-Aza; 3′-OCH_3; 1′-$NHSO_2CH_3$				+	−	NB
670. 1-NO_2; 3′-OCH_3; 1′-$NHSO_2CH_3$				+	−	NB
671. 1-CH_3; 3′-OCH_3; 1′-$NHSO_2CH_3$				−	−	NB
672. 1-OCH_3; 3′-OCH_3; 1′-$NHSO_2CH_3$				−	−	NB
673. 2-Aza; 3′-OCH_3; 1′-$NHSO_2CH_3$				−	−	NB
674. 2-$C(CH_3)_3$; 3′-OCH_3; 1′-$NHSO_2CH_3$				−	−	2.0

TABLE 1—*Continued*

Compound	−LogD$_{50}$[a]			−LogLD$_{10}$[b]		
	Exp.	Calc.[c]	Prob.[d]	Exp.	Calc.[c]	Prob.[f]
			%			%
675. 2-OCH_3; 3′-OCH_3; 1′-$NHSO_2CH_3$				−	−	NB
676. 2-$CONH_2$; 3′-OCH_3; 1′-$NHSO_2CH_3$				−	−	21.0
677. 3-$N(CH_3)SO_2CH_3$; 3′-OCH_3; 1′-$NHSO_2CH_3$				++	+	81.0
678. 3-$C(CH_3)_3$; 3′-OCH_3; 1′-$NHSO_2CH_3$				−	−	8.0
679. 3-SO_2CH_3; 3′-OCH_3; 1′-$NHSO_2Hx$				−	+	20.7
680. 2,7-$(NH_2)_2$; 1′-$NHSO_2CH_3$				+++	+++	98.3
681. 2,6-$(N_3)_2$; 1′-$NHSO_2CH_3$				−	+	NB
682. 2-OCH_3; 6-NH_2; 1′-$NHSO_2CH_3$				++	++	85.0
683. 2-OCH_3; 6-$NHCOCH_3$; 1′-$NHSO_2CH_3$				−	−	NB
684. 2-OCH_3; 6-NO_2; 1′-$NHSO_2CH_3$				−	−	NB
685. 2-OCH_3; 6-Cl; 1′-$NHSO_2CH_3$				−	−	NB
686. 3,4-benz; 1′-$NHSO_2CH_3$				−	+	NB
687. 1-Cl; 4-$CONH_2$; 3′-OCH_3; 1′-$NHSO_2CH_3$				+	−	NB
688. 2-OCH_3; 6-Cl; 3′-OCH_3; 1′-$NHSO_2CH_3$				+	+	81.0
689. 3-NO_2; 4,5-$(CH_3)_2$; 1′-$NHSO_2CH_3$				−	+	NB
690. 1′-$N[CH_2CH(OH)CH_2OH]SO_2CH_3$				++	−	NB
691. 4-CH_3; 3′-OCH_3; 1′-$N(COCH_3)SO_2CH_3$				++	++	90.1
692. 4-CH_3; 3′-OCH_3; 1′-$N(COBu)SO_2CH_3$				−	++	90.1
693. 4-CH_3; 3′-OCH_3; 1′-$N(COPe)SO_2CH_3$				+	++	90.1
694. 4-CH_3; 1′-$N[CO(CH_2)_2COOEt]SO_2CH_3$				+++	+	72.0
695. 4-CH_3; 3′-OCH_3; 1′-$N[CO(CH_2)_2COOPr]SO_2CH_3$				+	++	90.1
696. 1′-$NHSO_2CH(CH_3)CONH_2$				+	−	NB
697. 1′-$NHSO_2(CH_2)_2NH_2$				++	++	87.0
698. 1′-$NHSO_2(CH_2)_3NH_2$				++	++	87.0
699. 1′-$NHSO_2(CH_2)_4NH_2$				++	++	87.0
700. 10-CH_3; 3-NO_2; 1′-$NHSO_2(CH_2)_4NH_2$				++	++	87.0
701. 4-$CONH_2$; 3′-OCH_3; 1′-$NHSO_2(CH_2)_4NH_2$				++	+++	98.6
702. 3-NO_2; 5-CH_3; 1′-$NHSO_2(CH_2)_4NH_2$				−	++	87.0
703. 1′-$NHSO_2(CH_2)_5NH_2$				++	++	87.0
704. 1′-$NHSO_2(CH_2)_6NH_2$				++	++	87.0
705. 3-NO_2; 1′-$NHSO_2(CH_2)_6NH_2$				++	++	87.0
706. 4-$CONH_2$; 1′-$NHSO_2(CH_2)_3NHC(NH)NH_2$				++	−	NB
707. 1′-$NHSO_2(CH_2)_4NHC(NH)NH_2$				++	−	NB
708. 10-CH_3; 1′-$NHSO_2(CH_2)_4NHC(NH)NH_2$				+	−	NB
709. 3-Cl; 1′-$NHSO_2(CH_2)_4NHC(NH)NH_2$				+	−	NB
710. 3-NO_2; 1′-$NHSO_2(CH_2)_6NHC(NH)NH_2$				+	−	NB
711. 1′-$NHSO_2(CH_2)_2NHCO(CH_2)_2NH_2$				+	+	87.0

The regression coefficients of the corresponding fragments are a measure of the activating/inactivating contribution made to the biological activity and are used to calculate the potency of individual compounds. The program carries out the quantitative analysis using as descriptors the number of occurrences of each relevant fragment within each compound. Once the computer has been "trained" with a particular data base, test compounds which were not included in the original CASE analysis can be submitted for qualitative as well as quantitative predictions. Furthermore, the data base can be periodically updated with new compounds leading to increased accuracy of predictions.

Results and Discussion

In this CASE study, we chose to model both dose potency and host toxicity for an extensive series of 9-anilinoacridine derivatives. The biological activities and chemical structures of the compounds were obtained from the literature (16). The *in vivo* antileukemic activity was measured in terms of the drug dose (D_{50}) in mol/kg/day leading to a 50% increase in the life span of L1210 tumor-bearing mice. The dose (LD_{10}) proving lethal to 10% of the animals was taken as a measure of the compound's potential to precipitate toxic effects. After Klopman line notation coding (43) of the individual structures, an activity index suitable for entry into the CASE program was established for both biological endpoints. For the antileukemic data base only compounds that are experimentally tumor active or tumor inactive but host nontoxic were considered for inclusion. Tumor-inactive host-toxic compounds were not considered since toxic levels are reached before therapeutic doses are attained. In terms of dose potency, compounds with values of $-\log D_{50} \leq 3.88$ were arbitrarily classified as being inactive. Similarly, compounds with values of $-\log LD_{10} \leq 3.45$ were considered to be host nontoxic. Furthermore, within the biologically active class a gradient of activity is established in terms of marginally active (+), active (++), very active (+++), and extremely active (++++) compounds. The above scaling clearly does not reflect the true experimental classes of compound activity but is a reasonable distinction since our purpose is to extract the molecular fragments which contribute the greatest amount to the activity. The cutoff values were found to provide a good distribution between the active and so-called inactive classes. The experimentally most potent compounds are thus classified as being active.

