Articles

2-(Aminoalkyl)-5-nitropyrazolo[3,4,5-*kl*]acridines, a New Class of Anticancer Agents

David B. Capps, James Dunbar, Suzanne R. Kesten, Joan Shillis, and Leslie M. Werbel*

Warner-Lambert/Parke-Davis Pharmaceutical Research, Ann Arbor, Michigan 48106

Jacqueline Plowman

Division of Cancer Treatment, NCI, Bethesda, Maryland 20205

Donald L. Ward

Department of Chemistry, Michigan State University, East Lansing, Michigan 48824-1322

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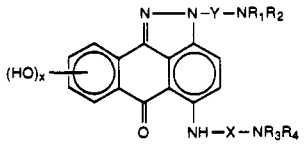
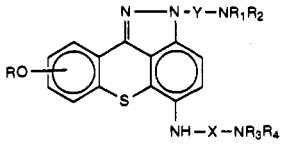
2-(Aminoalkyl)-5-nitropyrazolo[3,4,5-*kl*]acridines were prepared from substituted anilines via the 1-chloro-4-nitroacridones followed by condensation with [(alkylamino)alkyl]hydrazines. Impressive activity was demonstrated for the 9-hydroxy, 9-alkoxy, and 9-acyloxy analogs in vitro on a L1210 leukemia line and in vivo against the P388 leukemia. Advanced studies led to the selection of **3bbb** for clinical trial.

In the course of our work directed towards modifying the chromophore of the anthracenedione nucleus to provide DNA binders with lowered cardiotoxicity, we developed the anthrapyrazoles[1,2] (I) and the benzothiopyranoindazoles[3,4] (II) series with high level broad spectrum activity in preclinical models which are currently undergoing clinical trial.

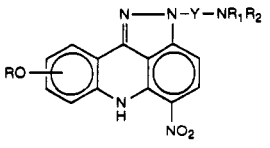


I



II

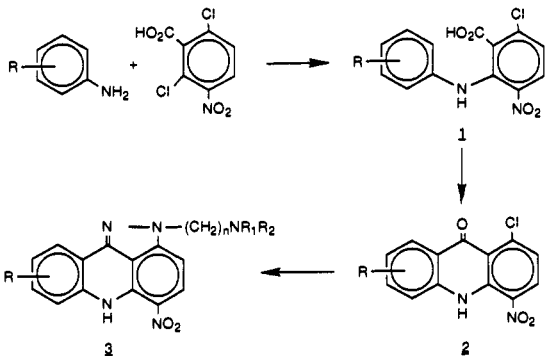
Further exploration led us to the 2-(aminoalkyl)-5-nitropyrazolo[3,4,5-*kl*]acridines (III). This class of compounds containing only one basic side chain and an electron-affinic nitro group proved to be a very exciting new class of antitumor agents.[5-8]



III

Herein we present a full discussion of the synthesis and early in vitro and in vivo anticancer activity of these compounds.

Scheme I



Chemistry

A general route to the pyrazoloacridines is depicted in Scheme I.

Treatment of 2,6-dichloro-3-nitrobenzoic acid with a substituted aniline in the presence of either a mixture of *N,N*-diisopropylethylamine and an excess of *N,N*-di-

(1) Showalter, H. D. H.; Johnson, J. L.; Werbel, L. M.; Leopold, W. R.; Jackson, R. C.; Elslager, E. F. 5-[(Aminoalkyl)amino]-substituted Anthra-[1,9-*cd*]pyrazol-6(2*H*)-ones as Novel Anticancer Agents. Synthesis and Biological Evaluation. *J. Med. Chem.* **1984**, *27*, 253–255.

(2) Leopold, W. R.; Nelson, J. M.; Plowman, J.; Jackson, R. C. Anthrapyrazoles, A New Class of Intercalating Agents with High Level, Broad Spectrum Activity Against Murine Tumors. *Cancer Res.* **1985**, *45*, 5532–5539.

(3) Werbel, L. M.; Elslager, E. F.; Ortwine, D. F.; Shillis, J. L.; Showalter, H. D. H.; Worth, D. F.; Plowman, J. 2-(Aminoalkyl)-5-amino-2*H*-[1]-benzothiopyrano[4,3,2-*cd*]-indazoles, A New Class of Anticancer Agents. *Proc. Am. Assocd. Cancer Res.* **1985**, *26*, 254.

(4) Leopold, W. R.; Fry, D. W.; Nelson, J. M.; Plowman, J. In Vivo Activity and Biochemical Characterization of Substituted [1]Benzothiopyrano[4,3,2-*cd*]-indazoles, A Novel Class of DNA-Binding Anticancer Agents. *Proc. Am. Assoc. Cancer Res.* **1985**, *26*, 253.

(5) Capps, D. B.; Kesten, S. R.; Shillis, J.; Plowman, J. 2-Aminoalkyl-5-nitropyrazolo[3,4,5-*kl*]acridines, A New Class of Anticancer Agents. *Proc. Am. Assoc. Cancer Res.* **1986**, *27*, 277.

(6) Sebolt, J. S.; Scavone, S. V.; Pinter, C. D.; Hamelehle, K. L.; VonHoff, D. D.; Jackson, R. C. Pyrazoloacridines, A New Class of Anticancer Agents with Selectivity Against Solid Tumors In Vitro. *Cancer Res.* **1987**, *47*, 4299–4304.

(7) Jackson, R. C.; Sebolt, J. S.; Shillis, J. L.; Leopold W. R. The Pyrazoloacridines. Approaches to the Development of a Carcinoma-Selective Cytotoxic Agent. *Cancer Invest.* **1990**, *8*, 39–47.

(8) LoRusso, P.; Wozniak, J.; Polin, L.; Capps, D.; Leopold, W. R.; Werbel, L. M.; Biernat, L.; Dan, M. E.; Corbett, T. H. Antitumor Efficacy of PD 115934 (NSC 366140) Against Solid Tumors of Mice. *Cancer Res.* **1990**, *60*, 4900–4905.

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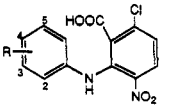
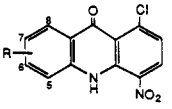
Table I. Preparation of (Arylamino)benzoic Acids



no.	R	formula	mp, °C	% yield	analysis (±0.40%)	method
1a	H	$C_{13}H_9ClN_2O_4$	199–204[a]	61	C,H,N	*a*
1b	4-CH_3	$C_{14}H_{11}ClN_2O_4$	192–197	64[c]	C,H,N	B[b]
1c	2-OCH_3	$C_{14}H_{11}ClN_2O_5$	–	38[e]	–	B[d]
1d	4-OCH_3	$C_{14}H_{11}ClN_2O_5$	210–212	83	C,H,N	B
1e	4-OC_2H_5	$C_{15}H_{13}ClN_2O_5$	174–176	47[g]	–	B[f]
1f	4-$OCH_2CH_2CH_3$	$C_{16}H_{15}ClN_2O_5$	194–196	71[g]	–	B
1g	4-$O(CH_2)_3CH_3$	$C_{17}H_{17}ClN_2O_5$	166–169	65[g]	–	B
1h	4-$OCH_2CH{=}CH_2$	$C_{16}H_{13}ClN_2O_5$	177–179	49	C,H,N,Cl	A[b]
1i	3-$OCH_2C_6H_5$	$C_{20}H_{15}ClN_2O_5$	155–157	40	–	A[i]
1j	4-$OCH_2C_6H_5$	$C_{20}H_{15}ClN_2O_5$	171–172	47	C,H,N	A
1k	4-SCH_3	$C_{14}H_{11}ClN_2O_4S$	173–174	56	–	B[j]
1l	4-$N(CH_3)_2$	$C_{15}H_{14}ClN_3O_4$	222–223	59	C,H,N	p
1m	4-$OCH_2CH_2N(C_2H_5)_2$	$C_{19}H_{22}ClN_3O_5$	212–215	45	C,H,N	p
1n	2,4-diOCH_3	$C_{15}H_{13}ClN_2O_6$	166–170	21	C,H,N,Cl	B[k]
1o	3,5-$(OCH_3)_2$	$C_{15}H_{13}ClN_2O_6$	174–177	59	–	B[l]
1p	3,4-$(OCH_3)_2$	$C_{15}H_{13}ClN_2O_6$	261–262	73	–	A[m]
1q	3,4-(–OCH_2O–)	$C_{14}H_9ClN_2O_6$	190–192	54	–	A[n]
1r	3-Cl 4-OCH_3	$C_{14}H_{10}Cl_2N_2O_5$	222–226	54[o]	–	B
1s	3-Cl	$C_{20}H_{14}Cl_2N_2O_5$	198–200	51	C,H,N	A[l,q]

[a] Reference 21, mp 206 °C (56%). [b] Heated 1.7 h at 135 °C. [c] Recrystallized from toluene. [d] Heated 1d at 140 °C. [e] Impure by TLC ($CHCl_3$/MeOH/Et_3N, 50:1:trace), mainly R_f 0.3. [f] Heated 5 h. [g] Contains starting acid as impurity. [h] Reaction mixture was extracted with 1 N NaOH and the extract acidified (dilute HCl). Starting 4-(2-propenyloxy)benzenamine. Claisen, L. *Ann.* **1919**, *418*, 78. Not distilled. [i] Heated 3d. [j] Heated 2d, extracted with dilute NH_4OH. [k] Heated 1d at 100 °C and then 3 h at 150 °C. Mixture extracted with 4% NH_4OH and acidified, and crude product was recrystallized from $CHCl_3$/cyclohexane. [l] Heated 4d. [m] Heated 2d. [n] Extracted with 0.5 N KOH, and extract acidified (dilute HCl). NMR is consistent with structure indicated. [o] TLC ($CHCl_3$/MeOH, 4:1) shows minor impurities. [p] See Experimental Section. [q] For starting benzeneamine see Experimental Section.

