Polyamine Analogues with Antitumor Activity

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A series of tetraamines derived from 1,8-diaminooctane was prepared and tested as antitumor agents. The reaction of 1,8-diaminooctane with acrylonitrile gave *N*,*N*′-bis(cyanoethyl)-1,8-diaminooctane, which was reduced to tetraamine **20**. Alkylation of the terminal nitrogen atoms of the tetra-Boc derivative of this compound by methyl or ethyl halide followed by removal of the Boc groups gave the bis(alkyl)polyamines **26a** and **26b**, respectively. These three compounds exhibit promising antitumor activity in the mouse L1210 leukemia model. Coadministration of a polyamine oxidase inhibitor potentiated the antitumor activity.

The importance of the naturally occurring polyamines putrescine (**1**), spermidine (**2**), and spermine (**3**) in tumor

$H_2N(CH_2)_4NH_2$

1

$H_2N(CH_2)_3NH(CH_2)_4NH_2$

2

$H_2N(CH_2)_3NH(CH_2)_4NH(CH_2)_3NH_2$

3

cells had been emphasized by the inhibition of tumor growth in experimental animal tumors by polyamine analogues[1] and polyamine biosynthesis inhibitors,[2] such as (difluoromethyl)ornithine. Following our observation that norspermidine (**4**) had good antitumor activity,[3] we

$H_2N(CH_2)_3NH(CH_2)_3NH_2$

4

$H_2N(CH_2)_mX(CH_2)_nNH_2$

5: $m, n = 3, 4$; $X = CH_2, NCH_3, S, SO_2, O$

synthesized and evaluated in the mouse L1210 leukemia model the series of spermidine and norspermidine analogues **5** listed in Table I, none of which were more active in this test than norspermidine. The series was extended by the addition of aminopropyl moieties to the terminal amino groups to give compounds of general structures **6** and **7**. Of these derivatives, tetramine **20** prepared from

$H_2N(CH_2)_3NH(CH_2)_mX(CH_2)_nNH_2$

6

$H_2N(CH_2)_3NH(CH_2)_mX(CH_2)_nNH_2(CH_2)_3NH_2$

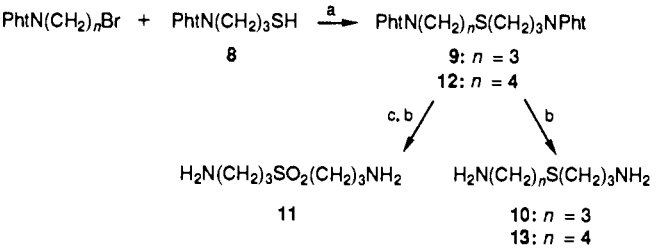
7

1,8-diaminooctane (**7**, $X = CH_2$, $m = 4$, $n = 3$; Table II) exhibited significantly improved antitumor activity. In this paper, we report the synthesis and antitumor activity in the mouse L1210 leukemia model of this series of polyamine analogues derived from norspermidine and 1,8-diaminooctane.

Chemistry

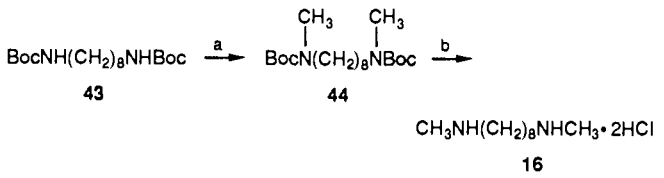
The synthesis of analogues of spermidine and norspermidine, where the central nitrogen was replaced by sulfur, is outlined in Scheme I. Reaction of thiol **8** with either *N*-3-(bromopropyl)- or *N*-4-(bromobutyl)phthalimide, followed by removal of the phthalimide protecting groups,

Scheme I[a]



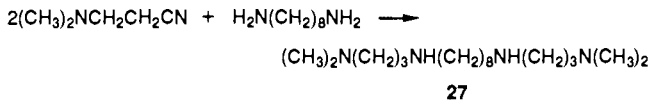
[a] Reagents and conditions: (a) *n*-BuLi, THF; (b) hydrazine hydrate; (c) *m*-chloroperbenzoic acid. Pht = phthalimide.

Scheme II[a]



[a] Reagents and conditions: (a) NaH, CH_3I, DMF; (b) anhydrous HCl, MeOH.

Scheme III



gave the desired analogues **10** and **13**. Oxidation of the intermediate sulfide **9**, followed by hydrolysis of the phthalimide groups, gave sulfone analogue **11**. A norspermidine analogue where the central nitrogen was replaced by oxygen (**14**) and N^4-methylnorspermidine (**15**) were prepared analogously to literature procedures[4,5] by reduction of the corresponding dinitrile. Reaction of the bis-*tert*-butoxycarbonyl derivative of 1,8-diaminooctane (**43**) with methyl iodide/sodium hydride, followed by removal of the Boc groups, gave N^1,N^8-dimethyl-1,8-diaminooctane (**16**, Scheme II). Similarly, norspermidine (**4**) was converted to N^1,N^7-dimethylnorspermidine (**17**). N^1,N^1,N^7,N^7-Tetramethylnorspermidine (**18**) was prepared by reduction of 3-(dimethylamino)proprionitrile according to the procedure of Rylander et al.[6] Dimethylamino analogue **27** was prepared by hydrogenation of 3-(dimethylamino)propionitrile in the presence of 1,8-diaminooctane (Scheme III) as in the preparation of **18**. Reaction of 1,8-diaminooctane with acrylonitrile gave a mixture of mono- and bis-adducts as reported by Brown