Two training data bases, one containing antileukemic activity and the other host toxicity, were composed and analyzed separately. According to the classification scheme discussed above, the dose potency training set contained 292 active and 169 inactive compounds. A total of 618 compounds, 387 active and 231 inactive, comprised the host toxicity set. In addition, two test sets, both containing 150 randomly chosen compounds, were excluded from the CASE analysis of the respective endpoints.

Submission of the dose potency training data base to the

CASE program (version 2.0) resulted in the *automatic* generation of 18 biophores and 8 biophobes out of a total of 197 fragments generated by the data base as potential descriptors for a QSAR. Furthermore, theoretically calculated (45) values of the logarithm of the partition coefficient and the square of the logarithm of the partition coefficient were included within the descriptor pool. Performance of a forward stepwise multivariate linear regression resulted in a 15-variable equation quantitatively modelling antileukemic activity:

$$\begin{aligned}\text{Log}(1/D_{50}) &= 4.11 + 0.63n_{I}F_{I} + 0.31n_{II}F_{II} + 0.20n_{III}F_{III} - \\ &\quad 1.85n_{IV}F_{IV} + 0.16n_{V}F_{V} + 0.51n_{VI}F_{VI} - 0.34n_{VII}F_{VII} - \\ &\quad 0.21n_{VIII}F_{VIII} + 0.41n_{IX}F_{IX} + 0.40n_{X}F_{X} + 0.37n_{XI}F_{XI} - \\ &\quad 0.40n_{XII}F_{XII} - 0.35n_{XIII}F_{XIII} - 0.26n_{XIV}F_{XIV} - \\ &\quad 0.08\log P \end{aligned} \quad (1)$$

$$R = 0.805, \quad N = 461. \quad F_{(15,445)} = 54.52, \quad S = 0.46$$

where n_aF_a is the number of times fragment F_a occurs in a particular compound. The primary fragments (and the associated expanded versions) incorporated within regression Eq. 1 are listed in Fig. 1. Comparisons of the calculated with experimental values of $-\log D_{50}$ are tabulated within Table 1. The results of the retrofit analysis do not appear to be as good as those obtained by Denny *et al.* (16), but are still significant considering the size of the data base.

In order to determine whether the CASE program had "learned" what structural features are needed to confer antileukemic activity, the training data base was submitted as an unknown. Qualitative conclusions as to the chances of a compound exhibiting the desired biological activity are tabulated in Table 1 and are expressed as overall probabilities. Overall, 87% of the compounds were correctly predicted as being either active or inactive. Compounds predicted to have no basis to support activity (NB) do not contain any statistically significant fragments. The activity values of these compounds were, however, used in the derivation of the regression equation. Although none of the fragments incorporated within the equation are present, the calculated log$P$ values places these compounds in the active range.

CASE analysis of the data base pertaining to host toxicity resulted in the generation of 34 molecular fragments. Forward stepwise multivariate regression analysis yielded an equation of the form:

$$\begin{aligned}\text{Log}(1/LD_{10}) &= 3.50 + 0.37n_{I}F_{I} + 0.42n_{II}F_{II} + 0.40n_{III}F_{III} + \\ &\quad 0.55n_{IV}F_{IV} + 0.33n_{V}F_{V} - 0.27n_{VI}F_{VI} + 0.40n_{VII}F_{VII} + \\ &\quad 0.10n_{VIII}F_{VIII} + 0.84n_{IX}F_{IX} + 0.54n_{X}F_{X} - 0.86n_{XI}F_{XI} - \\ &\quad 0.18n_{XII}F_{XII} + 0.63n_{XIII}F_{XIII} - 0.38n_{XIV}F_{XIV} - \\ &\quad 0.10n_{XV}F_{XV} + 0.48n_{XVI}F_{XVI} + 0.60n_{XVII}F_{XVII} + \\ &\quad 0.08n_{XVIII}F_{XVIII} \end{aligned} \quad (2)$$