Table II. Preparation of 1-Chloro-4-nitroacridones

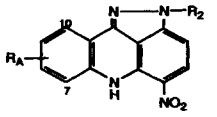


no.	R	formula	mp, °C	% yield	analysis (±0.40%)	method
2a	H	$C_{13}H_7ClN_2O_3$	252–255	55	C,H,N,Cl	*a*
2b	7-CH_3	$C_{14}H_9ClN_2O_3$	239–241	87	C,H,N	C[b]
2c	6-OH	$C_{13}H_7ClN_2O_4$	292–294	98[c]	C,H,N,Cl	*k*
2d	7-OH	$C_{13}H_7ClN_2O_4$	>325	84	C,H,N	*k*
2e	8-OH	$C_{13}H_7ClN_2O_4$	265–267	20	–	*k*
2f	5-OCH_3	$C_{14}H_9ClN_2O_4$	315–320	82	C,H,N	C[d]
2g	7-OCH_3	$C_{14}H_9ClN_2O_4$	262–263	88	C,H,N,Cl	B
2h	7-OC_2H_5	$C_{15}H_{11}ClN_2O_4$	244–246	70	C,H,N	C
2i	7-$OCH_2CH_2CH_3$	$C_{16}H_{13}ClN_2O_4$	174–175	65	C,H,N,Cl	E[e]
2j	7-$O(CH_2)_3CH_3$	$C_{17}H_{15}ClN_2O_4$	154–155	65	C,H,N,Cl	C
2k	7-$OCH_2CH{=}CH_2$	$C_{16}H_{11}ClN_2O_4$	171–172	48	C,H,N,Cl	E[f]
2l	6-$OCH_2C_6H_5$	$C_{20}H_{13}ClN_2O_4$	198–202	32	C,H,N	*k*
2m	7-$OCH_2C_6H_5$	$C_{20}H_{13}ClN_2O_4$	216–217	62	C,H,N	C[d]
2n	7-SCH_3	$C_{14}H_9ClN_2O_3S$	284–286	85	C,H,N,S	E[g]
2o	7-$N(CH_3)_2$	$C_{15}H_{12}ClN_3O_3$	>300	16	C,H,N	*k*
2p	7-$OCH_2CH_2N(C_2H_5)_2$	$C_{19}H_{20}ClN_3O_4$	148–151	67	C,H,N,S,H_2O[h]	*k*
2q	5,7-$(OCH_3)_2$	$C_{15}H_{11}ClN_2O_5$	289–293	82	C,H,N,Cl	C[d]
2r	6,8-$(OCH_3)_2$	$C_{15}H_{11}ClN_2O_5$	291–294	37	C,H,N	E[i]
2s	6,7-$(OCH_3)_2$	$C_{15}H_{11}ClN_2O_5$	>300	58	C,H,N,Cl[j]	E[b]
2t	6,7-(–OCH_2O–)	$C_{14}H_7ClN_2O_5$	284–285	57	C,H,N,Cl	*k*
2u	6-Cl, 7-OH	$C_{13}H_6Cl_2N_2O_4$	>310	100[c]	C,H,N	D
2v	6-Cl, 7-OCH_3	$C_{14}H_8Cl_2N_2O_4$	284–285	54	C,H,N,Cl	E
2w	8-Cl, 7-OH	$C_{13}H_6Cl_2N_2O_4$	276–279	93[c]	C,H,N	D
2x	8-Cl, 7-OCH_3	$C_{14}H_8ClN_2O_4$	251–253	11	C,H,N,Cl	E
2y	6-Cl, 7-$OCH_2C_6H_5$	$C_{20}H_{12}Cl_2N_2O_4$	244–246	66	C,H,N,Cl	*k*
2z	8-Cl, 7-$OCH_2C_6H_5$	$C_{20}H_{12}Cl_2N_2O_4$	272–274	12	C,H,N	*k*

[a] Reference 21, mp 247–248 °C (95%). [b] Refluxed 3 h. [c] Yield based on benzylether. [d] Refluxed 1.5 h. [e] Refluxed 0.5 h. [f] Heated 60 °C/24 h. [g] Refluxed 1 h. [h] Salt $C_{19}H_{20}ClN_3O_4 \cdot CH_3SO_3H \cdot 0.5H_2O$. [i] Refluxed 2 h. [j] 200-MHz NMR (Me_2SO-d_6) δ 3.9 (s, 3 H, OCH_3), 3.95 (s, 3 H, OCH_3), 7.4 (d, J = 8.9 Hz, 1 H, C_2-H), 7.5 (s, 1 H, C_5-H), 7.7 (s, 1 H, C_8-H), 8.55 (d, J = 8.9 Hz, C_3-H), 11.6 (s, 1 H, NH). [k] See Experimental Section.

methylaniline or simply in a large excess of *N,N*-dimethylaniline provided the corresponding (arylamino)benzoic acid 1 (Table I). Cyclization to the substituted 1-chloro-4-nitroacridone 2 (Table II) was effected by $POCl_3$ in $CHCl_3$ or 1,2-dichloroethane containing *N,N*-dimethylaniline. Condensation with an [(alkylamino)alkyl]hy-

Table III. Preparation and Biological Activity of Pyrazoloacridines



no.	R_A	R_2	mol formula (salt)	analysis of base (salt)	mp, °C of base (salt)	% yield base (salt)	method, temp, °C/time	reaction medium	salt recryst solvent	in vitro ID_{50} L1210 (M)	P388 leukemia ip/ip, daily ×5 in mice: dose (mg/kg per inject.)	P388 leukemia ip/ip, daily ×5 in mice: % T/C	P388 leukemia ip/ip, daily ×5 in mice: day 30 survivors
3a	H	$CH_2CH_2NEt_2$	$C_{18}H_{21}N_5O_2 \cdot CH_3SO_3H$	(C,H,N,S)	185–187 (239–241 dec)	74	F, RT/2 h, 45/2 h	THF–MeOH 1:1	MeOH–ether	1.9×10^{-7}	6.25	165	
3b	9-CH_3	$CH_2CH_2NEt_2$	$C_{20}H_{23}N_5O_2 \cdot CH_3SO_3H$	C,H,N (C,H,N,S)	213–217 (204–207)	88[a]	F, RT/20 h	THF–MeOH 1:1	MeOH–ether	8.6×10^{-7}	100	136	
3c	8-OH	$CH_2CH_2NEt_2$	$C_{18}H_{21}N_5O_2 \cdot CH_3SO_3H \cdot 1.2H_2O$	(C,H,N,S)	(239–241)	(24)	F,[b] RT/18 h	THF	THF–MeOH	8.3×10^{-6}	25	130	
3d	9-OH	$CH_2CH_2NEt_2$	$C_{18}H_{21}N_5O_2 \cdot CH_3SO_3H \cdot 0.8H_2O$	(C,H,N,S,H_2O)	(255–256 dec)	(64)	G,[c] RT/24 h	THF–MeOH 9:1	MeOH–H_2O	2.0×10^{-6}	3.0	180	
3e	10-OH	$CH_2CH_2NEt_2$	$C_{18}H_{21}N_5O_2 \cdot CH_3SO_3H \cdot H_2O$	(C,H,N,S)	208–210 (238–242)	(46)	H,[d] RT/18 h	THF	MeOH–EtOH	6.0×10^{-7}	200	117	
3f	7-OCH_3	$CH_2CH_2NEt_2$	$C_{20}H_{23}N_5O_2 \cdot CH_3SO_3H$	(C,H,N,S)	129–131 (195–198)	80	H,[c] 50/2 h, RT/18 h	THF–MeOH 1:1	MeOH–ether	6.4×10^{-7}	100	111	
3g	9-OCH_3	$CH_2CH_2NEt_2$	$C_{20}H_{23}N_5O_2 \cdot CH_3SO_3H$	C,H,N (C,H,N,S)	183–185 (237–240 dec)	70	F, RT/18 h	THF–MeOH 1:1	MeOH–ether–H_2O	4.7×10^{-7}	25	242	
3h	9-OEt	$CH_2CH_2NEt_2$	$C_{21}H_{25}N_5O_2 \cdot CH_3SO_3H$	(C,H,N,S)	165–167 (212–214)	59	H,[f] RT/18 h	THF	THF–MeOH	7.9×10^{-7}	12.5	220	
3i	9-$OCH_2CH_2CH_3$	$CH_2CH_2NEt_2$	$C_{20}H_{27}N_5O_2 \cdot CH_3SO_3H$	(C,H,N,S)	141–142 (209–210)	94	H	THF–MeOH 6:1	MeOH–EtOAc	4.6×10^{-7}	25	273	2/6
3j	9-$O(CH_2)_2CH_3$	$CH_2CH_2NEt_2$	$C_{20}H_{23}N_5O_2 \cdot CH_3SO_3H$	(C,H,N,S)	142–143 (187–189)	73	H,[c] RT/18 h	THF	THF–MeOH	1.2×10^{-6}	12.5	209	
3k	9-$O\text{-}CH_2CH{=}CH_2$	$CH_2CH_2NEt_2$	$C_{22}H_{25}N_5O_2 \cdot CH_3SO_3H$	(C,H,N,S)	125 (183–185)	52	H,[d] RT/10 h	THF	EtOH	5.8×10^{-7}	25	258	1/6
3l	8-$OCH_2C_6H_5$	$CH_2CH_2NEt_2$	$C_{26}H_{27}N_5O_2 \cdot CH_3SO_3H \cdot 0.5H_2O$	(C,H,N,S)	170–172 (166–171)	(52)	H,[d] RT/18 h	THF	$CHCl_3$–MeOH	1.8×10^{-7}	12.5	87	
3m	9-$OCH_2C_6H_5$	$CH_2CH_2NEt_2$	$C_{26}H_{27}N_5O_2 \cdot CH_3SO_3H$	C,H,N (C,H,N,S)	161–164 (216–218)	86[g]	F, RT/18 h	THF–MeOH 1:1	$CHCl_3$–MeOH	2.7×10^{-6}	50	200	
3n	9-SCH_3	$CH_2CH_2NEt_2$	$C_{20}H_{23}N_5O_2S \cdot CH_3SO_3H$	(C,H,N,S)	184–185 (220–221)	75	H,[f] RT/18 h	THF–MeOH 3:1	$CHCl_3$–MeOH	1.1×10^{-6}	50	114	
3o	9-$N(CH_3)_2$	$CH_2CH_2NEt_2$	$C_{21}H_{25}N_5O_2 \cdot 2CH_3SO_3H$	C,H,N (C,H,N,S)	192–196 (206–208)	74	F,[c] RT/24 h	THF–MeOH 1:1	MeOH–EtOAc	9.0×10^{-7}	25	178	1/6
3p	9-$OCH_2CH_2N(C_2H_5)_2$	$CH_2CH_2NEt_2$	$C_{28}H_{34}N_6O_2 \cdot 2CH_3SO_3H$	C,H,N (C,H,N,S)	137–139 (212–214)	65	H[h]	THF–MeOH 4:1	MeOH–EtOAc	5.0×10^{-7}	50	118	
3q	7,9-$(OCH_3)_2$	$CH_2CH_2NEt_2$	$C_{21}H_{25}N_5O_4 \cdot CH_3SO_3H \cdot H_2O$	(C,H,N,S,H_2O)	181–184 (241–241)	85	H,[c] RT/18 h	THF–MeOH 3:1	$CHCl_3$–MeOH–2-PrOH	7.6×10^{-7}	50	88	
3r	8,10-$(OCH_3)_2$	$CH_2CH_2NEt_2$	$C_{21}H_{25}N_5O_4 \cdot CH_3SO_3H \cdot 1.25H_2O$	(C,N,S,H_2O;H[i])	213–215 (240–241)	73	H,[c] RT/18 h	THF–MeOH 4:1	$CHCl_3$–MeOH	4.9×10^{-7}	50	94	
3s	8,9-$(OCH_3)_2$	$CH_2CH_2NEt_2$	$C_{21}H_{25}N_5O_4 \cdot 1.2CH_3SO_3H \cdot H_2O$	(C,N,S,H_2O;H[i])	190–196 (256–259)	65	H, RT/24 h	THF	MeOH–2-PrOH	1.1×10^{-6}	100	126	
3t	8,9-OCH_2O-	$CH_2CH_2NEt_2$	$C_{20}H_{21}N_5O_4 \cdot CH_3SO_3H \cdot H_2O$	(C,H,N,S,H_2O)	185–188 (246–248)	74	H,[h] RT/1 h	THF	$CHCl_3$–MeOH	1.6×10^{-7}	50	173	
3u	8-Cl, 9-OH	$CH_2CH_2NEt_2$	$C_{18}H_{20}ClN_5O_2 \cdot CH_3SO_3H \cdot H_2O$	C,H,N (C,H,N,S)	ca. 300 dec (274–277 dec)	56	F,[j] RT/24 h	THF	MeOH–H_2O–EtOAc	1.5×10^{-7}	50	125	
3v	8-Cl, 9-OCH_3	$CH_2CH_2NEt_2$	$C_{20}H_{22}ClN_5O_2 \cdot CH_3SO_3H \cdot 0.5H_2O$	(C,H,N,Cl,S,H_2O)	222–224 (262–266)	78	H, RT/18 h	THF	$CHCl_3$–EtOH	2.7×10^{-7}	25	112	
3w	9-OH, 10-Cl	$CH_2CH_2NEt_2$	$C_{18}H_{20}ClN_5O_2 \cdot CH_3SO_3H$	C,H,N (C,H,N,S)	239–241 dec (270–272 dec)	48	F[m]	THF	MeOH–H_2O–EtOAc	3.9×10^{-10}	6.0	196	1/6
3x	9-OCH_3, 10-Cl	$CH_2CH_2NEt_2$	$C_{20}H_{22}ClN_5O_2 \cdot CH_3SO_3H \cdot H_2O$	(C,H,N,S;H_2O[k])	202–204 (271–273)	(60)	H, RT/18 h	THF	THF–MeOH	6.1×10^{-6}	12.5	230	3/6