(1) Porter, C. W.; Sufrin, J. R. *Anticancer Res.* **1986**, *6*, 525 and references therein.
(2) Sunkara, P. S.; Prakash, N. J. *Novel Approaches to Cancer Chemotherapy*. Academic Press: Orlando, FL, 1984; Chapter 3 and references therein.
(3) Prakash, N. J.; Bowlin, T. L.; Davis, G.; Sunkara, P. S.; Sjoerdsma, A. American Association for Cancer Research, May 1987, Abstract 1260.
(4) Wiley, P. F. *J. Am. Chem. Soc.* **1946**, *68*, 1867.
(5) Bergeron, R. J.; Burton, P. S.; McGovern, S.; Kline, J. *Synthesis* **1981**, 732.
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Table I. Polyamine Analogues: Di- and Triamines. Physical Properties and Antitumor Activity[a] against L1210 Leukemia

no.	structure	mp, °C	dose,[b] mg/kg	% T/C[c]
4	$H_2N(CH_2)_3NH(CH_2)_3NH_2$		25	179
5a	$H_2N(CH_2)_7NH_2$[d]		50	na[e]
5b	$H_2N(CH_2)_8NH_2$[d]		50	na
10	$H_2N(CH_2)_3S(CH_2)_3NH_2 \cdot 2HCl$	209–210[f]	50	na
11	$H_2N(CH_2)_3SO_2(CH_2)_3NH_2 \cdot 2HCl$	190–191[g]	50	na
13	$H_2N(CH_2)_3S(CH_2)_4NH_2 \cdot 2HCl$	222–224	50	na
14	$H_2N(CH_2)_3O(CH_2)_3NH_2 \cdot 2HCl$	>300	50	na
15	$H_2N(CH_2)_3N(CH_3)(CH_2)_3NH_2$	80–100 (1.2 mm)	50	na
16	$CH_3NH(CH_2)_8NHCH_3 \cdot 2HCl$	224–226	50	na
17	$CH_3NH(CH_2)_3NH(CH_2)_3NHCH_3 \cdot 3HCl$	>280	50	na
18	$(CH_3)_2N(CH_2)_3NH(CH_2)_3N(CH_3)_2 \cdot 3HCl$	145–146	50	na
19	$H_2N(CH_2)_3NH(CH_2)_8NH_2 \cdot 3HCl$	270–273[h]	50	na
38	$[CH_2{=}C{=}CHCH_2NH(CH_2)_3]_2NH$	273–275 dec	50	na

[a] Animals in groups of six were inoculated ip with 10^5 L1210 cells on day 0. Control survival was 7.7 ± 0.5 days. [b] Every 3 h (×4) on days 3–6. [c] T/C is defined as survival time treated/survival time control × 100. [d] Purchased from Aldrich Chemical Co. [e] Na = not active. T/C < 110%. [f] Literature ref for free base—see ref 18. [g] Literature[19] mp 192–194 °C. [h] Literature[7] mp 276–277 °C.

Table II. Polyamine Analogues: Tetramines. Physical Properties and Antitumor Activity[a,b] against L1210 Leukemia

no.	structure[c]	mp, °C	% T/C[e]
20	$H_2N(CH_2)_3NH(CH_2)_8NH(CH_2)_3NH_2$[d]	>300[g]	350
21	$H_2N(CH_2)_3NH(CH_2)_3O(CH_2)_3NH(CH_2)_3NH_2$	274–278	na[f]
25b	$C_2H_5NH(CH_2)_3NH(CH_2)_8NH(CH_2)_3NHC_2H_5$	>280	145
26a	$CH_3NH(CH_2)_3NH(CH_2)_8NH(CH_2)_3NHCH_3$	>300	206
26b	$C_2H_5NH(CH_2)_3NH(CH_2)_8NH(CH_2)_3NHC_2H_5$	>300	135
26c	$n\text{-}C_3H_7NH(CH_2)_3NH(CH_2)_8NH(CH_2)_3NH\text{-}n\text{-}C_3H_7$	>300	na
26d	$n\text{-}C_4H_9NH(CH_2)_3NH(CH_2)_8NH(CH_2)_3NH\text{-}n\text{-}C_4H_9$	>300	na
26e	$BnNH(CH_2)_3NH(CH_2)_8NH(CH_2)_3NHBn$	>300	na
27	$(CH_3)_2N(CH_2)_3NH(CH_2)_8NH(CH_2)_3N(CH_3)_2$	240 dec	na
29	$H_2N(CH_2)_2CH(CH_3)NH(CH_2)_8NHCH(CH_3)(CH_2)_2NH_2$	>280	na
34	$H_2NCH(CH_3)(CH_2)_2NH(CH_2)_8NH(CH_2)_2CH(CH_3)NH_2$	206–207	206
42	$CH_2{=}C{=}CHCH_2NH(CH_2)_3NH(CH_2)_8NH(CH_2)_3NHCH_2CH{=}C{=}CH_2$	286–287	na
46	$H_2N(CH_2)_3N(CH_3)(CH_2)_8N(CH_3)(CH_2)_3NH_2$	>300	na

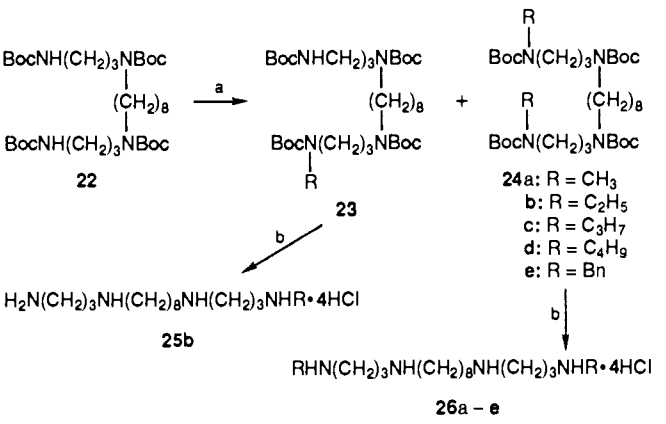
[a] Groups of six mice (BDF1 male) were inoculated ip with 10^5 cells on day 0. Control survival time was 7.5 ± 5 days. [b] Compounds were administered at a dose of 5 mg/kg q 3 h (×4) day 3–5. [c] Compounds were tetrahydrochloride salts. [d] Dose was 6.25 mg/kg q 3 h (×4) day 3–7. [e] See footnote *c*, Table I. [f] Inactive compounds were inactive at a dose of 10 mg/kg as well. [g] Literature[7] mp 307–309 °C.

and Woodcock.[7] This mixture was separated by distillation and the mono- and bis-adducts were reduced (H_2, PtO_2) to give the triamine (**19**) and tetraamine (**20**).

The potent antitumor activity of tetraamine **20** (Table II) directed our synthetic program to tetraamine derivatives. Analogue **21**, in which an oxygen atom was introduced in the C-8 portion, was prepared by reaction of diamine **14** with acrylonitrile followed by catalytic reduction of the bis-adduct. Derivatives incorporating alkyl groups on the terminal nitrogen atoms (Scheme IV) were obtained by reacting compound **22** with 2 equiv of alkyl halide in the presence of potassium *tert*-butoxide. When R was ethyl, the product was a mixture of monoalkyl (**23b**) and dialkyl (**24b**) compounds, which were separated by flash chromatography on silica gel. The Boc protecting groups were removed from **23b** and **24b** with anhydrous HCl in alcohol to give tetraamine tetrahydrochloride salts **25b** and **26a–e**.