$$R = 0.740, \quad N = 618, \quad F_{(18,599)} = 40.17, \quad S = 0.42$$

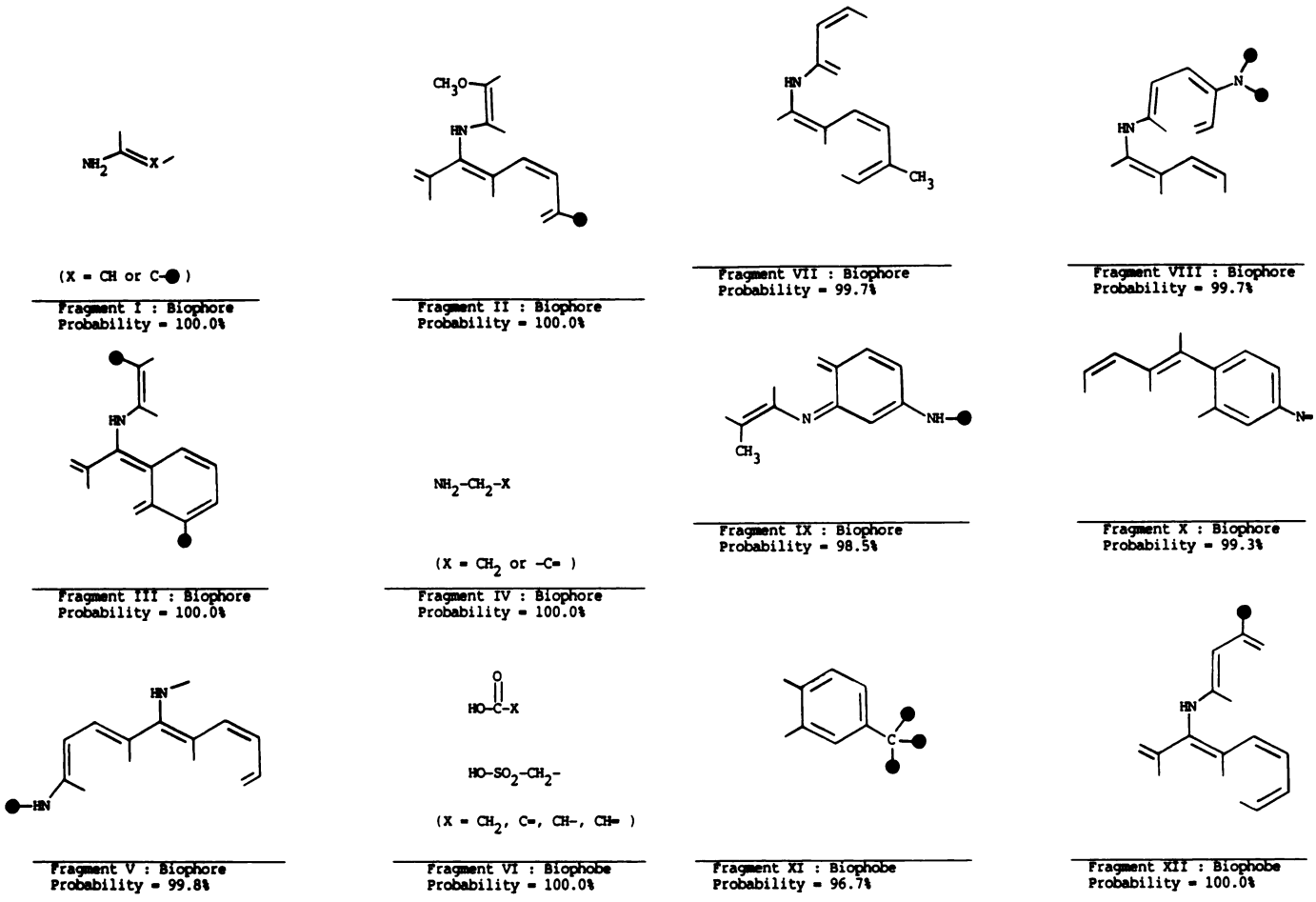


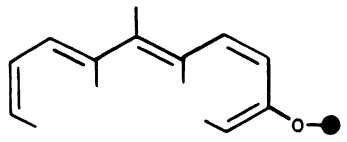
Fig. 2. Fragments used in QSAR equation estimating $-\text{Log}D_{10}$. ●, a non-hydrogen substituent.

The calculated as well as actual values are tabulated in Table 1, while the corresponding fragments are listed in Fig. 2. Submission of the training data base as an unknown resulted in an overall predictive accuracy of 77%. The accuracy increases to 91% if we choose to exclude compounds belonging to the marginal (+) class. Thus, it can be seen that CASE correctly predicts compounds that lie at the extremes of inactivity and activity.

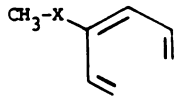
In order to truly test the predictive capabilities of the CASE program, the two test data sets which were excluded from the training data bases were submitted for analysis. If a compound is predicted to have a high probability of possessing the desired activity, the appropriate regression equation is then utilized in order to quantitatively estimate the degree of activity. Results for the predictions of both antileukemic activities and host toxicities are tabulated in Tables 2 and 3, respectively. Sixty-seven per cent of the compounds in the dose potency test set were correctly predicted on a qualitative basis, whereas an overall accuracy of 65% was calculated for the toxicity set. Exclusion of the marginal compounds increased the predictive accuracies to 78% and 72%, respectively.

The goal of any drug program dedicated to the development of chemotherapeutic agents effective against neoplasms should be directed toward increasing the selectivity of the compounds rather than the dose potency. We may draw some general conclusions as to the structural features (such as substitution patterns, types of substituents, etc.) necessary for antileukemic activity as well as host toxicity by analyzing the terms incorporated within the respective regression equations. In this way the features which contribute most to the potency of the drugs without concomitant increase in host toxicity can be identified and utilized in drug development programs. Such objectives are currently being pursued in our group.

As can be seen by the inclusion of the logarithm of the partition coefficient within regression Eq. 1, hydrophilicity contributes to antileukemic activity without increasing the host toxicity of the compounds. The regression coefficient, however, indicates that this term is not the dominant factor involved. Since this variable is the least significant of the variables incorporated within Eq. 1, we felt it not necessary to list the individual values for the entire data base of compounds. Previous investigations (16, 46, 47) have shown that hydrophilicity, while being beneficial, is one of the less important determinants of antileukemic activity.

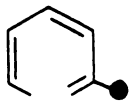


Fragment XIII : Biophore
Probability = 97.0%

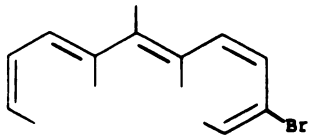


(X = C=O or SO_2

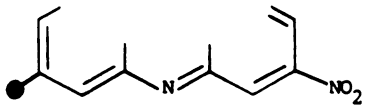
Fragment XIV : Biophobe
Probability = 96.7%



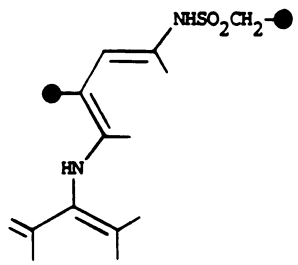
Fragment XV : Biophobe
Probability = 100.0%