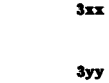
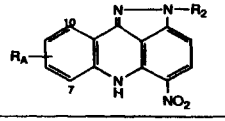
3y	9-OCOCH$_3$	$CH_2CH_2NEt_2$	$C_{21}H_{28}N_6O_4 \cdot CH_3SO_3H$	(C,H,N,S[o])	176–178 (250–251 dec)	51	I, RT/2.5 h	CH_2Cl_2	MeOH–EtOAc	3.8×10^{-6}	3.12	263	4/6
3z	9-OCOC(CH$_3$)$_3$	$CH_2CH_2NEt_2$	$C_{24}H_{32}N_6O_4 \cdot CH_3SO_3H$	C,H,N (C,H,N,S)	255–258 dec (233–235 dec)	69	I,[p] RT/90 h	CH_2Cl_2	MetOH–EtOAc–ether	1.0×10^{-6}	6.25	263	5/6
3aa	9-OCO(CH$_2$)$_2$CH$_3$	$CH_2CH_2NEt_2$	$C_{22}H_{30}N_6O_4 \cdot CH_3SO_3H$	C,H,N (C,H,N,S)	167–161 (220–222)	63	I, 50°/2.5 h	$1,2\text{-}Cl_2C_2H_4$	MeOH–EtOAc	4.3×10^{-6}	6.25	252	1/6
3bb	9-OCO(CH$_2$)$_6$CH$_3$	$CH_2CH_2NEt_2$	$C_{27}H_{38}N_6O_4 \cdot CH_3SO_3H \cdot 0.5H_2O$	C,H,N (C,H,N,S)	136–138 (159–163)	57	I, 50°/2 h	$1,2\text{-}Cl_2C_2H_4$	MeOH–EtOAc	6.4×10^{-6}	6.25	260	3/6
3cc	9-OCOC$_6$H$_5$	$CH_2CH_2NEt_2$	$C_{26}H_{28}N_6O_4 \cdot CH_3SO_3H \cdot H_2O$	C,H,N (C,H,N,S)	192–195 (225–228)	67	I,[q] 75°/5 h	$1,2\text{-}Cl_2C_2H_4$	MeOH–EtOAc	3.0×10^{-6}	6.25	238	1/6
3dd	9-OCOOC$_2$H$_5$	$CH_2CH_2NEt_2$	$C_{23}H_{30}N_6O_5 \cdot CH_3SO_3H$	C,H,N (C,H,N,S)	176–179 (197–199)	72	I, RT/1.5 h	CH_2Cl_2	MeOH–EtOAc	3.2×10^{-6}	3.13	243	
3ee	9-OTBDMS	$CH_2CH_2NEt_2$	$C_{28}H_{42}N_6O_4Si \cdot CH_3SO_3H$	C,H,N (N,S;C,H)	218–220 (207–213)	91	r	CH_2Cl_2	CH_3CN	1.7×10^{-6}	12.5	228	2/6
3ff	9-OH	$CH_2CH_2NMe_2$	$C_{17}H_{17}N_5O_3 \cdot CH_3SO_3H \cdot 1.1H_2O$	(C,H,N,S;H$_2$O[r])	239–240 (260–262)	66	J, 50°/2 h, RT/18 h	THF	MeOH–H_2O	2.7×10^{-6}	3.12	228	2/6
3gg	9-OCH$_3$	$CH_2CH_2NMe_2$	$C_{18}H_{19}N_5O_3 \cdot CH_3SO_3H \cdot 0.5H_2O$	C,H,N (C,H,N,S)	219–222 (237–240 dec)	70	F,[t] RT/18 h	THF–MeOH 1:1	MeOH–H_2O–ether	4.0×10^{-7}	50	275	3/6
3hh	9-OC$_2$H$_5$	$CH_2CH_2NMe_2$	$C_{19}H_{21}N_5O_3 \cdot 1.35CH_3SO_3H \cdot 0.25H_2O$	(C,H,N,S,H$_2$O)	195–197 (214–216)	(26)	H[u]	THF–MeOH 10:1	$CHCl_3$–MeOH	2.7×10^{-7}	12.5	234	1/6
3ii	9-N(CH$_3$)$_2$	$CH_2CH_2NMe_2$	$C_{19}H_{22}N_6O_3 \cdot 2CH_3SO_3H \cdot 2H_2O$	(C,N,S;H[v])	(260–206 dec[w])	70	F,[x] RT/3 h	THF–MeOH 1:1	MeOH–EtOAc	6.0×10^{-7}	25	189	
3jj	7,9-(OCH$_3$)$_2$	$CH_2CH_2NMe_2$	$C_{19}H_{21}N_5O_5 \cdot CH_3SO_3H$	(C,H,N,S)	239–241 (260–262)	84	F[y]	THF–MeOH 3:1	$CHCl_3$–MeOH	2.1×10^{-7}	200	128	
3kk	9-OCOCH$_3$	$CH_2CH_2NMe_2$	$C_{19}H_{19}N_5O_4 \cdot 1.25CH_3SO_3H \cdot 0.75H_2O$	(C,H,N,S)	206–215 (130–135)	68	I,[z] reflux/5 h	CH_2Cl_2	CH_2Cl_2–EtOAc	1.2×10^{-6}	3.12	265	3/6
3ll	9-OCOC(CH$_3$)$_3$	$CH_2CH_2NMe_2$	$C_{22}H_{25}N_5O_4 \cdot CH_3SO_3H \cdot 1/2H_2O$	(C,H,N,S)	208–225 (254–258)	56	I, 50°/4 h	$1,2\text{-}Cl_2C_2H_4$	EtOAc	2.9×10^{-6}	3.12	236	2/6
3mm	H	$CH_2CH_2NHCH_2CH_2OH$	$C_{17}H_{17}N_5O_2 \cdot HCl$	(C,H,N,Cl)	(>300)	(77)	G, 60°/16 h	THF–MeOH 1:1	–	2.2×10^{-7}	25	235	
3nn	9-CH$_3$	$CH_2CH_2NHCH_2CH_2OH$	$C_{18}H_{19}N_5O_2 \cdot HCl$	(C,H,N,Cl)	(>300)	(68)	G, RT/7 h	THF–MeOH 1:1	–	5.9×10^{-7}	50	115	
3oo	9-OH	$CH_2CH_2NHCH_2CH_2OH$	$C_{17}H_{17}N_5O_4 \cdot CH_3SO_3H$	(C,H,N,S)	(256–258)	(26)	J, RT/120 h	MeOH	H_2O–MeOH	4.6×10^{-6}	6.25	275	6/6
3pp	9-OCH$_3$	$CH_2CH_2NHCH_2CH_2OH$	$C_{18}H_{19}N_5O_3 \cdot HCl$	(C,H,N,Cl)	(>315)	(69)	G, RT/3 h	THF–MeOH 2:1	–	4.5×10^{-7}	50	163	
3qq	9-OC$_2$H$_5$	$CH_2CH_2NHCH_2CH_2OH$	$C_{19}H_{21}N_5O_4 \cdot HCl \cdot 0.25H_2O$	(C,H,N,H$_2$O)	(283–285)	(32)	G,[aa] RT/18 h	THF–MeOH 4:5	DMF–MeOH	3.2×10^{-7}	50	195	
3rr	9-O(CH$_2$)$_2$CH$_3$	$CH_2CH_2NHCH_2CH_2OH$	$C_{21}H_{25}N_5O_4 \cdot CH_3SO_3H \cdot 0.4H_2O$	(C,H,N,S,H$_2$O)	170–172 (239–241)	(42)	J, RT/18 h	MeOH	$CHCl_3$–MeOH	6.5×10^{-7}	12.5	175	
3ss	9-OCH$_3$	CH_2CH_2OH	$C_{18}H_{14}N_4O_4$	C,H,N	275–276	95	F	THF–MeOH 2:1	–	inactive	–	–	–
3tt	9-OCH$_3$	CH_2CH_2Cl	$C_{18}H_{13}ClN_4O_3$	C,H,N,Cl	261–263 dec	48	r	–	–	–	–	–	–
3uu	9-OCH$_3$	CH_2CH_2NHEt	$C_{19}H_{19}N_5O_3 \cdot 1.25CH_3SO_3H \cdot 0.6H_2O$	(C,H,N,S,H$_2$O)	168–170 (228–230)	68	r	–	$CHCl_3$–MeOH	2.1×10^{-7}	50	240	1/6
3vv	9-OH		$C_{19}H_{19}N_5O_3 \cdot CH_3SO_3H \cdot H_2O$	(C,H,N,S)	266[ac] (212–214)	40	F, 45°/23 h	THF–MeOH 1:1	MeOH–EtOAc	3.0×10^{-6}	3.12	250	
3ww	9-OCH$_3$		$C_{20}H_{21}N_5O_3 \cdot CH_3SO_3H$	C,H,N (C,H,N,S)[ac]	200–203 (236–238)	56	F[dd]	THF–MeOH 1:1	MeOH–EtOAc	1.6×10^{-7}	25	211	
3xx	9-OCOCH$_3$		$C_{21}H_{21}N_5O_4 \cdot CH_3SO_3H \cdot 1/2H_2O$	C,H,N (C,H,N,S,H$_2$O)	196–197 (240–242)	41	I, 40°/18 h	$1,2\text{-}Cl_2C_2H_4$	THF–MeOH	2.2×10^{-6}	3.12	236	1/6
3yy	H	$CH_2CH_2CH_2NMe_2$	$C_{18}H_{19}N_5O_3 \cdot 1.15CH_3SO_3H \cdot 0.5H_2O$	(C,H,N,S,H$_2$O)	248–253[ff] (242–246)	38	G, RT/18 h	THF	$CHCl_3$–MeOH	1.9×10^{-7}	12.5	214	1/6
3zz	8-OH	$CH_2CH_2CH_2NMe_2$	$C_{18}H_{19}N_5O_3 \cdot HCl \cdot H_2O$	(C,H,N,Cl)	(298)	(57)	G,[gg] RT/18 h	THF	–	6.7×10^{-6}	50	140	
3aaa	9-OH	$CH_2CH_2CH_2NMe_2$	$C_{18}H_{19}N_5O_3 \cdot CH_3SO_3H \cdot H_2O$	(C,H,N,S)	244–247 (259–261)	72	G,[hh] 60°/88 h	THF–MeOH 1:1	MeOH–H_2O–EtOAc	1.8×10^{-6}	3.12	270	3/6
3bbb	9-OCH$_3$	$CH_2CH_2CH_2NMe_2$	$C_{19}H_{21}N_5O_3 \cdot CH_3SO_3H$	C,H,N (C,H,N,S)	176–178 (229–232)	89	H,[ii] RT/7.5 h	THF–MeOH 1:1	MeOH–H_2O–EtOAc	4.2×10^{-7}	25	261	2/6