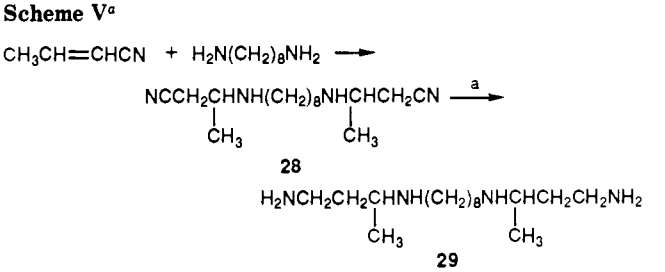
The effect of methyl branching on the aminopropyl group was investigated. Polyamines **29** and **34**, which contained methyl groups α to the central and terminal amino function, respectively, were synthesized. Compound **29** was prepared by Michael addition of 1,8-diaminooctane to crotononitrile followed by reduction of the bis-adduct (Scheme V). Compound **34** (Scheme VI) was prepared from *N,N'*-dibenzyl-1,8-diaminooctane (**30**).[8] Reaction of **30** with methyl vinyl ketone (delivered in a stream of argon to a methanol solution of the amine[9]) gave the unstable

Scheme IV[a]



[a] Reagents and conditions: (a) NaH, RX, DMF; (b) HCl, MeOH.

Scheme V[a]

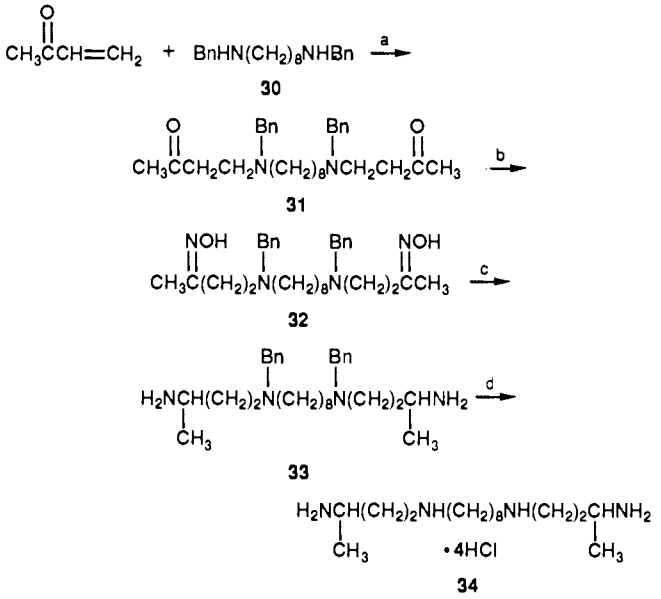


[a] Reagents and conditions: (a) H_2, PtO_2, ethanol.

bis-ketone **31**. Bis-ketone **31** was converted in the same flask to the more stable bis-oxime **32**. Reduction of the bis-oxime with LAH in THF followed by hydrogenolysis

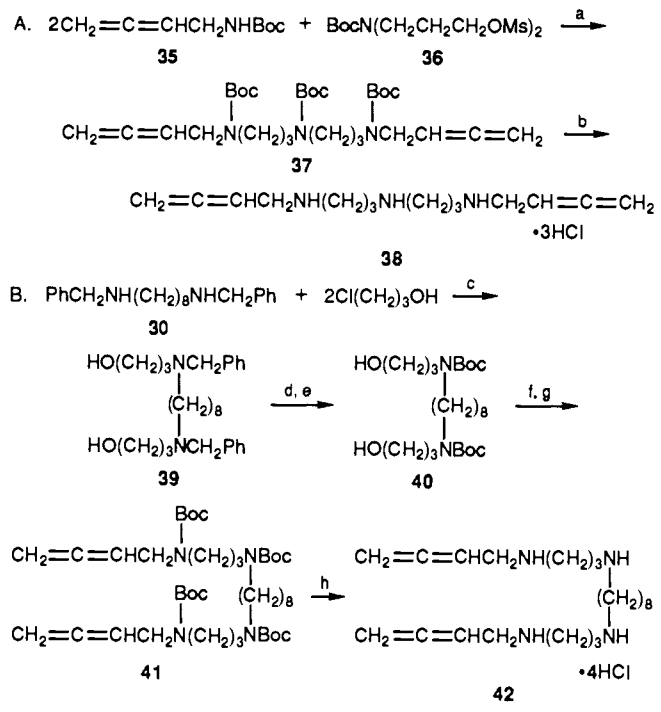
(7) Brown, D.; Woodcock, D. *Pestic. Sci.* **1973**, *4*, 485.
(8) Wittbecker, E.; Houtz, R. C.; Watkins, W. W. *J. Am. Chem. Soc.* **1947**, *69*, 579.
(9) DeBoek, C. D. *J. Org. Chem.* **1974**, *39*, 2426.

Scheme VI[a]



[a] Reagents and conditions: (a) CH_3OH; (b) $NH_2OH{\cdot}HCl$, NaOH, aqueous CH_3OH; (c) LAH, THF; (d) H_2, $Pd(OH)_2$, EtOH/HCl.

Scheme VII[a]

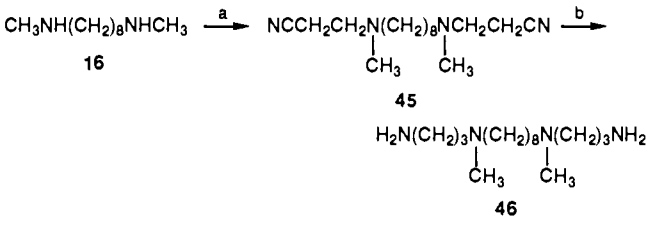


[a] Reagents and conditions: (a) DMF, K-*t*-BuO; (b) HCl, EtOH; (c) K_2CO_3, NaI, *n*-BuOH; (d) H_2, Pd; (e) di-*tert*-butyldicarbonate, CH_2Cl_2; (f) CH_3SO_2Cl, pyridine; (g) DMF, K-*t*-BuO, **35**; (h) HCl, EtOH.

of the benzyl groups over Pearlman's catalyst[10] gave tetraamine **34**.