Fragment XVI : Biophore
Probability = 98.5%



Fragment XVII : Biophore
Probability = 87.8%



Fragment XVIII : Biophore
Probability = 99.9%

Fig. 2—Continued

TABLE 2
Predictions of dose potencies

Test compound	−LogD$_{50}$[a] Act.	Calc.[b]	Prob.[c] %
1. 10—CH_3; 2—$NHCOCH_3$	+	−	NB[d]
2. 10—CH_3; 3—NH_2	++	+++	96.2
3. 3—I; 1′—COOH	−	−	21.6
4. 3—$NHCH_3$; 1′—SO_2NH_2	+	++	84.0
5. 3,6—$(NH_2)_2$; 1′—SO_2NH_2	+++	+++	83.0
6. 3—NH_2; 1′—SO_2NHPr	+	++	96.2
7. 3—NH_2; 1′—SO_2NHPe	+	++	96.2
8. 3—NH_2; 1′—OCH_3	+++	+++	20.6
9. 3′—CH_3	−	−	9.0
10. 4—CH_3; 1′—CH_2COOH	+	−	21.0
11. 4—Et; 1′—$(CH_2)_2COOH$	+	−	21.0
12. 1′—CH_2CONH_2	+	−	21.0
13. 1′—$(CH_2)_3CONH_2$	+	−	21.0
14. 1′—$(CH_2)_5CONH_2$	−	−	21.0
15. 1′—CH═CHCONH$_2$	−	−	11.0
16. 1′—$(CH═CH)_2COOH$	+	−	11.0
17. 1′—CH═CHPhCOOH	+	−	5.0
18. 1′—NH_2	+	++	83.0
19. 3′—OCH_3; 1′—NH_2	++	++	83.0
20. 4—CH_3; 3′—OCH_3; 1′—NH_2	+++	++	95.4
21. 1′,2′—(NHCH═N)	+	−	NB
22. 10—CH_3; 1′—$NHCOCH_3$	−	−	NB
23. 1′—NHCOPr	+	−	NB
24. 1′—$NHCO(CH_2)_2CH(CH_3)_2$	−	−	5.0
25. 1′—$NHCOCHEt_2$	+	−	NB
26. 3—NH_2; 1′—NHCOPh	++	+	57.4
27. 1′—NHCOOEt	+	−	NB
28. 1′—$NHCONHCH_3$	+	−	NB
29. 3′—CH_3; 1′—$NHCONHCH_3$	−	−	NB
30. 3—NO_2; 1′—$NHCONHPhCH_2NH_2$	+++	++	79.9
31. 1′—$NHCONHPh(CH_2)_3NH_2$	++	−	21.0
32. 1′—$NHCONHPh(CH_2)_6NH_2$	+	−	21.0
33. 3—NO_2; 1′—NHCONHPh-$CH_2CH(NH_2)COOH$	−	++	58.3
34. 1′—NHCONHPhCOOH	+	−	5.0
35. 1′—$NHCONHPh(CH_2)_4COOH$	+	−	21.0
36. 1′—$NHCONHPhNHSO_2CH_3$	−	−	NB
37. 1′—NHCONHPhNHC(NH)NHC(NH)NH_2	++	−	NB
38. 1′—$NHCONHPhC(CH_3)NNHC(NH)NH_2$	++	++	74.0
39. 3—$NHCOCH_3$; 1′—$N(COOCH_3)SO_2CH_3$	++	++	84.0
40. 3′—CH_3; 2′—$NHSO_2CH_3$	−	−	NB
41. 10—CH_3; 1—$NHSO_2CH_3$	+	−	NB
42. 10—CH_3; 1′—$NHSO_2Et$	+	−	NB
43. 1′—$NHSO_2Bu$	−	−	NB
44. 2′—NH_2; 1′—$NHSO_2CH_3$	+	+	100.0
45. 3′—OH; 1′—$NHSO_2CH_3$	++	−	NB
46. 3′—OCH_3; 1′—$NHSO_2Pr$	++	−	NB
47. 3′—OCH_3; 1′—$NHSO_2Hp$	+	−	NB
48. 2—$NHCOCH_3$; 1′—$NHSO_2CH_3$	−	−	NB
49. 10—CH_3; 2—$NHCOCH_3$; 1′—$NHSO_2CH_3$	+	−	NB
50. 10—CH_3; 3—NH_2; 1′—$NHSO_2CH_3$	++++	+++	96.2
51. 3—$N_3(CH_3)Pr$; 1′—$NHSO_2CH_3$	+++	++	84.0
52. 3—$NHCOCH_3$; 1′—$NHSO_2Bu$	+++	++	84.0
53. 3—NHCOEt; 1′—$NHSO_2CH_3$	++	++	84.0
54. 3—NO_2; 1′—$NHSO_2Et$	++	++	84.0
55. 3—NO_2; 1′—$NHSO_2Pe$	+	++	84.0
56. 3—CH_3; 1′—$NHSO_2Et$	++	++	84.0
57. 4—CH_2OH; 1′—$NHSO_2CH_3$	+	−	NB
58. 4—Et; 1′—$NHSO_2CH_3$	−	−	NB
59. 4—OEt; 1′—$NHSO_2CH_3$	+	−	NB
60. 3—NH_2; 2′—OCH_3; 1′—$NHSO_2CH_3$	+++	+++	62.1
61. 2—$CH(CH_3)_2$; 3′—OCH_3; 1′—$NHSO_2CH_3$	−	−	81.0
62. 3—Aza; 3′—OCH_3; 1′—$NHSO_2CH_3$	+	−	14.0
63. 3—NH_2; 3′—CH_3; 1′—$NHSO_2CH_3$	++	+++	96.2
64. 3—$NHCH_3$; 3′—OCH_3; 1′—$NHSO_2CH_3$	++++	+++	95.7
65. 3—$NHCOCH_3$; 3′—OCH_3; 1′—$NHSO_2Pe$	++	+++	95.7
66. 3—NO_2; 3′—OCH_3; 1′—$NHSO_2Et$	+++	+++	100.0
67. 3—NO_2; 3′—OCH_3; 1′—$NHSO_2Pe$	+	++	95.7
68. 3—NO_2; 3′—OCH_3; 1′—$NHSO_2Hp$	−	++	95.7
69. 3—Et; 3′—OCH_3; 1′—$NHSO_2CH_3$	++	+++	85.6
70. 3—CN; 3′—OCH_3; 1′—$NHSO_2CH_3$	+	+++	95.7
71. 3—Cl; 3′—OCH_3; 1′—$NHSO_2CH_3$	+++	+++	95.7
72. 10—CH_3; 3—Br; 3′—OCH_3; 1′—$NHSO_2CH_3$	++	+++	95.7
73. 4-Aza; 3′—OCH_3; 1′—$NHSO_2Et$	+	−	100.0
74. 4-Aza; 3′—OCH_3; 1′—$NHSO_2Pe$	+	−	14.0
75. 4—NO_2; 3′—OCH_3; 1′—$NHSO_2CH_3$	−	+	81.0
76. 4,3′—$(CH_3)_2$; 1′—$NHSO_2CH_3$	+	−	NB
77. 4—F; 3′—OCH_3; 1′—$NHSO_2CH_3$	++	+	81.0
78. 4—OEt; 3′—OCH_3; 1′—$NHSO_2CH_3$	++	+	81.0
79. 4—OBu; 3′—OCH_3; 1′—$NHSO_2Pe$	−	+	81.0
80. 4—$OCH_2CH(OH)CH_2OH$; 3′—OCH_3; 1′—$NHSO_2CH_3$	+++	++	81.0
81. 4—$CONH_2$; 3′—CH_3; 1′—$NHSO_2CH_3$	−	−	NB
82. 4—$CONH_2$; 3′—OCH_3; 1′—$NHSO_2CH_3$	++	++	81.0
83. 4—$CONH_2$; 3′—OCH_3; 1′—$NHSO_2Pe$	+	+	81.0
84. 4—CONHBu; 3′—OCH_3; 1′—$NHSO_2CH_3$	+	+	81.0
85. 4—CONHBu; 3′—OCH_3; 1′—$NHSO_2Pe$	−	+	81.0
86. 4—$CONH(CH_2)_2OH$; 3′—OCH_3; 1′—$NHSO_2CH_3$	++	++	81.0
87. 4—$CONHCH_2CONH_2$; 3′—OCH_3; 1′—$NHSO_2CH_3$	++	++	81.0
88. 4—$CONHCH_2CONH(CH_2)_2NH(CH_2)_2OH$; 3′—$OCH_3$; 1′—$NHSO_2CH_3$	+	++	81.0
89. 2—NH_2; 3—Cl; 1′—$NHSO_2CH_3$	+	++	100.0
90. 3—NHCHO; 4—CH_3; 1′—$NHSO_2CH_3$	++++	++	84.0
91. 3—NO_2; 4—CH_3; 1′—$NHSO_2CH_3$	+	++	84.0
92. 3,4—$(OCH_3)_2$; 1′—$NHSO_2CH_3$	−	++	84.0
93. 3—NO_2; 5—CH_3; 1′—$NHSO_2Et$	++	++	84.0
94. 3—Cl; 5—CH_3; 1′—$NHSO_2CH_3$	+	++	84.0
95. 3—I; 5—CH_3; 1′—$NHSO_2CH_3$	++	++	84.0
96. 3—$NHCOCH_3$; 6—OCH_3; 1′—$NHSO_2CH_3$	−	++	86.0
97. 3—NO_2; 6—CH_3; 1′—$NHSO_2CH_3$	+	−	NB
98. 3,6—$(OCH_3)_2$; 1′—$NHSO_2CH_3$	+	−	NB
99. 2—NH_2; 3—Br; 3′—OCH_3; 1′—$NHSO_2CH_3$	+++	+++	100.0
100. 3,4—(CH═CHCH═N); 3′—OCH_3; 1′—$NHSO_2CH_3$	+++	−	14.0
101. 3—$NHCOOCH_3$; 5—CH_3; 3′—OCH_3; 1′—$NHSO_2CH_3$	+++	+++	95.7
102. 3—Br; 5—OCH_3; 3′—OCH_3; 1′—$NHSO_2CH_3$	+++	+++	95.7
103. 3,6—$(NO_2)_2$; 3′—OCH_3; 1′—$NHSO_2CH_3$	−	+	81.0
104. 3—Cl; 6—OCH_3; 3′—OCH_3; 1′—$NHSO_2CH_3$	+	+	81.0
105. 3—NH_2; 4,5—$(CH_3)_2$; 1′—$NHSO_2CH_3$	++++	+++	100.0
106. 2—NH_2; 3,4—$(CH_3)_2$; 3′—OCH_3; 1′—$NHSO_2CH_3$	+++	+++	100.0
107. 3—NO_2; 4,5—$(CH_3)_2$; 3′—OCH_3; 1′—$NHSO_2CH_3$	−	+++	95.7
108. 3—NO_2; 5,6—$(CH_3)_2$; 3′—OCH_3; 1′—$NHSO_2CH_3$	++	++	96.9
109. 1′—$NHSO_2(CH_2)_2NHCOCH_3$	+	−	NB
110. 1′—$NHSO_2(CH_2)_2N(CH_3)COCH_3$	−	−	NB
111. 1′—$NHSO_2(CH_2)_2NHCOOCH_3$	−	−	NB