Table III. (Continued)



no.	R_A	R_2	mol formula (salt)	analysis of base (salt)	mp, °C of base (salt)	% yield base (salt)	method, temp, °C/time	reaction medium	salt recryst solvent	in vitro ID_{50} L1210 (M)	P388 leukemia ip/ip, daily ×5 in mice: dose (mg/kg per inject.)	P388 leukemia ip/ip, daily ×5 in mice: % T/C	P388 leukemia ip/ip, daily ×5 in mice: day 30 survivors
3ccc	9-OC_2H_5	$CH_2CH_2CH_2NMe_2$	$C_{20}H_{26}N_5O_2 \cdot CH_3SO_3H$	(C,H,N,S)	175–176 (266–268)	84	H[ii]	THF–MeOH 8:1	$CHCl_3$–MeOH	2.2×10^{-7}	12.5	236	
3ddd	9-$OCH_2CH{=}CH_2$	$CH_2CH_2CH_2NMe_2$	$C_{21}H_{26}N_5O_2 \cdot CH_3SO_3H \cdot 2H_2O$	(C,H,N,S[kk])	152–154 (248–242)	56	H, RT/18 h	THF	MeOH–H_2O	2.2×10^{-8}	12.5	221	
3eee	9-OCH_3, 10-Cl	$CH_2CH_2CH_2NMe_2$	$C_{18}H_{23}ClN_5O_2 \cdot CH_3SO_3H \cdot H_2O$	(C,H,N,Cl,S,H_2O)	192–193 (273–275)	38	H, RT/2 h	THF	$CHCl_3$–MeOH	1.0×10^{-7}	6.25	221	1/6
3fff	9-$OCOCH_3$	$CH_2CH_2CH_2NMe_2$	$C_{20}H_{21}N_5O_4 \cdot CH_3SO_3H$	(C,H,N,S)	(260–264)	72	I, 80°/3 h	1,2-$Cl_2C_2H_4$	MeOH–EtOAc	1.9×10^{-8}	3.12	252	2/6
3ggg	9-$OCOC(CH_3)_3$	$CH_2CH_2CH_2NMe_2$	$C_{23}H_{27}N_5O_4 \cdot CH_3SO_3H$	(C,H,N,S)	(243–245)	70	I, 60°/1.5 h	1,2-$Cl_2C_2H_4$	MeOH–EtOAc	7.7×10^{-8}	1.56	263	2/6
3hhh	9-OCH_3	$CH_2CH_2CH_2NEt_2$	$C_{21}H_{28}N_5O_2 \cdot CH_3SO_3H \cdot H_2O$	(H,N,S;C,H_2O[mm])	143–145[nn] (191–193)	78	H, RT/2 h	THF–MeOH 5:1	$CHCl_3$–MeOH	1.3×10^{-8}	25	210	

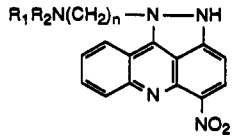
[a] Crude precipitate washed with MeOH and H_2O and recrystallized from toluene. [b] Liquor was decanted from reaction mixture and treated with 1 N MeOH–CH_3SO_3H, precipitating salt. [c] Hydrochloride salt was stirred 18 h in 0.5 N $NaHCO_3$ and resulting free base dissolved in hot MeOH–CH_3SO_3H, filtered, and cooled, precipitating salt. [d] Gummy evaporated residue triturated with MeOH, producing crystalline free base. [e] Evaporation residue in $CHCl_3$ washed with dilute aqueous Na_2CO_3 and chromatographed over SiO_2 in $CHCl_3$–MeOH (50:1). [f] Crude base chromatographed over SiO_2 in $CHCl_3$–MeOH (100:1). [g] Recrystallized from toluene and $CHCl_3$–cyclohexane. [h] Evaporation residue washed (H_2O) and chromatographed (SiO_2) in $CHCl_3$–MeOH (10:1). [i] H: calcd, 5.88; found, 5.37. [k] Evaporated reaction solution to 1/20th volume, added MeOH, and base precipitated. [l] Recrystallized from DMF–MeOH (1:1). [m] Hydrazine reagent was added over 0.5 h to acridone suspension at 0 °C and then stirred 5 h without cooling. [n] H_2O: Calcd, 3.40; found, 1.36 (sample insoluble). [o] 200 MHz NMR (Me_2SO-d_6) δ 1.2 (t, J = 7.2 Hz, 6 H, NCH_2CH_3), 2.3 (2 s, 6 H, CH_3SO_3H and CH_3COO), 3.2 (crude q, 4 H, NCH_2CH_3), 3.3 (HDO), 3.7 (crude t, 2 H, CH_2NEt_2), 4.8 (t, J = 6.5 Hz, 2 H, NCH_2), 7.0 (d, J = 9.4 Hz, 1 H, C_3-H), 7.3 (dd, J = 2.6 Hz, J = 9.0 Hz, 1 H, C_7-H), 7.7 (d, J = 2.6 Hz, 1 H, C_7-H), 8.0 (d, J = 9.0 Hz, 1 H, C_6-H), 8.15 (d, J = 9.4 Hz, 1 H, C_4-H), 9.2 (bs, 1 H, NH), 11.3 (s, 1 H, SO_3H). [p] Base recrystallized from CH_3CN, not chromatographed. [q] Base recrystallized from toluene–cyclohexane, not chromatographed. [r] See Experimental Section. [s] H_2O: Calcd, 4.35; found, 3.11 (sample partly insoluble). [t] Base in $CHCl_3$ washed with dilute aqueous Na_2CO_3, dried, and evaporated. [u] Reaction mixture prepared at −10 °C and stirred 2 h without cooling. [v] H: Calcd, 5.76; found, 5.30. [w] After loss of H_2O. [x] Base chromatographed over SiO_2 in $CHCl_3$–MeOH (50:1). [y] Reaction mixture prepared at 0 °C and stirred 18 h without cooling. [z] Base not chromatographed. Final salt homogeneous by TLC ($CHCl_3$–MeOH, 4:1). [aa] Crude precipitate recrystallized from DMF–MeOH. [bb] Washed base recrystallized from EtOH. [cc] Recrystallized from *N,N*-dimethylacetamide. [dd] Added hydrazine to 0 °C mixture over 2 h and stirred 18 h without cooling. [ee] 200 MHz NMR (Me_2SO-d_6) δ = 1.6 (m, 4 H, *N*-βCH_2), 2.5 (m, 4 H + DMSO, N-αCH_2), 2.95 (t, J = 6.4 Hz, 2 H, CH_2-pyr), 3.8 (s, 3 H, OCH_3), 4.5 (t, J = 6.2 Hz, 2 H, $NNCH_2$), 6.85 (d, J = 9.4 Hz, 1 H, C_3-H), 7.15 (dd, J = 3.0 Hz, J = 9.2 Hz, 1 H, C_7-H), 7.35 (d, J = 3 Hz, 1 H, C_9-H), 7.9 (d, J = 9.2 Hz, 1 H, C_6-H), 8.05 (d, J = 9.4 Hz, 1 H, C_4-H), 11.2 (s, 1 H, NH). [ff] HCl salt (mp 248–253 °C, 38%) converted to base in aqueous NH_3 and extracted with $CHCl_3$. [gg] Crude salt washed with EtOH. [hh] HCl salt was dissolved in 80 °C water and $NaHCO_3$ was added to pH 8–9, precipitating base. [ii] Evaporated residue washed (H_2O) and recrystallized from toluene–isooctane. [jj] Mixture initially −10 °C and stirred 3 h without cooling. [kk] Salt insoluble in K-F reagent. [ll] Mixture filtered, concentrated, and diluted with MeOH, precipitating base. [mm] C: Calcd, 51.85; found, 51.42; H_2O: calcd 3.53; found, 2.23. [nn] Base recrystallized from MeOH.