Scheme VII illustrates the syntheses of the bis-allenylamines **38** and **42**. The synthesis of **38** relied on the alkylation of Boc-butadienylamine[11] (**35**) with the bis-mesylate derivatives of Boc-bis(3-hydroxypropyl)amine (**36**) followed by deprotection with ethanolic HCl. Compound **40** was prepared from diol **39**, obtained by reacting

Scheme VIII[a]



[a] Reagents and conditions: (a) CH_2=CHCN, EtOH; (b) H_2, PtO_2, EtOH.

N^1,N^8-dibenzyl-1,8-diaminooctane (**30**) with 3-chloropropanol, followed by sequential debenzylation with Pearlman's catalyst[10] and reprotection of the amine with a Boc group. Compound **46** resulted (Scheme VIII) from bis-cyanoethylation of diamine **16** and reduction of the bis-cyanoethyl derivative to the tetraamine in the presence of H_2/PtO_2.

Results and Discussion

Table I lists the spermidine and norspermidine analogues prepared and evaluated against L1210 ascitic leukemia in mice. With the exception of norspermidine (**4**), none of these compounds exhibited significant antitumor activity when tested at a dose of 50 mg/kg. Antitumor activity data for the tetraamine derivatives are shown in Table II. All compounds were first evaluated at a dose of 5.0 mg/kg (q 3 h × 4) from days 3–5 posttumor inoculum except compound **20**, which was dosed at 6.25 mg/kg from day 3–7. In this model, **25b**, **26a**, **26b**, and **34** exhibited moderate antitumor activity and **20** exhibited very potent antitumor activity. HPLC analysis[12] of polyamines in tumor tissues from mice administered compound **20** revealed the presence of triamine **19**, suggesting that tetraamine **20** could be metabolized by amine oxidases.[13] Compounds **29**, **34**, and **42** were therefore synthesized since the methyl group or the butadienyl group should inhibit oxidative metabolism. However, only **34** showed activity in the L1210 model at the test dose of 5 mg/kg (Table II). Alkyl groups also were introduced on the terminal nitrogen atoms of tetraamine **20** to inhibit metabolism by amine oxidases. For these derivatives, the antitumor activity appeared to decrease as the size of the alkyl group increased (Table II, compounds **26a–e**). Permethylation of the terminal amino groups (**27**) or methylation of the central nitrogen atoms (**46**) of compound **20** resulted in the loss of antitumor activity. Interestingly, the two butadienyl compounds **38** and **42** were potent irreversible inhibitors of polyamine oxidase (PAO) in vitro and in vivo, i.e. as effective as the putrescine derivative **47**[11] (Table III). However, **38** and **42** were inactive in the L1210 model.

The four analogues **25b**, **26a**, **26b**, and **34** were selected for further evaluation in the L1210 model. The compounds were administered either alone or in combination with

(10) Pearlman, W. M. *Tetrahedron Lett.* **1967**, 1663.
(11) Bey, P.; Bolkenius, F. N.; Seiler, N.; Casara, P. *J. Med. Chem.* **1985**, *28*, 1.
(12) Sunkara, P. S.; Rosenberg, A. L. *Cancer Res.* **1987**, *47*, 933. Bowlin, T. L.; McKown, B. J.; Sunkara, S. P. *Cell. Immunol.* **1986**, *98*, 341.
(13) Israel, M.; Zoll, E. C.; Muhammad, N.; Modest, E. J. *J. Med. Chem.* **1974**, *16*, 1.
(14) Hansen, J. B.; Nielsen, M. C.; Enrbar, U.; Buchardi, O. *Synthesis* **1982**, *22*, 404.
(15) Höltta, E. *Biochemistry* **1977**, *16*, 91.
(16) Bolkenius, F. N.; Bey, P.; Seiler, N. *Biochim. Biophys. Acta* **1985**, *838*, 69.
(17) Bradford, M. *Anal. Biochem.* **1976**, *72*, 248.
(18) Rinaldi, A.; Dernini, S.; Fadda, M. B.; De Murro, L. *Ital. J. Biochem.* **1975**, *24*, 207.
(19) US Patent 3,801,548 (Phillips Petroleum), May 6, 1969; *Chem. Abstr.* **1974**, *81*, 51307*k*.

Table III. Polyamine Oxidase Inhibition[a]

no.	structure	rat liver PAO in vitro K_i, μM	rat liver PAO in vitro τ_{50}, min	in vivo dose, mg/kg	in vivo PAO activity pmol/min per mg of protein
38	$[CH_2{=}C{=}CHCH_2NH(CH_2)_3]_2NH$	3.0	4.0	1	1.0
42	$[CH_2{=}C{=}CHCH_2NH(CH_2)_3NH]_2(CH_2)_8$	2.5	2.0	1	4.1
47	$CH_2{=}C{=}CHCH_2NH(CH_2)_4NHCH_2CH{=}C{=}CH_2$	1.7	1.0	2.5	3.9
				25	1.9
control				0	18.7

[a] Mice were dosed ip with drugs 24 h prior to determination of PAO activity in the liver. Rat liver polyamine oxidase was purified by the procedure of Höltta[15] through the DEAE-cellulose chromatography step. K_i and τ_{50} were determined, with the partially purified PAO, as described by Bey et al.[11] Mouse livers were homogenized and PAO activity was determined as described in Bolkenius et al.[16] Protein concentrations were estimated by the method of Bradford[17] using bovine serum albumin as the standard.

Table IV. Antitumor Activity of Polyamine Analogues Administered as Single Agents or in Combination with a Polyamine Oxidase Inhibitor against L1210 Leukemia in BDF1 Male Mice[a]

no.	dose, mg/kg, ip days 1-9 1 dose/day	mean survival time, days ± SD (n = 5)	% T/C[d]
control		8 ± 0.3	
25b	5	7.6 ± 0.4	100
	5*[,c]	8.4 ± 0.4	105
	10	9.0 ± 0.4	112
	10*	12.4 ± 0.5	155
26a	5	11.4 ± 1.3	142
	5*	12.6 ± 1.5	157
	10	13.8 ± 0.9	172
	10*	25.4 ± 3.8	317
26b	5	9.8 ± 1.1	122
	5*	11.4 ± 1.3	142
	10	9.0 ± 0.3	112
	10*	23.0 ± 2.0	287
control for **34**		6.8 ± 1.1	
34[e]	5[e]	13.3 ± 1.0	195
	5[b]	25.6 ± 6.2	376

[a] 10^5 L1210 cells inoculated ip into BDF1 male mice on day 0. [b] Given with 2.5 mg/kg of di-allenylputrescine (**47**). [c] An asterisk denotes compounds given with 5.0 mg/kg of diallenylputrescine (**47**). [d] See footnote *c*, Table I. [e] Drug given every 3 h (×4) days 3-5.