[a] See Table 1 for definitions of −, +, ++, +++, ++++.
[b] Based on the occurrence of fragments listed in Fig. 1 and Eq. 1.
[c] Overall probability of being an active antitumor agent, based on fragments with probability $p > 70\%$.
[d] NB, no basis found to support activity; compound is presumed to be inactive.

TABLE 2—*Continued*

Test compound	−LogD$_{50}$[a] Act.	Calc.[b]	Prob.[c] %
112. 3,5—$(CH_3)_2$; 1′—$NHSO_2(CH_2)_2NHCONH_2$	+	++	84.0
113. 1′—$NHSO_2(CH_2)_2N(CONHCH_2CO)$	+	−	NB
114. 1′—$(CH_2)_3NHSO_2CH_3$	−	−	21.0
115. 3—NO_2; 1′—$NHSO_2(CH_2)_3NH_2$	++	++	84.0
116. 3—NO_2; 5,6—$(CH_3)_2$; 1′—$NHSO_2(CH_2)_4NH_2$	+	+	99.9
117. 2,6—$(NH_2)_2$; 1′—$NHSO_2(CH_2)_2NHC(NH)NH_2$	+	++	83.0
118. 2,6—$(NH_2)_2$; 1′—$NHSO_2(CH_2)_3NHC(NH)NH_2$	+++	++	83.0
119. 3,6—$(NO_2)_2$; 1′—$NHSO_2(CH_2)_3NHC(NH)NH_2$	−	−	NB
120. 3—NO_2; 1′—$NHSO_2(CH_2)_6NHC(NH)NH_2$	+	++	84.0
121. 3—NO_2; 1′—$NHSO_2Ph$	++	+++	98.8
122. 1′—$NHSO_2PhNHCOCH_3$	++	++	94.0
123. 3—NO_2; 1′—$NHSO_2PhCONHCH_3$	+++	++	81.2
124. 1′—$N(COBu)SO_2CH_3$	−	−	NB
125. 3—$NHCOCH_3$; 1′—$N(COHp)SO_2CH_3$	++	++	84.0
126. 3—$NHCOCH_3$; 1′—$N(COC_{17}H_{35})SO_2CH_3$	−	−	84.0
127. 3—$NHCOCH_3$; 1′—$N[COCH(CH_3)Et]SO_2CH_3$	+	++	84.0
128. 3—NO_2; 1′—$N(CO—Oct)SO_2CH_3$	+	+	84.0
129. 3—NO_2; 5—CH_3; 1′—$N(COCH_3)SO_2CH_3$	++	++	99.8
130. 3—NO_2; 5—CH_3; 3′—OCH_3; 1′—$N(COEt)SO_2CH_3$	−	+++	95.7
131. 2—NO_2	−	−	NB
132. 2′—$(CH═CH)_2COOH$	−	−	0.8
133. 3′—OH	−	−	9.0
134. 3′—Br	−	−	9.0
135. 3′—$COOCH_3$	−	−	1.0
136. 1′—NO_2	−	−	NB
137. 3—$NHCOCH_3$; 1′—$(CH_2)_5COOH$	−	+	58.3
138. 3′—OH; 1′—COOH	−	−	5.0
139. 1′—SO_3H	−	−	NB
140. 1′—$CONH_2$	−	−	5.0
141. 1′—$SO_2NH(CH_2)_2NH_2$	−	−	NB
142. 2′,5′—$(NHSO_2CH_3)_2$	−	−	0.6
143. 3′—Aza; 1′—$NHSO_2CH_3$	−	−	NB
144. 2—Aza; 1′—$NHSO_2CH_3$	−	−	14.0
145. 2—$CONH_2$; 1′—$NHSO_2CH_3$	−	−	5.0
146. 4—$NHCOCH_3$; 1′—$NHSO_2CH_3$	−	−	NB
147. 3′,5′—$(OCH_3)_2$; 1′—$NHSO_2CH_3$	−	++	81.0
148. 2—NO_2; 3′—OCH_3; 1′—$NHSO_2CH_3$	−	+	81.0
149. 2,7—$(NHCOCH_3)_2$; 1′—$NHSO_2CH_3$	−	−	NB
150. 3—Cl; 6—CF_3; 3′—OCH_3; 1′—$NHSO_2CH_3$	−	+	81.0