Table IV

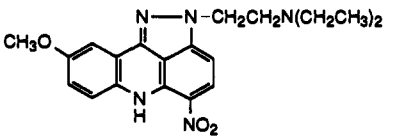
no.	R_A	R_2	in vitro ID_{50} (M) L1210	in vitro ID_{50} (M) HCT-8	ratio ID_{50} HCT-8/L1210
3g	9-OCH_3	$CH_2CH_2NEt_2$	4.7×10^{-7}	1.2×10^{-7}	0.26
3bbb	9-OCH_3	$(CH_2)_3NMe_2$	4.2×10^{-7}	1.4×10^{-7}	0.33
3n	9-SCH_3	$CH_2CH_2NEt_2$	1.1×10^{-6}	3.5×10^{-7}	0.32
3d	9-OH	$CH_2CH_2NEt_2$	2.0×10^{-9}	1.3×10^{-8}	6.5
3aaa	9-OH	$(CH_2)_3NMe_2$	1.8×10^{-9}	1.2×10^{-8}	6.7
3y	9-$OCOCH_3$	$CH_2CH_2NEt_2$	3.8×10^{-9}	5.3×10^{-9}	1.4
3z	9-$OCOC(CH_3)_3$	$CH_2CH_2NEt_2$	1×10^{-9}	9.7×10^{-9}	0.97
3ggg	9-$OCOC(CH_3)_3$	$(CH_2)_3NMe_2$	7.7×10^{-9}	2.7×10^{-8}	3.5
3uu	9-OCH_3	CH_2CH_2NHEt	2.1×10^{-7}	1.2×10^{-7}	0.57
3nn	9-OCH_3	$CH_2CH_2NHCH_2CH_2OH$	4.5×10^{-7}	1.9×10^{-7}	0.42

drazine then provided the desired pyrazoloacridines **3** (Table III). Variations on these generic methods needed to prepare specific compounds are described in the Experimental Section and referred to in the tables. Estersof ring-substituted hydroxypyrazoloacridines were prepared with the appropriate acid chlorides (**3aa**, **3y**, **3z**, **3bb**, **3dd**, **3kk**, **3ll**, **3xx**, **3fff**, and **3yyy**).

To confirm the pyrazoloacridine structures as depicted and to eliminate the alternative addition/closure of the hydrazine to form **4**, a crystal structure determination was performed on **3g**.



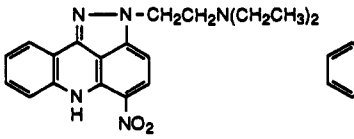
4



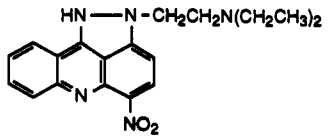
3g

The structure determined from the crystallographic analysis (**5**) clearly defines the basic structure and addition of the hydrazine as proposed. Analysis of the bond lengths and angles of the ring system is most consistent with the location of the hydrogen at N9 providing some evidence for the tautomeric structure as depicted.

To address further the concern about the exact geometry of the crystal structure, particularly that associated with the hybridization of the central ring system, molecular orbital calculations utilizing MNDO from MOPAC 5.0[9] were performed on both possible tautomeric forms with geometry optimization. With tautomer A, the one indicated by the crystal data, the heat of formation was calculated to be 105.64 kcal/mol with geometry optimization. Tautomer B was constructed from the crystal coordinates and the calculation repeated resulting in a heat of formation of 122.47 kcal/mol. The orientation of the flexible side chain was varied to check for consistency within conformers. The calculations were repeated with geometry optimization, tautomer A having a heat of formation of 108.34 kcal/mol and tautomer B having a heat of formation of 121.08 kcal/mol. The difference in energy of the two tautomers appears to be consistent and in support of tautomer A as the preferred form of hybridization. Comparisons of the resulting geometry of the molecular orbital calculations versus both the crystal structure and gas phase molecular mechanics minimizations utilizing Maximin[10] in the SYBYL[11] modeling program do not show any large deviations from the crystal structure. The charge set used in the minimizations were those obtained from the MNDO calculations.



Tautomer A



Tautomer B

Additional confirmation was also obtained by repeating the calculations with the AM1 Hamiltonian in MOPAC 5.0[12] which gave very similar energy differences between the two tautomeric forms.

Biology

Initial screening was performed in vitro on a L1210 leukemia line (Table III) and was followed by in vivo studies against the P388 leukemia (CD2F1) (Table III). Particularly impressive activity was demonstrated by the 9-hydroxy, 9-alkoxy, and 9-acyloxy analogs. An early suggestion of solid tumor selectivity was shown by the 9-alkoxy analogs (Table IV) in a comparison in vitro against the L1210 and the human colon line HCT-8.

The pyrazoloacridines, as expected, were generally potent DNA binders. For example, in measuring the displacement of ethidium from calf thymus DNA the C50 (concentration in nanomoles of drug needed to reduce fluorescence of the ethidium–DNA complex by 50%) was 187 for **3bbb** compared with 63 for adriamycin.[23] These data thus could not be correlated with antitumor activity nor used as a selection procedure.

The pyrazoloacridines also showed the advantage of selectivity against hypoxic cells, but again this was a property of the entire class and did not allow selection of an optimum clinical candidate.[6] Moreover, both 9-hydroxy- and 9-ether-substituted pyrazoloacridines were active against a panel of multidrug-resistant cell lines.[13]

To select a member of this series which might have clinical potential against the common carcinomas which are generally not susceptible to antitumor agents, a variety of studies were undertaken. The approach has been summarized in reference 7. The 9-ether-substituted pyrazoloacridines examined in vitro against a panel including nine carcinomas and six leukemia lines showed solid tumor selectivity.[6] In addition, **3bbb** had selectivity

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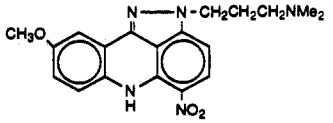
against colon carcinoma 38 and pancreatic carcinoma O3 relative to leukemia L1210 in the Corbett multiple tumor soft agar disk-diffusion assay.[24] Confirmation of the carcinoma selectivity of **3bbb** was also obtained in the National Cancer Institute's large panel of human tumor cell lines.[7]

The 9-ether-substituted pyrazoloacridines, which were carcinoma selective in vitro, and **3bbb** in particular were active against several experimental tumor models including those in which tumor implant and drug injection sites are different.[7]

On the basis of all these data pyrazoloacridine **3bbb** has been selected for clinical evaluation, and trials are underway.



3bbb

Experimental Section

Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. ^{1}H NMR spectra were determined at 90 MHz on a Varian EM-390, at 100 MHz on an IBM WP100SY, or at 200 MHz on a Varian XL-200 spectrometer in Me_2SO-d_6 of $CDCl_3$ with tetramethylsilane as an internal standard. Compounds also had IR spectra consistent with their structures as determined on a Nicolet 205X FT/IR. TLC was performed with E. Merck silica gel 60 F-254 precoated glass plates (0.25 mm).

6-Chloro-3-nitro-2-[[4-(phenylmethoxy)phenyl]amino]-benzoic Acid (1j). Method A. A solution of 80.0 g (0.40 mol) of 4-(benzyloxy)aniline in 120 mL of *N,N*-dimethylaniline was added to 92.0 g (0.39 mol) of 2,6-dichloro-3-nitrobenzoic acid (**21**) and 70 mL (0.40 mol) of *N,N*-diisopropylethylamine in 150 mL of *N,N*-dimethylaniline. The mixture was heated 18 h under N_2 on a steam bath, cooled, diluted with 1 L of $CHCl_3$, and stirred with 1 L of 1 N NaOH. The orange sodium salt precipitate was collected and slurried in 5% HCl giving 68.0 g (47%) of (**1j**), mp 171–172 °C. Anal. ($C_{20}H_{15}ClN_2O_5$) C, H, N.

1-Chloro-7-methoxy-4-nitro-9(10*H*)-acridinone (2g). Method B. A mixture of 119 g (0.5 mol) of 2,6-dichloro-3-nitrobenzoic acid,[21] 129 g (1.05 mol) of 4-methoxyaniline, and 500 mL of *N,N*-dimethylaniline was heated on a steam bath under N_2 for 18 h. The mixture was diluted (1 L of $CHCl_3$) and extracted with 1 L of 1 N NaOH in 3 portions. The combined extracts were acidified with hydrochloric acid, and the red precipitate was washed with H_2O providing 134 g (83%) of 6-chloro-2-[(4-methoxyphenyl)-amino]-3-nitrobenzoic acid (**1d**), mp 210–212 °C. Anal. ($C_{14}H_{11}ClN_2O_5$) C, H, N.

A mixture of 132.8 g (0.412 mol) of **1d**, 250 mL (2.7 mol) of $POCl_3$, 12 mL of *N,N*-dimethylaniline, and 1.2 L of 1,2-dichloroethane was heated under reflux for 1 h and allowed to cool to 40 °C. The resulting red needles were collected providing 110.5 g (88%) of **2g**, mp 262–263 °C. Anal. ($C_{14}H_9ClN_2O_4$) C, H, N, Cl.

1-Chloro-7-ethoxy-4-nitro-9(10*H*)-acridinone (2h). Method C. Fifteen grams (45 mmol) of **1e**, 1.5 mL (12 mol) of *N,N*-dimethylaniline, 30 mL (320 mmol) of $POCl_3$, and 200 mL of $CHCl_3$ was heated under reflux 2 h and allowed to stand overnight. Maroon crystals (9.9 g, 70%) of **2h**, mp 244–246 °C were collected. Anal. ($C_{15}H_{11}ClN_2O_4$) C, H, N.