Table V. Modulation of the Antitumor Activity of Compound **20** against L1210 Leukemia by Putrescine or Spermidine[a]

compd	treatment	mean survival, in days ± SD (n = 5)
control		7.7 ± 0.5
20	25 mg/kg ip days 1-7, 1 dose/day	16.2 ± 1.7
20	25 mg/kg plus, 25 mg/kg putrescine days 1-7, 1 dose/day	15.0 ± 1.1
20	25 mg/kg plus 25 mg/kg spermidine dayds 1-7, 1 dose/day	8.3 ± 0.8

[a] BDF1 male mice (groups of six) were inoculated ip with 10^5 L1210 cells on day 0.

PAO inhibitor **47** (Table IV). The results clearly indicated that concomitant administration of the PAO inhibitor improved the antitumor activity of these polyamines, suggesting the possibility that these compounds were metabolized by PAO.

The mechanism of action of these compounds is currently under study. The antitumor activity of tetraamine **20** was found to be reversed by the coadministration of spermidine but not putrescine (Table V). This reversal may be due, in part, to competition for an uptake system. An examination of tumor cell polyamine concentrations showed that intracellular level of drug was lowered by coadministration of spermidine (Table VI).

In summary, a series of new tetraamines, derived from norspermidine and 1,8-diaminooctane, was synthesized. Several of these compounds exhibited significant antitumor activity at doses of 10 mg/kg or less. The antitumor activity was potentiated in vivo by coadministration of a PAO inhibitor, consistent with inactivation of these antitumor agents by PAO.

Experimental Section

NMR spectra were obtained on a Varian VXR-300 or a Varian EM-360L spectrometer. Chemical shifts were reported downfield from TMS in spectra obtained in $CDCl_3$ and DMSO-d_6 and from DSS, in spectra obtained in D_2O. IR spectra were obtained on a Perkin-Elmer 1800 spectrometer. MS were obtained on a Finnigan MAT 4600 spectrometer. All melting points were determined on a Thomas-Hoover melting point apparatus and were uncorrected. All compounds gave elemental analyses within ±0.4% of theory unless otherwise indicated.

3-Phthalimidopropyl Thiol (8). A mixture of (3-bromopropyl)phthalimide (13.4 g, 0.05 mol) and thiourea (3.8 g, 0.05 mol) in ethanol (250 mL) was heated at reflux temperature for 18 h. The solid, which precipitated upon cooling, was filtered to give 13.3 g (77%) of isothiouronium compound **48**: mp 236-237 °C; IR (KBr) 3300, 1720, 1646, 1400, 1020, and 720 cm^{-1}; NMR (Me_2SO-d_6) δ 9.0 (s, 4 H, exch D_2O), 7.7 (s, 4 H), 3.7 (t, J = 6.0 Hz, 2 H), 3.2 (t, J = 6.0 Hz, 2 H), and 1.9 (m, 2 H); MS (CI/CH_4) 263 (M + H). Anal. ($C_{12}H_{13}N_3O_2S$·HBr) C, H, N. Nitrogen gas was bubbled through a suspension of **48** (20 g, 0.058 mol) in dioxane (600 mL) for 30 min, *unsym*-*N*,*N*-dimethylethylenediamine (15 mL) was added, and the mixture was heated under nitrogen at 80 °C for 4 h. The dioxane was removed at aspirator pressure and the residue was dissolved in ethyl acetate. After washing with aqueous HCl, the organic layer was dried and evaporated. The residue was recrystallized from ethyl acetate/hexane to give 9.6 g (75%) of **8** as a white solid: mp 47-48 °C;

Table VI. Effect of Putrescine or Spermidine Coadministered with Compound **20** on the Tumor Cell Concentration (L1210) of Polyamines[a]

treatment	polyamines, pmol/10^6 cells (average of three determinations) putrescine	spermidine	spermine	**20**
compound **20**, 25 mg/kg, 1 dose/day, days 4-6	37.4	1711	1110	580
compound **20**, 25 mg/kg, 1 dose/day, + putrescine, 25 mg/kg	120	1060	799	520
compound **20**, 25 mg/kg, 1 dose/day, + spermidine, 25 mg/kg	51.7	2174	817	114

[a] Animals were inoculated ip with 10^5 L1210 cells on day 0; beginning on day 4, the animals were treated ip with the compounds at the indicated doses; 4 h after the last dose, animals were sacrificed and tumor cells collected by peritoneal lavage; polyamines were quantitated by HPLC (ref 13).

IR (KBr) 1770, 1720, 1390, and 720 cm^{-1}; NMR (Me_2SO-d_6) δ 7.8 (s, 4 H), 2.6 (t, J = 6.0 Hz, 2 H), 2.45 (m, 3 H, one exchanges D_2O), and 1.9 (m, 2 H); MS (EI) m/z 221 $(M)^+$. Anal. ($C_{11}H_{11}NO_2S$) C, H, N.

3,3'-Thiobis(1-phthalimidopropane) (9). A solution of thiol **8** (2.6 g, 11.7 mmol) in THF (400 mL) was cooled to −70 °C. A solution of *n*-butyllithium in hexane (5 mL of 2.4 M, 12 mmol) was added dropwise and the solution was stirred for 10 min. A solution of (3-bromopropyl)phthalimide (3.15 g, 11.7 mmol) in THF (50 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 3 h, warmed to ambient temperature, and stirred for 1 h. The solvent was evaporated and the residue was partitioned between ethyl acetate and water. The organic layer was washed with water and brine and then dried and evaporated. The residue was chromatographed on a flash silica gel column (9/1 toluene/EtOAc) to yield, after recrystallization from hexane/dichloromethane, 2.2 g (43%) of **9** as a white solid: mp 116–117 °C; IR (KBr) 1720, 1700, 1400, 1020, and 720 cm^{-1}; NMR (Me_2SO-d_6) δ 7.75 (s, 8 H), 3.6 (t, J = 7.3 Hz, 4 H), 2.6 (t, J = 7.3 Hz, 4 H), and 2.0–1.65 (m, 4 H); MS (CI/CH_4) m/z 409 (M + H). Anal. ($C_{22}H_{20}N_2O_4S$) C, H, N. Similarly prepared was **12**, mp 119–120 °C.