TABLE 3
Predictions of host toxicity

Test compound	−LogLD$_{10}$[a] Act.	Calc.[b]	Prob.[c] %
1. 10—CH_3; 3—NH_2	++	++	62.9
2. 1′—$COOCH_3$	−	+	21.0
3. 3—N_3; 1′—COOH	+	+	100.0
4. 3—NH_2; 1′—CN	+	++	80.4
5. 3—$NHCH_3$; 1′—SO_2NH_2	++	+	73.0
6. 3,6—$(NH_2)_2$; 1′—SO_2NH_2	+++	+++	85.0
7. 1′—OCH_3; 2′—$NHSO_2CH_3$	−	−	15.0
8. 1′—$(CH_2)_2SO_2NH_2$	+	−	NB[d]
9. 4—CH_3; 1′—$(CH_2)_2COOH$	++	−	17.0
10. 1′—$(CH_2)_3COOH$	−	−	17.0
11. 1′—$(CH_2)_8COOH$	+	−	17.0
12. 1′—$(CH_2)_5CONH_2$	+	−	NB
13. 1′—CH═CHCOOH	−	−	0.2
14. 10—CH_3; 1′—NH_2	+	++	85.0
15. 3—$NHCOCH_3$; 1′—NH_2	++	+++	93.9
16. 10—CH_3; 2′—NH_2	−	+	50.0
17. 2′—NH_2; 5′—CH_3	+	+	50.0
18. 1′—$N(CH_2CH_2)_2NCONH_2$	++	−	NB
19. 1′—NHCOPr	+	−	NB
20. 1′—$NHCOCH(CH_3)_2$	−	−	NB
21. 1′—NHCO—c—C_5H_9	+	−	NB
22. 1′—$NHCOOCH_2CH(OH)CH_2OH$	++	−	NB
23. 3′—OCH_3; 1′—$NHCONHCH_3$	+	−	NB
24. 1′—$NHCONHNHCOOCH_3$	−	−	NB
25. 1′—$NHCONHPhCH_2COOH$	−	−	17.0
26. 1′—$NHCONHPh(CH_2)_5COOH$	+	−	17.0
27. 1′—$NHCONHPhNHC(NH)NH_2$	++	+	91.0
28. 10—CH_3; 3—NH_2; 1′—$NHCONHPhC(CH_3)NNHC(NH)NH_2$	++	++	85.0
29. 3—$NHCOCH_3$; 1′—$N(COOCH_3)SO_2CH_3$	+	++	87.4
30. 2′—$NHSO_2CH_3$	−	−	15.0
31. 10—CH_3; 1′—$NHSO_2Et$	+	−	NB
32. 3′—OCH_3; 1′—$NHSO_2Et$	+++	+	75.0
33. 3′—OEt; 1′—$NHSO_2CH_3$	+	−	NB
34. 2—N_3; 1′—$NHSO_2CH_3$	−	−	NB
35. 3—NH_2; 1′—$NHSO_2CH_3$	++++	++	85.0
36. 3—$NHCOOCH_3$; 1′—$NHSO_2CH_3$	+	+	73.0
37. 3—$N_3(CH_3)Pr$; 1′—$NHSO_2CH_3$	+++	++	100.0
38. 3—$NHCOCH_3$; 1′—$NHSO_2Pe$	++	+	73.0
39. 3—NO_2; 1′—$NHSO_2Et$	+++	−	NB
40. 3—NO_2; 1′—$NHSO_2Pr$	−	−	NB
41. 3—NO_2; 1′—$NHSO_2Pe$	+	−	NB
42. 4—NH_2; 1′—$NHSO_2CH_3$	+	+	85.0
43. 4—CH_3; 1′—$NHSO_2CH_3$	++	−	NB
44. 4—OPr; 1′—$NHSO_2CH_3$	−	−	NB
45. 3—$NHCOOCH_3$; 3′—OCH_3; 1′—$NHSO_2CH_3$	+++	++	92.0
46. 3—$N_3(CH_3)Pr$; 3′—OCH_3; 1′—$NHSO_2CH_3$	+++	++	100.0
47. 3—$NHCOCH_3$; 3′—OCH_3; 1′—$NHSO_2Bu$	++	++	97.2
48. 3—$NHCOCH_3$; 3′—OCH_3; 1′—$NHSO_2Pe$	+	++	97.2
49. 3—$NHCOCH_3$; 3′—CH_3; 1′—$NHSO_2CH_3$	−	+	73.0
50. 3—N(—$COCH_2NHCO$—); 3′—OCH_3; 1′—$NHSO_2CH_3$	+++	+	81.0
51. 3—NO_2; 3′—CH_3; 1′—$NHSO_2CH_3$	−	−	NB
52. 3—Et; 3′—OCH_3; 1′—$NHSO_2CH_3$	++	+	81.0
53. 3—CF_3; 3′—OCH_3; 1′—$NHSO_2CH_3$	+	−	8.0
54. 4—Aza; 3′—OCH_3; 1′—$NHSO_2Pr$	+	+	75.0
55. 4—Aza; 3′—OCH_3; 1′—$NHSO_2Hp$	−	+	75.0
56. 4—CH_3; 3′—OCH_3; 1′—$NHSO_2Et$	+++	++	91.4

[a] See Table 1 for definitions of −, +, ++, +++, ++++.
[b] Based on the occurrence of fragments listed in Fig. 2 and Eq. 2.
[c] Overall probability of being host toxic, based on fragments with probability $p > 70\%$.
[d] NB, no basis found to support activity; compound is presumed to be inactive.