1,8-Dichloro-2-hydroxy-5-nitro-9(10*H*)-acridinone (2w). Method D. A suspension of 3.56 g (0.0086 mol) of **2z** in 500 mL of CH_2Cl_2 containing 0.018 mol of BCl_3 was stirred at room temperature for 24 h, when 2.2 mL (0.054 mol) of $MeSO_3H$ in 35 mL of MeOH was added all at once. The suspension became a solution momentarily and then a red solid **2w** precipitated: mp 276–279 °C dec; 2.59 g (93%); 200 MHz NMR (Me_2SO-d_6) δ 3.3 (HDO), 7.3 (d, 1 H, J = 8.9 Hz, C_2-H), 7.4 (d, 1 H, J = 9.1 Hz, C_5-H), 7.8 (d, 1 H, J = 9.1 Hz, C_6-H), 8.45 (d, 1 H, J = 8.9 Hz, C_3-H), 10.3 (s, 1 H, OH), 11.3 (s, 1 H, NH). Anal. ($C_{13}H_6Cl_2N_2O_4$) C, H, N.

1,6-Dichloro-7-methoxy-4-nitro-9(10*H*)-acridinone (2v) and 1,8-Dichloro-2-methoxy-5-nitro-9(10*H*)-acridinone (2x). Method E. A mixture of **1r** (108 g, 0.302 mol), *N,N*-dimethylaniline (10 mL, 80 mmol), and 170 mL (1.82 mol) of $POCl_3$ in 0.9 L of 1,2-dichloroethane was heated 2 h under reflux and filtered hot. The orange precipitate of **2y** was collected and washed ($CHCl_3$): 55.0 g (54%); mp 284–285 °C; 200 MHz NMR (Me_2SO-d_6) δ 4.0 (s, 3 H, OCH_3), 7.4 (d, J = 10.7 Hz, 1 H, C_2-H), 7.7 (s, 1 H, C_5-H), 8.4 (s, 1 H, C_8-H), 8.6 (d, J = 10.7 Hz, 1 H, C_3-H), 11.6 (s, 1 H, NH). Anal. ($C_{14}H_8ClN_2O_4$) C, H, N, Cl.

From the cooled filtrate a two-component mixture (35 g) separated which was chromatographed over 1 kg of SiO_2 with CH_2Cl_2. Fractions containing the red isomer **2x** yielded 11.0 g (11%): mp 251–253 °C; 200 MHz NMR (Me_2SO-d_6) δ 3.9 (s, 3 H, OCH_3), 7.35 (d, J = 7.7 Hz, 1 H, C_2-H), 7.7 (d, J = 10.7 Hz, 1 H, C_5-H), 8.0 (d, J = 10.7 Hz, 1 H, C_6-H), 8.55 (d, J = 7.7 Hz, 1 H, C_3-H), 11.4 (s, 1 H, NH). Anal. ($C_{14}H_8ClN_2O_4$) C, H, N, Cl.

1-Chloro-7-methoxy-4-nitro-9(10*H*)-acridinone (2g). Diphenylamine **1d** (27.3 g, 0.0846 mol) was suspended in 100 mL of $POCl_3$, stirred, and warmed gradually. The mixture gradually thickened, and an additional 50 mL of $POCl_3$ was added after 1 h. The mix was heated to gentle boiling for 2.5 h, cooled, and filtered. The orange precipitate was triturated with water, leading to a rather violent reaction, and the resulting solid was washed with water and dried to provide 21.7 g.

The dark red $POCl_3$ filtrate was concentrated to a small volume and treated with 100 mL of water and 30 mL of 4 N HCl and warmed on a steam bath for 2 h. The red precipitate was collected and dried to give 4.8 g. The 21.7-g lot was dissolved in 750 mL of boiling toluene, evaporated to 450 mL, and allowed to cool to provide 19.6 g of solid, mp 216–219 °C, which was still impure by TLD. The crops were combined suspended in 300 mL of boiling acetic acid. Twenty milliliters of water was added, and the mixture was heated to boiling for 15 min. The mix was cooled and a dark red solid collected, washed with water, and dried in vacuo to give 17.35 g, mp 261–263 °C. Anal. ($C_{14}H_9ClN_2O_4$) C, H, N.

3-Chloro-4-(phenylmethoxy)benzenamine. The sodium salt of 2-chloro-4-nitrophenol (130 g, 0.66 mol) was added to 500 mL of DMF, followed by 10 g of NaI and 73.0 mL (0.64 mol) of benzyl chloride. The mixture was stirred 70 h at room temperature and then treated with 400 mL of H_2O, dropwise at first, and the mixture filtered. The precipitate was dissolved in EtOAc, washed with H_2O, and evaporated to give 148 g (88%) of 2-chloro-4-nitro-1-(phenylmethoxy)benzene, mp 116–118 °C. Anal. ($C_{13}H_{10}ClNO_3$) C, H, N.

The above compound (105.5 g, 0.40 mol) in 800 mL of THF and 200 mL of MeOH was reduced to the amine with hydrogen at atmospheric pressure in the presence of Raney nickel catalyst,

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concentrated to 96.5 g of 3-chloro-4-(phenylmethoxy)benzylamine, and used without further characterization.

1-Chloro-7-hydroxy-4-nitro-9(10*H*)acridinone (2d). A stirred suspension of 12.1 g (0.032 mol) of 2m in 500 mL of glacial AcOH containing 5.0 mL of methanesulfonic acid was refluxed for 8 h, cooled to 70 °C, and filtered. The red precipitate was washed with AcOH, ether, and dried to 7.73 g (84%), mp >325 °C. Anal. ($C_{13}H_7ClN_2O_4$) C, H, N.

1-Chloro-4-nitro-6-(phenylmethoxy)-9(10*H*)-acridinone (2l), 1-Chloro-8-hydroxy-4-nitro-9(10*H*)-acridinone (2e), and 1-Chloro-6-hydroxy-4-nitro-9(10*H*)-acridinone (2c). A mixture of 4.1 g (10.3 mmol) of 1j, 8.0 mL (86 mmol) of $POCl_3$, 0.5 mL (4 mmol) of *N,N*-dimethylaniline, and 25 mL of 1,2-dichloroethane was heated 30 min under reflux and concentrated to 15 mL. Gold needles of 2l (1.25 g, 32%), mp 198–202 °C, were collected: 200 MHz NMR (Me_2SO-d_6) δ 5.2 (s, 2 H, OCH_2Ph), 6.8 (d, J = 2.2 Hz, 1 H, C_5-H), 7.0 (dd, J = 2.2 Hz, 1 H, 9.0 Hz, C_7-H), 7.2 (d, J = 9.0 Hz, 1 H, C_2-H), 7.4 (m, 5 H, phenyl *H*), 8.25 (d, J = 9.0 Hz, 1 H, C_8-H), 8.45 (d, J = 9.0 Hz, 1 H, C_3-H), 11.5 (s, 1 H, NH).

The filtrate, concentrated to an oil, was dissolved in 5 mL of AcOH and diluted gradually with H_2O to give 2.75 g of a crude solid which was chromatographed in $CHCl_3$ over SiO_2 (250 g) providing additional 2l (mp 203–205 °C, 0.98 g, 20%), preceded by 0.60 g (20%) of 2e: mp 265–267 °C; 200 MHz NMR ($CDCl_3$) δ 6.8 (m, 2 H, C_5-H, C_7-H), 7.25 ($CHCl_3$), 7.3 (d, J = 9.0 Hz, 1 H, C_2-H), 7.6 (dd, J = 8.2 Hz, 1 H, C_6-H), 8.6 (d, J = 9.0 Hz, 1 H, C_3-H), 11.7 (brs, 1 H, NH), 13.1 (s, 1 H, OH).

A slurry of 9.0 g (24 mmol) of 2l in 0.5 L of 1,2-dichloroethane containing 30 mL of 1.0 M BBr_3 in CH_2Cl_2 (30 mmol) was heated 2 h under reflux, and MeOH (5 mL) was added dropwise. Upon cooling, 6.9 g (98%) of yellow 2c was collected, mp 292–294 °C. Anal. ($C_{13}H_7N_2O_4Cl$) C, H, N, Cl.

9-Chloro-6-nitro-1,3-dioxolo[4,5-*b*]acrid-10(5*H*)-one (2t). A mixture of 10.0 g (0.03 mol) of 1q, 8.0 mL (0.086 mol) of $POCl_3$, 0.5 mL (0.004 mol) of *N,N*-dimethylaniline, and 300 mL of 1,2-dichloroethane was heated under reflux 3 h and filtered hot. The filter cake was washed (dichloroethane, MeOH) providing 5.5 g (57%) of 2t, mp 284–285 °C. No chromatographic or spectral evidence of the other possible isomer was found in this reaction mixture: 200 MHz NMR (Me_2SO-d_6) δ 3.5 (bs, ~1 H, *H*DO), 6.2 (s, 2 H, OCH_2O), 7.28 (d, J = 8.8 Hz, 1 H, C_2-H), 7.3 (s, 1 H, C_5-H), 7.5 (s, 1 H, C_8-H), 8.45 (d, J = 8.8 Hz, 1 H, C_3-H), 11.4 (s, 1 H, NH). Anal. ($C_{14}H_7N_2O_5Cl$·0.25H_2O) C, H, N, Cl.

1,6-Dichloro-4-nitro-7-(phenylmethoxy)-9(10*H*)-acridinone (2y) and 1,8-Dichloro-5-nitro-2-(phenylmethoxy)-9-(10*H*)-acridinone (2z). A mixture of 95.6 g (0.22 mol) of 1s, 1 L of 1,2-dichloroethane, 22 mL (0.17 mol) of *N,N*-dimethylaniline, and 96 mL (1.03 mL) of $POCl_3$ was stirred under reflux for 2 h and allowed to stand overnight. The precipitate (85.2 g, 93%) contains two components by TLC (SiO_2, CH_2Cl_2): orange, R_f 0.65 and maroon, R_f 0.45. A hot solution of 50 g of the precipitate in 1.1 L of DMF was allowed to stand 4 h and filtered, providing 24.5 g (46%) of the orange R_f 0.65 isomer 2y mp 244–246 °C, after recrystallizations from DMF and toluene. Anal. ($C_{20}H_{12}Cl_2N_2O_4$) C, H, N, Cl. The liquor, containing both isomers, was evaporated to 21.2 g, mp 220–230 °C. Five grams of this was dissolved in 1 L of hot $CHCl_3$ and 20 mL of MeOH and was combined with 100 g of silica gel (Kieselgel 60, EM *Reagents*) and evaporated to a powder on a rotary evaporator. The powder was added to a column of 700 g of silica gel and a chromatogram developed with $CHCl_3$–MeOH (100:1). The two components were separated, providing 2.5 g (20% additional yield) of the faster-moving 2y and 1.52 g (12%) of the slower-moving red isomer 2z: mp 272–274 °C; 200 MHz NMR (Me_2SO-d_6) δ 3.5 (s, 4 H, HDO), 5.3 (s, 2 H, CH_2O), 7.3–7.5 (m, 6 H, phenyl + C_2-H), 7.75 (d, 1 H, J = 9.4 Hz, C_5-H), 7.95 (d, 1 H, J = 9.4 Hz, C_6-H), 8.5 (d, 1 H, J = 8.9 Hz, C_3-H), 11.4 (s, 1 H, NH). Anal. ($C_{20}H_{12}Cl_2N_2O_4$) C, H, N.