3,3'-Thiobis(1-propanamine) Dihydrochloride (10). To a suspension of **9** (2.1 g, 5.1 mmol) in ethanol (50 mL) was added hydrazine hydrate (1.2 mL, 70%). The mixture was heated at reflux for 18 h and then concentrated in vacuo. To the residue was added concentrated HCl (80 mL), H_2O (40 mL), and methanol (40 mL). This mixture was heated at 90 °C for 3 h and filtered. The filtrate was evaporated and the residue was recrystallized from 2-propanol/H_2O to give 250 mg (22%) of **10**, mp 209–210 °C; IR (KBr) 3000, 1600, and 1500 cm^{-1}; NMR (Me_2SO-d_6) δ 8.2 (b s, 6 H), 3.2–2.5 (m, 8 H), and 2.25–1.75 (m, 4 H); MS (EI) 148 $(M)^+$. Anal. ($C_6H_{16}N_2S$·2HCl) C, H; N: calcd, 12.67; found, 12.21. Similarly prepared was **13**, mp 222–224 °C. Anal. ($C_7H_{18}N_2S$·2HCl·$^1/_2H_2O$) C, H, N.

3,3'-Sulfonylbis(1-propanamine) Dihydrochloride (11). A solution of **9** (8.5 g, 21 mmol) in chloroform (400 mL) was chilled in an ice bath. A solution of *m*-chloroperbenzoic acid (10.6 g, 50 mmol) in chloroform (400 mL) was added dropwise. The ice bath was removed and the solution was stirred for 70 h at ambient temperature. The solution was extracted with aqueous Na_2CO_3 and the organic layer was dried and evaporated. The residue was recrystallized (ethyl acetate/methanol) to give 3.5 g (38%) of bis(3-phthalimidopropyl) sulfone (**49**): mp 169–170 °C; IR (KBr) 1770, 1720, 1400, 1370, 1120, and 720 cm^{-1}; NMR (Me_2SO-d_6) δ 7.8 (s, 8 H), 3.7 (t, J = 7.3 Hz, 4 H), 3.2 (m, 4 H + H_2O), and 2.25–1.8 (m, 4 H); MS (CI/CH_4) m/z 441 (M + 1). Anal. ($C_{22}H_{20}N_2O_6S$) H, N; C: calcd, 59.98; found, 59.43. Treatment of the sulfone with hydrazine hydrate the HCl as described for **10** gave **11**: mp 190–191 °C; IR (KBr) 3000, 1590, 1515, 1280, 1020, 780, 595, and 520 cm^{-1}; NMR (Me_2SO-d_6) δ 8.15 (b s, 6 H), 3.4–3.05 (b s, 4 H), 2.8 (t, J = 7.3 Hz, 4 H), and 2.2–1.8 (m, 4 H); MS (CI/CH_4) 181 (M + H). Anal. ($C_6H_{16}N_2O_2S$·2HCl) C, H, N.

***N,N'*-Dimethyl-1,8-octanediamine Dihydrochloride (16).** *N,N'*-Bis(*tert*-Boc)-1,8-octanediamine[14] (**43**, 0.68 g, 2 mmol) was dissolved in DMF (4 mL) and NaH (0.16 g of 60% oil dispersion, 4 mmol) was added. The mixture was stirred for 1 h at ambient temperature, methyl iodide (2.87 g, 5 mmol) was added, and stirring was continued for 18 h. The reaction mixture was evaporated and the dimethylated product (320 mg) was obtained by flash chromatography of the residue (EtOAc, 15% in hexane): NMR ($CDCl_3$) δ 3.20 (t, J = 7 Hz, 4 H), 2.85 (s, 6 H) 1.65 (m, 4 H), 1.50 (18 H), and 1.35 (m, 8 H). This material was dissolved in ethanol (2 mL), a 2 N solution of HCl gas in ether (6 mL) was added, and the mixture was stirred for 4 h. The precipitate was filtered, washed with ether, and vacuum dried to give 200 mg (41%) of white solid: mp 224–226 °C; IR (KBr) 2950, 2800, and 1450 cm^{-1}; NMR (Me_2SO-d_6) δ 2.85 (t, J = 8 Hz, 4 H), 2.6 (s, 6 H), 1.6 (m, 4 H), and 1.35 (m, 8 H). Anal. ($C_{10}H_{24}N_2$·2HCl) C, H, N.

***N*-(3-Aminopropyl)-*N'*-[3-(ethylamino)propyl]-1,8-octanediamine Tetrahydrochloride (25b).** To a solution of the tetrakis-*tert*-butoxycarbonyl derivative of *N,N'*-bis(3-aminopropyl)-1,8-octanediamine [**22**, 9.5 g, 0.0144 mol, prepared from the tetramine and di-*tert*-butyl dicarbonate in aqueous THF: NMR ($CDCl_3$) δ 3.15 (m, 12 H), 1.55 (m, 4 H), 1.50 (m, 36 H), and 1.36 (m, 12 H)] in DMF (45 mL) was added potassium *tert*-butoxide (2.91 g, 0.026 mol) and the mixture was cooled to 0 °C. Iodoethane (4.06 g, 0.026 mol) was added and the mixture was stirred for 18 h. The solvent was evaporated in vacuo and the residue was partitioned between ethyl acetate and water. The organic layer was separated, dried ($MgSO_4$), and evaporated. The residue was chromatographed on a flash silica gel column (20% EtOAc/hexane) to give the product (**23b**) as a thick oil: NMR ($CDCl_3$) δ 3.37–3.00 (m, 14 H), 1.80 (m, 4 H), 1.50 (s, 36 H), 1.22 (m, 12 H), and 1.12 (t, J = 6.6 Hz, 3 H). The residue was dissolved in ethanol (5 mL) and a solution of anhydrous HCl in ether (60 mL, 2 N) was added. After 24 h, the mixture was filtered to give 1.35 g (21% over two steps) of **25b** as a white solid: mp >310 °C; IR (KBr) 3550, 2920, 2774, and 1460 cm^{-1}; NMR (D_2O) δ 3.3–2.9 (m, 16 H), 2.35–1.95 (m, 4 H), and 1.95–1.2 (m, 15 H); MS (CI/CH_4) 286, (M + H). Anal. ($C_{16}H_{38}N_4$·4HCl·$^1/_2H_2O$) C, H, N, Cl.