TABLE 3—*Continued*

Test compound	−LogLD$_{10}$[a]		
	Act.	Calc.[b]	Prob.[c]
			%
57. 4—Ph; 3′—OCH_3; 1′—$NHSO_2CH_3$	+	+	51.4
58. 4—OCH_3; 3′—OCH_3; 1′—$NHSO_2Bu$	++	++	91.4
59. 4—OBu; 3′—OCH_3; 1′—$NHSO_2Pe$	+	++	91.4
60. 4—$OCH_2CONHCH_3$; 3′—OCH_3; 1′—$NHSO_2CH_3$	−	+	78.0
61. 4—OCH_2CH_2OH; 3′—OCH_3; 1′—$NHSO_2CH_3$	+++	+	78.0
62. 4—$CONH_2$; 3′—OCH_3; 1′—$NHSO_2CH_3$	++	+	78.0
63. 4—$CONHCH_3$; 3′—OCH_3; 1′—$NHSO_2CH_3$	+	+	78.0
64. 4—CONHBu; 3′—OCH_3; 1′—$NHSO_2Pe$	−	++	91.4
65. 4—$CONHCH_2CH(OH)CH_2OH$; 3′—OCH_3; 1′—$NHSO_2CH_3$	+	+	78.0
66. 4—$CON(CH_3)_2$; 3′—OCH_3; 1′—$NHSO_2CH_3$	++	+	78.0
67. 2—NH_2; 3—Cl; 1′—$NHSO_2CH_3$	+	++	98.3
68. 3—NH_2; 5—CH_3; 1′—$NHSO_2CH_3$	++++	++	85.0
69. 3—$NHCOCH_3$; 5—OCH_3; 1′—$NHSO_2CH_3$	−	+	73.0
70. 3—NO_2; 5—CH_3; 1′—$NHSO_2CH_3$	+	−	NB
71. 3—I; 5—CH_3; 1′—$NHSO_2CH_3$	++	−	NB
72. 3—NH_2; 6—OCH_3; 1′—$NHSO_2CH_3$	+	++	85.0
73. 3—$NHCOCH_3$; 6—NO_2; 1′—$NHSO_2CH_3$	+++	++	94.0
74. 3—NO_2; 6—CH_3; 1′—$NHSO_2CH_3$	−	++	92.0
75. 3,6—$(Br)_2$; 1′—$NHSO_2CH_3$	−	−	NB
76. 3,4,3′—$(CH_3)_3$; 1′—$NHSO_2CH_3$	++	−	NB
77. 3,4—benz; 3′—OCH_3; 1′—$NHSO_2CH_3$	+	−	NB
78. 3—$NHCOOCH_3$; 5—CH_3; 3′—OCH_3; 1′—$NHSO_2CH_3$	+++	++++	100.0
79. 3—NO_2; 5,3′—$(CH_3)_2$; 1′—$NHSO_2CH_3$	−	+	78.0
80. 3—Cl; 5—CH_3; 3′—OCH_3; 1′—$NHSO_2CH_3$	++	++	93.8
81. 3—I; 5,3′—$(OCH_3)_2$; 1′—$NHSO_2CH_3$	+++	++	93.8
82. 3,6—$(NO_2)_2$; 3′—OCH_3; 1′—$NHSO_2CH_3$	−	+++	98.5
83. 4,5,3′—$(CH_3)_3$; 1′—$NHSO_2CH_3$	+	++	78.0
84. 2—NH_2; 3—Br; 5—CH_3; 1′—$NHSO_2CH_3$	++	++	98.3
85. 3—NO_2; 4,6—$(CH_3)_2$; 1′—$NHSO_2CH_3$	−	++	92.0
86. 3,4,6—$(CH_3)_3$; 1′—$NHSO_2CH_3$	+	++	92.0
87. 2—NH_2; 3,4—$(CH_3)_2$; 3′—OCH_3; 1′—$NHSO_2CH_3$	++	++	98.3
88. 3—NO_2; 4,5—$(CH_3)_2$; 3′—OCH_3; 1′—$NHSO_2CH_3$	−	++	93.8
89. 3—NO_2; 5,6—$(CH_3)_2$; 3′—OCH_3; 1′—$NHSO_2Et$	++	+++	92.7
90. 3—$NHCH_3$; 5,6—$(CH_3)_2$; 3′—OCH_3; 1′—$NHSO_2CH_3$	++++	++++	99.8
91. 3—NO_2; 1′—$NHSO_2(CH_2)_2NHCOCH(CH_3)NH_2$	++	−	NB
92. 1′—$NHSO_2(CH_2)_2CONH_2$	−	−	6.0
93. 1′—$NHSO_2(CH_2)_2NHCOCH_2NH_2$	+	−	NB
94. 10—CH_3; 3—NH_2; 1′—$NHSO_2(CH_2)_2NH_2$	++	+++	97.4
95. 3—NO_2; 1′—$NHSO_2(CH_2)_4N(CH_3)_2$	+++	−	NB
96. 3—NO_2; 1′—$NHSO_2(CH_2)_5NH_2$	+	++	87.0
97. 2,6—$(NH_2)_2$; 1′—$NHSO_2(CH_2)_2NHC(NH)NH_2$	++	++	98.3

Test compound	−LogD$_{50}$[a]		
	Act.	Calc.[b]	Prob.[c]
			%
98. 3,6—$(NO_2)_2$; 1′—$NHSO_2(CH_2)_3NHC(NH)NH_2$	−	++	94.0
99. 3—NO_2; 1′—$NHSO_2(CH_2)_5NHC(NH)NH_2$	+	−	NB
100. 2—NH_2; 1′—$NHSO_2Ph$	++	++	62.9
101. 3—NO_2; 1′—$NHSO_2Ph$—m—$NHC(NH)NH_2$	++	−	NB
102. 1′—$NHSO_2PhSO_2CH_3$	+	−	2.0
103. 1′—$N(COPr)SO_2CH_3$	−	−	NB
104. 3—NH_2; 1′—$N(COEt)SO_2CH_3$	++++	+++	93.6
105. 3—$NHCOCH_3$; 1′—$N(COPr)SO_2CH_3$	+	++	87.4
106. 3—$NHCOCH_3$; 1′—$N(COC_{10}H_{21})SO_2CH_3$	++	++	87.4
107. 3—$NHCOCH_3$; 1′—$N(COC_{17}H_{35})SO_2CH_3$	−	+++	87.4
108. 3—NO_2; 1′—$N(COCH_3)SO_2CH_3$	+	+	72.0
109. 3—NO_2; 1′—$N(COPe)SO_2CH_3$	+++	+	72.0
110. 3—NO_2; 5—CH_3; 1′—$N(COEt)SO_2CH_3$	+	+	72.0
111. 3—NO_2; 5—CH_3; 3′—OCH_3; 1′—$N(COEt)SO_2CH_3$	−	+++	97.5
112. 2′—$N(CH_3)COCH_3$	+	−	15.0
113. 2′—CH_3	−	−	15.0
114. 3′—NH_2	+	++	94.5
115. 3′—$NHSO_2CH_3$	−	−	23.0
116. 3′—$C(CH_3)_3$	−	−	23.0
117. 3′—OEt	+	−	23.0
118. 3′,5′—$(OCH_3)_2$	++	−	NB
119. 1′—NH_2; 2′—OCH_3	−	+	91.0
120. 3—NO_2; 1′—NH_2	+	++	85.0
121. 3—NO_2; 1′—$N(CH_2CH_2)_2NCH_3$	++	+	72.0
122. 1′,2′—(N=C[$(CH_2)_3COOH$]NH)	−	−	19.0
123. 3—NH_2; 1′—NO_2	+	++	85.0
124. 3—NO_2; 1′—CH_2NH_2	++	++	94.0
125. 1′—$(CH_2)_2OH$	+	−	NB
126. 3—NO_2; 1′—$(CH_2)_5NH_2$	++	++	87.0
127. 3—OCH_3; 1′—CH_2COOH	+	+	90.9
128. 3—NO_2; 1′—OCH_3	+	−	NB
129. 2′—OCH_3; 1′—$NHSO_2CH_3$	+	−	15.0
130. 1—OCH_3; 1′—$NHSO_2CH_3$	−	−	NB
131. 3—SO_2NH_2; 1′—$NHSO_2CH_3$	+	−	NB
132. 2—Cl; 3′—OCH_3; 1′—$NHSO_2CH_3$	−	−	NB
133. 2,3—benz; 3′—OCH_3; 1′—$NHSO_2CH_3$	+	−	NB
134. 4—CH_3; 3′—OCH_3; 1′—$N(COEt)SO_2CH_3$	++	++	90.1
135. 4—CH_3; 3′—OCH_3; 1′—$N(COPr)SO_2CH_3$	+	++	90.1
136. 1′—$NHSO_2(CH_2)_2PhNH_2$	−	+	85.0
137. 10—CH_3; 1′—$NHSO_2(CH_2)_2NHCO(CH_2)_2NH_2$	+	++	87.0
138. 2′—Aza	−	−	NB
139. 3′—$CH_2NHSO_2CH_3$	−	−	23.0
140. 3—$NHSO_2CH_3$; 1′—NH_2	−	+++	93.9
141. 3—$NHCH_3$; 1′—$O(CH_2)_3COOH$	−	+	35.6
142. 1′—SO_3H	−	−	45.0
143. 1′—$CONH_2$	−	+	21.0
144. 2′,6′—$(NHSO_2CH_3)_2$	−	−	15.0
145. 3′—Aza; 1′—$NHSO_2CH_3$	−	−	NB
146. 1—Aza; 1′—$NHSO_2CH_3$	−	−	NB
147. 2—OCH_3; 1′—$NHSO_2CH_3$	−	−	NB
148. 4—COOEt; 1′—$NHSO_2CH_3$	−	−	NB
149. 2,6—$(NHCOCH_3)_2$; 1′—$NHSO_2CH_3$	−	−	NB
150. 1′—$NHSO_2(CH_2)_2COOCH_3$	−	+	6.0