1-Chloro-7-(dimethylamino)-4-nitro-9(10*H*)-acridinone (2o). A solution of 41.0 g (0.30 mol) of *N,N*-dimethyl-*p*-phenylenediamine, 100 mL of *N,N*-dimethylaniline, and 23.6 g (0.10 mol) of 2,6-dichloro-3-nitrobenzoic acid was heated for 7 h on a stream bath. The resulting cake was suspended in CH_2Cl_2 and filtered, and the solid was washed with water. Recrystallization from DMF–EtOH provided 19.8 g (59%) of 6-chloro-2-[[4-(dimethylamino)phenyl]amino]-3-nitrobenzoic acid 1l, mp 222–223 °C dec. Anal. ($C_{15}H_{14}ClN_3O_4$) C, H, N.

To a solution of 8.40 g (0.025 mol) of 1l in 300 mL of 1,2-dichloroethane and 19.0 mL (0.135 mol) of triethylamine was added 4.2 mL (0.045 mol) of $POCl_3$, and the mixture was stirred 2 h. MeOH (10 mL) was added, and the mixture was evaporated to a residue which was triturated with 80 mL of MeOH and filtered. The solid, after trituration with dilute NH_4OH, was recrystallized from DMF providing 2o: mp >300 °C; a black solid, 1.3 g (16%). Anal. ($C_{15}H_{12}ClN_2O_3$) C, H, N.

1-Chloro-7-[2-(diethylamino)ethoxy]-4-nitro-9(10*H*)-acridinone (2p). To a stirred solution of 48.3 g (0.30 mol) of sodium 4-nitrophenoxide in 250 mL of DMF was added 46.0 g (0.34 mol) of 2-chloro-*N,N*-diethylethanamine. After 20 h the mixture was filtered and concentrated in vacuo, and the residue was dissolved in CH_2Cl_2, washed (H_2O, 3X), dried ($MgSO_4$), and evaporated. The residue, in CH_3OH, was charcoaled liberally and evaporated to provide 61.1 g (85%) of *N,N*-diethyl-2-(4-nitrophenoxy)-ethanamine as a yellow oil: TLC (SiO_2; $CHCl_3$–MeOH, 25:1) one spot, R_f 0.5. Anal. ($C_{12}H_{18}N_2O_3$) C, H, N. The above oil (26.2 g, 0.11 mol) in THF was hydrogenated in the presence of Raney nickel catalyst, filtered, and evaporated to give 25.0 g of the diamine. The diamine, together with 23.6 g (0.10 mol) of 2,6-dichloro-3-nitrobenzoic acid and 17.5 mL (0.10 mol) of *N,N*-diisopropylethylamine in 60 mL of *N,N*-dimethylaniline, was heated at 60 °C for 24 h under Ar. Chloroform (300 mL) was added and orange 6-chloro-2-[[4-(2-(diethylamino)ethoxy]phenyl]amino]-3-nitrobenzoic acid, 1m, collected: 18.4 g (45%); mp 212–215 °C. Anal. ($C_{19}H_{22}ClN_3O_5$) C, H, N.

A suspension of 1m (18.3 g, 0.045 mol) in 120 mL of 1,2-dichloroethane and 28.5 mL (0.224 mol) of *N,N*-dimethylaniline was treated with 5.0 mL (0.054 mol) of $POCl_3$, stirred, and heated at 50 °C for 19 h under Ar and filtered. The precipitate was shaken with $CHCl_3$ and 100 mL of 0.5 N NaOH, and the organic layer was evaporated, suspended in cyclohexane, and collected, providing 11.75 g (67%) of 2p, mp 148–150 °C. A sample of 2p in methanolic CH_3SO_3H–EtOAc gave a red salt, mp 162–164 °C. Anal. ($C_{19}H_{20}ClN_3O_4$·CH_3SO_3H·0.5H_2O) C, H, N, S, H_2O.

***N,N*-Diethyl-9-methoxy-5-nitropyrazolo[3,4,5-*kl*]acridine-2(6*H*)-ethanamine (3g). Method F.** A suspension of 7.62 g (0.025 mol) of 2g in 90 mL of THF and 90 mL of MeOH containing 6.8 g (0.052 mol) of *N,N*-diethyl-2-hydrazinoethanamine was stirred 18 h at 25 °C. The mixture was cooled in ice and filtered. The precipitate was washed with cold THF–MeOH, suspended in H_2O, collected, and dried to provide 7.6 g (80%) of 3g: mp 183–185 °C; 100 MHz NMR (Me_2SO-d_6) δ 1.2 (t, J = 7.7 Hz, 6 H, NCH_2CH_3), 2.3 (s, 3 H, CH_3SO_3H), 3.2 (q, 4 H + HDO, NCH_2-CH_3), 3.7 (crude t, 2 H, CH_2NEt_2), 3.9 (s, 3 H, OCH_3), 4.9 (t, J = 6 Hz, 2 H, $CH_2CH_2NEt_2$), 7.0 (d, J = 11.5 Hz, 1 H, C_3-H), 7.15 (dd, J = 10 Hz, J = 3 Hz, 1 H, C_8-H), 7.4 (d, J = 3 H, 1 H, C_{10}-H), 8.05 (d, J = 10 Hz, 1 H, C_7-H), 8.15 (d, J = 11.5 Hz, C_4-H), 9.2 (brs, 1 H, NH), 11.4 (s, 1 H, CH_3SO_3H). Anal. ($C_{20}H_{23}N_5O_3$) C, H, N.

A 1.14-g portion was converted to the methanesulfonic acid salt in 25 mL of hot MeOH containing 0.34 g of CH_3SO_3H and a few drops of H_2O, mp 228–231 °C dec. Anal. ($C_{20}H_{23}N_5O_3$·CH_3-SO_3H) C, H, N, S.

2-[[2-(9-Methoxy-5-nitropyrazolo[3,4,5-*kl*]acridin-2(6*H*)-yl)ethyl]amino]ethanol (3pp). Method G. A solution of 1.46 (0.0124 mol) of 2-[(2-hydrazinoethyl)amino]ethanol in 20 mL of MeOH was added to a suspension of 3.14 g (0.0103 mol) of 2g in 40 mL of THF and the mixture stirred 3 h. The organic solid was collected triturated in warm THF, DMF, and acetone (3X), successively, and dried to give 2.8 g (69%) of 3pp, mp >315 °C with darkening above 285 °C. Anal. ($C_{18}H_{19}N_5O_4$·HCl) C, H, N, Cl.

***N,N*-Diethyl-5-nitro-9-propoxypyrazolo[3,4,5-*kl*]acridine-2(6*H*)-ethanamine (3i). Method H.** A suspension of 2.0 g (0.006 mol) of 2i and 1.6 g (0.0122 mol) of *N,N*-diethyl-2-hydrazinoethanamine[25] in 200 mL of THF–MeOH (6:1) was stirred overnight at room temperature and the solvent evaporated. The

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residue was triturated with MeOH and then with H_2O and dried, providing **3i** (2.3 g, 94%), mp 141–142 °C. The base was dissolved in 40 mL of warm MeOH containing 6.0 mL (0.006 mol) of 1 N methanolic CH_3SO_3H, filtered, and diluted with an equal volume of warm EtOAc. The salt separated; mp 209–210 °C, 2.3 g (75%). Anal. ($C_{22}H_{27}N_5O_3 \cdot CH_3SO_3H$) C, H, N, S.

2-[2-(Diethylamino)ethyl]-2,6-dihydro-5-nitropyrazolo-[3,4,5-*kl*]acridin-9-yl Butanoate (3aa). Method I. A mixture of 1.47 g (0.004 mol) of **3a**, 100 mL of dry 1,2-dichloroethane, 0.63 mL (0.006 mol) of butyryl chloride, and 1.74 mL (0.010 mol) of *N,N*-diisopropylethylamine was stirred at 50 °C for 2.5 h under nitrogen and evaporated to dryness. The residue was triturated with water, collected, dissolved in $CHCl_3$, washed with 5% $NaHCO_3$, and chromatographed over silica gel ($CHCl_3$–MeOH, 50:1). The desired eluate contained 1.10 g (63%) of **5aa**, mp 157–161 °C. Anal. ($C_{23}H_{27}N_5O_4$), C, H, N. A solution of 1.09 g (0.0025 mol) of the ester in 50 mL of warm EtOAc was treated with 2.5 mL of 1 N methanolic CH_3SO_3H. The salt was recrystallized from MeOH–ethyl acetate, mp 220–222 °C. Anal. ($C_{23}H_{27}N_5O_4 \cdot CH_3SO_3H$) C, H, N, S.

2,6-Dihydro-2-[2-[(2-hydroxyethyl)amino]ethyl]-5-nitropyrazolo[3,4,5-*kl*]acridin-9-ol (3oo). Method J. A mixture of 2.0 g (6.9 mmol) of **2d** and 2.5 g (21 mmol) of 2-[(2-hydrazinoethyl)amino]ethanol and 250 mL of MeOH was stirred 120 h and filtered. The crude **3oo** was dissolved in 200 mL of warm 0.1 N aqueous CH_3SO_3H, filtered, concentrated to 20 mL, and diluted with 250 mL of EtOH, providing 0.85 g (26%) of salt, mp 256–258 °C. Anal. ($C_{17}H_{17}N_5O_4 \cdot CH_3SO_3H$) C, H, N, S.