***N,N'*-Bis[3-(ethylamino)propyl]-1,8-octanediamine Tetrahydrochloride (26b).** To a solution of the tetrakis-*tert*-butoxycarbonyl derivative of *N,N'*-bis(3-aminopropyl)-1,8-octanediamine (3.29 g, 0.05 mol) in DMF (15 mL) was added potassium *tert*-butoxide (1.23 g, 0.011 mol) and the mixture was stirred for 20 min at ambient temperature. The mixture was cooled to 0 °C, iodoethane (1.7 g, 0.011 mol) was added, and the mixture was stirred for 18 h. The solvent was evaporated at reduced (1 mm) pressure and the residue was suspended in ethyl acetate (700 mL). The mixture was washed with water (3 × 100 mL) and brine (100 mL). The organic layer was dried ($MgSO_4$) and evaporated. The residue was chromatographed on a flash silica gel column (20% EtOAc/hexane). The fraction containing the diethyl adduct were evaporated, the residue (1 g, 1.4 mmol) was dissolved in ethanol (2 mL), and 20 mL of a 2 N solution of anhydrous HCl in ether was added. The mixture was stirred for 24 h and filtered to give 480 mg (21% over the two steps) of **26b**: mp >280 °C; IR (KBr) 3450, 2950, 2780, 2480, and 1450 cm^{-1}; NMR (D_2O) δ 3.3–2.85 (m, 16 H), 2.3–1.95 (m, 4 H), 1.85–1.5 (m, 4 H), and 1.5–1.15 (7, 12 H); MS (CI/CH_4) 315 (M + H). Anal. ($C_{18}H_{42}N_4$·4HCl) C, H, N, Cl.

Similarly prepared were the following.

26a: mp >300 °C; NMR (D_2O) δ 3.15 (t, J = 7 Hz, 8 H), 3.05 (t, J = 7 Hz, 4 H), 2.75 (s, 6 H), 2.10 (m, 4 H), 1.70 (m, 4 H), and 1.35 (m, 8 H); IR (KBr) 3420, 2860, 2460, 1590, and 1460 cm^{-1}; MS (CI/CH_4) 287 (M + H). Anal. ($C_{16}H_{38}N_4$·4HCl) C, H, N, Cl.

26c: mp >300 °C; NMR (D_2O) δ 3.15 (m, 8 H), 3.05 (m, 8 H), 2.10 (m, 4 H), 1.70 (m, 8 H), 1.35 (m, 8 H), and 0.95 (t, J = 6 Hz, 6 H); IR (KBr) 3435, 2950, 2515, and 1510 cm^{-1}; MS (CI/CH_4) 343 (M + H). Anal. ($C_{20}H_{46}N_4$·4HCl) C, H, N, Cl.

26d: mp >300 °C; NMR (D_2O) δ 3.15 (m, 8 H), 3.05 (m, 8 H) 2.10 (m, 4 H), 1.70 (m, 8 H), 1.40 (m, 12 H), and 0.95 (t, J = 6 Hz, 6 H); IR (KBr) 3420, 2950, 1560, and 1400 cm^{-1}; MS (CI/CH_4) 371 (M + H). Anal. ($C_{22}H_{50}N_4$·4HCl) C, H, N, Cl.

26e: mp >300 °C; NMR (CDCl/TFA) δ 7.40 (m, 10 H), 4.25 (m, 4 H), 3.25 (m, 8 H), 3.10 (m, 4 H), 2.45 (m, 4 H), 1.70 (m, 4 H), and 1.35 (m, 8 H); IR (KBr) 3420, 2940, 1585, and 1440 cm^{-1}; MS (CI/CH_4) 439 (M + H). Anal. ($C_{28}H_{46}N_4$·4HCl) C, H, N, Cl.

***N,N'*-Bis[3-(dimethylamino)propyl]-1,8-octanediamine Tetrahydrochloride (27).** A solution of 1,8-Diaminooctane (14.4 g, 0.1 mol), β-(dimethylamino)propionitrile (19.6 g, 0.2 mol), and 5% rhodium on carbon (2 g) in ethanol (50 mL) was treated with hydrogen at 45 lb in^{-2} until the theoretical amount of hydrogen had been absorbed. The catalyst was removed by filtration and the solvent was evaporated. Volatile materials were removed at 130 °C (0.1 mm), leaving a residue which was homogeneous by capillary GC analysis. This material was dissolved in methanol (200 mL) and the solution was treated with HCl gas. The solid that precipitated was filtered and recrystallized from methanol/2-propanol to give 1.5 g (3.2%) of **27**: mp 240–242 °C dec; IR (KBr) 3410, 2920, and 1460 cm^{-1}; NMR (D_2O) δ 3.3 (t, J = 7.6 Hz, 4 H), 3.1 (m, 8 H), 2.95 (s, 12 H), 2.18 (m, 4 H), 1.7 (m, 4 H), and 1.35 (m, 8 H); MS (CI/CH_4) 314 (M + H). Anal. ($C_{18}H_{42}N_4$·4HCl) C, H; N: calcd, 12.17; found, 11.55; Cl: calcd, 30.81; found, 29.46.

Similarly prepared was **18**: mp 145–146 °C; NMR (D_2O) δ 3.25 (m, 4 H), 3.15 (m, 4 H), 2.92 (s, 6 H), 2.18 (m, 4 H); IR (KBr) 3330, 2840, 2670, 1475 cm^{-1}; MS (CI/isobutane) 188 (M + H). Anal. ($C_{10}H_{25}N_3$·3HCl·H_2O) C, H, N, Cl.