Assignments of specific mechanistic activities to the molecular fragments is difficult since the data analyzed were determined *in vivo* and consist of biologically complex phenomena such as metabolism and transport as well as interaction with cellular DNA. General principles, however, can be derived as to what is needed for therapeutic success. In regard to antileukemic activity, the following biophores, listed in decreasing "potency," contribute to enhanced activity: I, VI, IX, X, XI, II, III, V. Fragment I consists of an acridine moiety substituted in the 3-position. It has previously been shown (2, 16) that small substituents at this position enhance activity. Analysis of regression Eq. 2, however, shows that substitution by a secondary amine, azido, oxygen, or bromo-substituent (fragments V, X, XIII, and XVI, respectively) enhances the compound's toxicity. Furthermore, a methanesulfonamide at this position acts as a biophobe (see fragment IV, Fig. 1). Antileukemic fragment VI pertains to a 3,4,6-substitution pattern on the acridine nucleus. No toxic fragment explicitly incorporating a 3,4,6-trisubstitution pattern exists within Eq. 2. Appropriate choices of substituents (i.e., avoiding substituents which may give rise to toxic fragments II, VII, IX, X, XIII, and XVI) should increase the dose potency with minimal to no increase in toxicity.

The therapeutic benefits of dose potent fragment IX and its associated expanded features as well as fragment II are offset by toxic fragments I and IV. The presence of an amino or alkylamino derivative increases both the potency as well as the toxicity of the compound as shown previously (16). In the case of the amino and alkylamino functionalities, this can be due to two factors. At physiological pH the amines may be protonated, leading to a positively charged species which can enhance the binding to cellular DNA (17). Alternatively, the lone pair of electrons on the nitrogen can be donated into the π-system. It has previously been determined (16) that electron-donating substituents in the acridine ring enhance the antileukemic and toxic activity presumably by stabilizing the 9-anilinoacridines to attack by plasma thiols (30).

Fragment X of regression Eq. 1 is a biophore and pertains to a 3,6-disubstitution pattern. Previous investigators (16) had found that 3,6-disubstitution decreased the antileukemic activity of 9-anilinoacridines. Our results, however, show that this particular substituent pattern with the 3-position specifically consisting of a secondary amine enhances the activity. It may be assumed that if the NH— is part of an amide functionality, *in vivo* hydrolysis may afford the amine derivative. What one should avoid, however, is a methanesulfonamide at the 3-position since this leads to a decrease in antileukemic activity (see fragment IV of Figure 1).

Two antileukemic fragments (III and XI) describe a therapeutically beneficial substitution pattern on the anilino moiety. Specifically, an oxygen substituent at the 3′-position as well as an ethanesulfonamide at the 1′-position enhance activity. Toxic fragment XVIII, however, incorporates a similar substitution pattern and contributes to toxicity. The respective regression coefficients indicate that the therapeutic benefits outweigh the toxic effects. Furthermore, substituents arranged as shown in fragments XIV and VIII (Fig. 1) lead to a decrease in activity. Toxic fragments II and III with the 3′-position shown with respect to the acridine substitution pattern must be avoided since the contribution to toxicity outweighs the antileukemic activity. Electron-donating substituents on the anilino ring are known to increase (16) the dose potency, either by contributing to tighter DNA binding (14) or by lowering the oxidation potential and thus allowing the formation of the quinoneimine metabolite (which may be a factor in the activity of the 9-anilinoacridines).

Up to this point in the discussion, every fragment which contributes to antileukemic potency has the potential to contribute to the host toxicity. The inability to separate therapeutic effects from toxic effects is a general problem in this area of research. Fragment V of regression Eq. 1 seems to overcome this problem. The presence of a 1′-benzenesulfonamide enhances the antileukemic activity (unfortunately, it is also the least potent of the biophores) without any effect on the toxicity. Other authors (16) have come to the same conclusion. It may be that the presence of this functionality enhances charge-transfer and ion-dipole interactions with an adjacent cellular macromolecule. Clearly, further work should be pursued on the benzenesulfonamide derivatives.

Biophobes, VII, XII, and XIII (Fig. 1) should be avoided in the design of antileukemic agents since the activity decreases in the presence of these molecular fragments. Furthermore, toxic biophores III, VII, VIII, and XVII (Fig. 2) should be avoided since toxicity increases with no corresponding increase of dose potency. There are five fragments (VI, XI, XII, XIV, XV) which decrease the toxicity of the 9-anilinoacridines (see Fig. 2). Biophobes XII, XIV, and XV also contain features that would lead to decreased antileukemic activities. Biophobes VI and XI, however, decrease the host toxicity without having any effect on the potency. Further work on derivatives containing these features should be pursued since these fragments may allow a modulation of host toxicity.

Conclusion

Application of the CASE methodology to a series of 9-anilinoacridine derivatives led to the *automatic* generation of molecular fragments relevant to the expressions of antileukemic activity and host toxicity. These descriptors were used to derive regression equations useful for the quantitative estimation of the degree of biological activity. The results obtained within this study lead to a better understanding of the host toxicity and antitumor activity of the 9-anilinoacridines. New compounds can be submitted to the CASE program and predictions as to the type and degree of activity can be made. Furthermore, identification of features that decrease the toxicity can lead to the design of antileukemic agents with minimal side effects. Current work in this laboratory is progressing toward this goal.

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