9-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-*N,N*-diethyl-5-nitropyrazolo[3,4,5-*kl*]acridine-2(6*H*)-ethanamine (3ee). A mixture of 1.47 g (4 mmol) of **3d**, 40 mL of CH_2Cl_2, 1.05 g (7 mmol) of *tert*-butyldimethylsilyl chloride, 1.4 mL (8 mmol) of *N,N*-diisopropylethylamine, and 0.1 g (0.8 mmol) of 4-(dimethylamino)pyridine was stirred at 25 °C for 72 h. The dark yellow solution was washed with H_2O and chromatographed over SiO_2 with $CHCl_3$–MeOH (50:1), providing 1.75 g (91%) of **3ee**, mp 218–220 °C. Anal. ($C_{25}H_{35}N_5O_3Si$) C, H, N. The methanesulfonic acid salt crystallized from MeOH–$CHCl_3$–EtOAc containing 1 equiv of CH_3SO_3H and was recrystallized to mp 207–213 °C from CH_3CN: 200 MHz NMR (Me_2SO-d_6) δ 0.2 (s, 6 H, $Si(CH_3)_2$), 0.95 (s, 9 H, $SiC(CH_3)_3$), 1.2 (t, J = 7 Hz, 6 H, NCH_2CH_3), 2.3 (s, 3 H, CH_3SO_3H), 3.2 (m, 4 H, NCH_2CH_3), 3.3 (HDO), 3.7 (crude t, 2 H, CH_2NEt_2), 4.8 (t, J = 6 Hz, 2 H, $NNCH_2$), 7.0 (d, J = 9.3 Hz, C_3-H), 7.1 (dd, J = 2.8 Hz, J = 9.0 Hz, C_7-H), 7.3 (d, J = 2.8 Hz, C_9-H), 8.0 (d, J = 9.0 Hz, C_6-H), 8.1 (d, J = 9.3 Hz, C_4-H), 9.3 (brs, 1 H), 11.3 (s, 1 H, CH_3SO_3H). Anal. ($C_{25}H_{35}N_5O_3Si \cdot CH_3SO_3H$) N, S; C: calcd, 54.05; found, 53.28; H: calcd, 6.80; found, 7.25.

***N*-Ethyl-9-methoxy-5-nitropyrazolo[3,4,5-*kl*]acridine-2-(6*H*)-ethanamine (3uu).** A mixture of 2.36 g (7.2 mmol) of **3ss**, 2.75 g (14.4 mmol) of tosyl chloride, 1.06 g (8.7 mmol) of 4-(dimethylamino)pyridine, 2.0 mL (14.3 mmol) of triethylamine, and 40 mL of DMF was held at 100 °C for 10 min and allowed to stand overnight. The precipitate was recrystallized from 10 mL of DMF providing 1.19 g (48%) of 2-(2-chloroethyl)-2,6-dihydro-9-methoxy-5-nitropyrazolo[3,4,5-*kl*]acridine (**3tt**), mp 261–263 °C dec. Anal. ($C_{16}H_{13}ClN_4O_3$) C, H, N, Cl.

A slurry of 1.43 g (4.15 mmol) of **3tt** in 20 mL of $EtNH_2$ in a pressure vessel was shaken at 100 °C for 18 h and evaporated. The residue was triturated with MeOH providing 1.0 g (68%) of slightly impure base (**3uu**), mp 168–170 °C, which was converted to the methanesulfonate, mp 228–230 °C, in $CHCl_3$–MeOH. Anal. ($C_{18}H_{19}N_5O_3 \cdot 1.25CH_3SO_3H \cdot 0.6H_2O$) C, H, N, S, H_2O.

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Supplementary Material Available: Method for crystal structure determination, positional parameters and their estimated standard deviations (Table I), general temperature factor expressions—U's (Table II), bond distances (Table III), and bond angles (Table IV) (8 pages). Ordering information is given on any current masthead page.

Registry No. **1a**, 55776-07-3; **1b**, 55830-46-1; **1c**, 99009-55-9; **1d**, 55776-09-5; **1e**, 99009-56-0; **1f**, 99009-58-2; **1g**, 99009-60-6; **1h**, 144346-81-6; **1i**, 99140-54-2; **1j**, 99009-51-5; **1k**, 144346-82-7; **1l**, 99009-73-1; **1m**, 99009-62-8; **1n**, 99009-66-2; **1o**, 99009-68-4; **1p**, 144346-83-8; **1q**, 144346-84-9; **1r**, 99009-70-8; **1s**, 144346-85-0; **2a**, 20621-51-6; **2b**, 21814-53-9; **2c**, 99140-53-1; **2d**, 99009-49-1; **2e**, 99140-55-3; **2f**, 21814-51-7; **2g**, 21814-48-2; **2h**, 22171-47-7; **2i**, 99009-57-1; **2j**, 99009-59-3; **2k**, 144346-86-1; **2l**, 99795-88-7; **2m**, 99009-50-4; **2n**, 22171-48-8; **2o**, 99009-72-0; **2p**, 99009-61-7; **2q**, 99009-65-1; **2r**, 99009-67-3; **2s**, 144346-87-2; **2t**, 144346-88-3; **2u**, 144346-89-4; **2v**, 99009-71-9; **2w**, 144346-90-7; **2x**, 99009-69-5; **2y**, 144346-91-8; **2z**, 144346-92-9; **3a**, 99008-47-6; **3a**·$MeSO_3H$, 99008-48-7; **3b**, 99008-99-8; **3b**·$MeSO_3H$, 99009-00-4; **3c**, 144346-93-0; **3c**·$MeSO_3H$, 144346-94-1; **3d**, 99008-65-8; **3d**·$MeSO_3H$, 99008-66-9; **3e**, 144346-95-2; **3e**·$MeSO_3H$, 144346-96-3; **3f**, 99009-53-7; **3f**·$MeSO_3H$, 99009-54-8; **3g**, 99008-55-6; **3h**, 99008-67-0; **3h**·$MeSO_3H$, 99008-68-1; **3i**, 99008-69-2; **3i**·$MeSO_3H$, 99008-70-5; **3j**, 99008-71-6; **3j**·$MeSO_3H$, 99008-72-7; **3k**, 144346-97-4; **3k**·$MeSO_3H$, 144346-98-5; **3l**, 144346-99-6; **3l**·$MeSO_3H$, 144347-00-2; **3m**, 144347-01-3; **3m**·$MeSO_3H$, 144347-02-4; **3n**, 144347-03-5; **3c**·$MeSO_3H$, 144347-04-6; **3o**, 99008-97-6; **3o**·$2MeSO_3H$, 99008-98-7; **3p**, 99008-73-8; **3p**·$2MeSO_3H$, 99008-74-9; **3q**, 99008-77-2; **3q**·$MeSO_3H$, 99008-78-3; **3r**, 99008-79-4; **3r**·$MeSO_3H$, 99008-80-7; **3s**, 144347-05-7; **3s**·$1.2MeSO_3H$, 144347-06-8; **3t**, 144347-07-9; **3t**·$MeSO_3H$, 144347-08-0; **3u**, 144347-09-1; **3u**·$MeSO_3H$, 144347-10-4; **3v**, 144347-11-5; **3v**·$MeSO_3H$, 144347-12-6; **3w**, 110999-54-7; **3w**·$MeSO_3H$, 144347-13-7; **3x**, 99008-81-8; **3x**·$MeSO_3H$, 144347-14-8; **3y**, 99008-85-2; **3y**·$MeSO_3H$, 99008-86-3; **3z**, 99008-87-4; **3z**·$MeSO_3H$, 99008-88-5; **3aa**, 99008-89-6; **3aa**·$MeSO_3H$, 99008-90-9; **3bb**, 99008-91-0; **3bb**·$MeSO_3H$, 99008-92-1; **3cc**, 99008-93-2; **3cc**·$MeSO_3H$, 99008-94-3; **3dd**, 99008-95-4; **3dd**·$MeSO_3H$, 99008-96-5; **3ee**, 99008-83-0; **3ee**·$MeSO_3H$, 99008-84-1; **3ff**, 144347-15-9; **3ff**·$MeSO_3H$, 144347-16-0; **3gg**, 99008-57-8; **3gg**·$MeSO_3H$, 99008-58-9; **3hh**, 99009-05-9; **3hh**·$1.35MeSO_3H$, 144347-17-1; **3ii**, 99009-08-2; **3ii**·$2MeSO_3H$, 99009-09-3; **3jj**, 99009-06-0; **3jj**·$MeSO_3H$, 99009-07-1; **3kk**, 144347-18-2; **3kk**·$1.25MeSO_3H$, 144347-19-3; **3ll**, 144347-20-6; **3ll**·$MeSO_3H$, 144347-21-7; **3mm**, 99008-52-3; **3mm**·HCl, 99008-51-2; **3nn**, 99009-15-1; **3nn**·HCl, 99009-14-0; **3oo**, 110999-53-6; **3oo**, 144347-22-8; **3pp**, 99008-62-5; **3pp**·HCl, 99008-61-4; **3qq**, 99009-11-7; **3qq**·HCl, 99009-10-6; **3rr**, 99009-12-8; **3rr**·$MeSO_3H$, 144347-23-9; **3ss**, 99009-75-3; **3tt**, 99009-74-2; **3uu**, 99009-03-7; **3uu**·$1.25MeSO_3H$, 99009-04-8; **3yy**, 129337-42-4; **3yy**·$MeSO_3H$, 144347-24-0; **3zz**, 144347-31-9; **3zz**·HCl, 144347-25-1; **3aaa**, 99009-18-4; **3aaa**·$MeSO_3H$, 99009-19-5; **3bbb**, 99009-20-8; **3bbb**·$MeSO_3H$, 99009-21-9; **3ccc**, 99009-22-0; **3ccc**·$MeSO_3H$, 99009-23-1; **3ddd**, 144347-26-2; **3ddd**·$MeSO_3H$, 144347-27-3; **3eee**, 144347-28-4; **3eee**·$MeSO_3H$, 144347-29-5; **3fff**, 99009-24-2; **3fff**·$MeSO_3H$, 99009-25-3; **3ggg**, 99009-26-4; **3ggg**·$MeSO_3H$, 99009-27-5; **3hhh**, 99009-16-2; **3hhh**·$MeSO_3H$, 144347-30-8; 4-(benzyloxy)aniline, 6373-46-2; 2,6-dichloro-3-nitrobenzoic acid, 55775-97-8; 4-methoxyaniline, 104-94-9; 3-chloro-4-(phenylmethoxy)benzenamine, 144347-32-0; sodium 2-chloro-4-nitrophenol, 619-08-9; *N,N*-dimethyl-*p*-phenylenediamine, 99-98-9; sodium 4-nitrophenoxide, 824-78-2; 2-chloro-*N,N*-diethylethanamine, 100-35-6; *N,N*-diethyl-2-(4-nitrophenoxy)ethanamine, 19881-36-8; *N,N*-diethyl-2-(4-aminophenoxy)ethanamine, 38519-63-0; *N,N*-diethyl-2-hydrazinoethanamine, 924-29-8.