N,N'-Bis(3-amino-1-methylpropyl)-1,8-diaminooctane Tetrahydrochloride (29). A solution of 1,8-diaminooctane (7.2 g, 0.05 mol) and crotononitrile (6.7 g, 0.1 mol) in ethanol (50 mL) was stirred at ambient temperature for 48 h. The reaction mixture was evaporated to give 13.4 g (96%) of crude dinitrile (**28**): NMR (D_2O) δ 2.77 (m, 2 H), 2.40 (m, 8 H), 1.70 (br m, 2 H), 1.25 (m, 12 H), 1.05 (d, J = 6 Hz, 6 H). The dinitrile (13.4 g, 0.048 mol) and PtO_2 (0.75 g) were added to a mixture of AcOH (100 mL) and 12 N HCl (24 mL) and hydrogenated on a Parr shaker until the theoretical amount of H_2 uptake occurred. The catalyst was filtered and the filtrate was evaporated. The residue was recrystallized from methanol/acetone/H_2O to give 6.5 g (30%) of **29**: mp >280 °C; NMR (Me_2SO-d_6) δ 8.55 (b m, 10 H), 3.10–2.7 (m, 10 H), and 2.35–1.00 (m, 22 H); IR (KBr) 3440, 2920, 1600, and 1470 cm^{-1}; MS (CI/CH_4) 287 (M + H). Anal. ($C_{16}H_{38}N_4 \cdot 4HCl \cdot {}^1/_2H_2O$) C, H, N, Cl.

N,N'-Bis(3-aminobutyl)-1,8-octanediamine Tetrahydrochloride (34). A solution of *N,N'*-dibenzyl-1,8-diaminooctane (17.5 g, 0.054 mol) in methanol (700 mL) was stirred as a stream of argon containing methyl vinyl ketone was passed through the solution. Addition was continued until the required amount (8.4 g, 0.12 mol) of methyl vinyl ketone had been transferred. The solution was stirred for a total of 18 h. The solvent was removed to give bis-ketone **31** (24.8 g, 96%) as a gum: NMR ($CDCl_3$) δ 7.25 (s, 10 H), 3.50 (s, 4 H), 2.8–2.2 (m, 12 H), 2.05 (s, 6 H), 1.45 (m, 4 H), and 1.25 (m, 8 H). The product was unstable and was used immediately. To a solution of bis-ketone **31** (24.8 g, 0.054 mol) in methanol (700 mL) cooled in an ice bath were added hydroxylamine hydrochloride (9 g, 0.12 mol) and 25% NaOH (19.2 g). The mixture was stirred at ambient temperature overnight. Removal of the methanol upon rotary evaporation left an aqueous residue which was extracted with dichloromethane. Concentration of the organic layers gave a residue which was purified by flash chromatography (EtOAc) to yield bisoxime **32** (10 g, 38%) as an analytically pure gum: IR ($CHCl_3$) 3590, 2930, 1660, and 1450 cm^{-1}; NMR ($CDCl_3$) δ 7.8 (m, 2 H), 7.25 (m, 10 H), 3.45 (m, 4 H), 2.4 (m, 8 H), 2.25 (m, 4 H), 1.7 (s, 6 H), 1.4 (m, 4 H), and 1.2 (m, 8 H); MS (CI/CH_4) 495 (M + H). Anal. ($C_{30}H_{46}N_4O_2$) C, H, N.

A solution of bisoxime **32** (3.8 g, 7.7 mol) in THF (20 mL) was added dropwise to a suspension of LAH (1.4 g, 37 mol) in THF (60 mL). The mixture was stirred at reflux temperature for 48 h. The mixture was cooled and excess hydride was destroyed by careful addition of water (1.5 mL) and 1 N NaOH (4.5 mL). The mixture was filtered and the filtrate was evaporated. Kugelrohr distillation yielded 0.71 g (20%) of **33** as a thick oil: $bp_{0.2}$ 230–235 °C; IR (film) 2928, 2865, 2800, 1593, and 1450 cm^{-1}; NMR ($CDCl_3$) δ 7.25 (m, 10 H), 3.5 (s, 4 H), 2.95 (m, 2 H), 2.45 (t, J = 7.5 Hz, 4 H), 2.4 (dd, 4 H), 1.45 (m, 12 H), 1.25 (m, 8 H), and 1.0 (d, J = 6 Hz, 6 H); MS (CI/CH_4) 467 (M + H). Anal. ($C_{30}H_{50}N_4$) C, H, N.

A solution of **33** (0.7 g, 1.5 mmol) and Pearlman's catalyst (20% $Pd(OH)_2$/C, 0.2 g) in 10 mL of ethanol was treated with H_2 on a Parr hydrogenation apparatus at 45 lb/in^2 until the theoretical uptake of H_2 had occurred. The catalyst was removed by filtration and the filtrate was treated with 10 mL of 1 N HCl in methanol. Evaporation to dryness and repeated crystallization from methanol gave 40 mg (6%) of **34** as a white solid: mp 206–207 °C; IR (KBr) 3420, 2950, 1605, 1525, and 1470 cm^{-1}; NMR (D_2O) δ 2.74 (m, 2 H), 2.58 (t, J = 7.0 Hz, 4 H), 2.53 (t, J = 5 Hz, 4 H), 2.01 (m, 4 H), 1.85 (m, 4 H), and 1.35 (d, J = 6.5 Hz, 6 H); MS (CI/CH_4) 287 (M + H). Anal. ($C_{16}H_{38}N_4 \cdot 4HCl$) C, H, N; Cl: calcd, 32.80; found, 31.49.

N-2,3-Butadienyl-N'-[3-(2,3-butadienylamino)propyl]-1,3-propanediamine Trihydrochloride (38). To a solution of Boc-bis(3-hydroxypropyl)amine [11.5 g, 0.05 mol; prepared from bis(3-hydroxypropyl)amine and di-*tert*-butyl dicarbonate] and triethylamine (18.5 g, 0.18 mol) in dichloromethane (500 mL) chilled to 0 °C was added dropwise a solution of methanesulfonyl chloride (12.5 g, 0.11 mol) in dichloromethane (85 mL). The mixture was stirred for 1.5 h, diluted with dichloromethane (250 mL), and extracted with 1 N acetic acid, aqueous $NaHCO_3$, H_2O, and brine. The organic layer was dried and evaporated, and the residue was purified by flash silica gel chromatography (ethyl acetate/hexane (3/2 v/v)) to give bis-mesylate **36** (8.8 g, 45% as a waxy solid: IR (KBr) 2980, 2340, 1680, 1440, and 1355 cm^{-1}; NMR ($CDCl_3$) δ 4.2 (t, J = 6.4 Hz, 4 H), 3.3 (t, J = 6.9 Hz, 4 H), 3.0 (s, 6 H), 1.9 (m, 4 H), and 1.4 (s, 9 H). MS (CI/CH_4) 390 (M + H). Anal. ($C_{13}H_{27}NO_8S_2$) C, H, N, S.

Sodium iodide (6.7 g, 44 mol), NaH (1.96 g of 60% dispersion in oil, 49 mmol), and compound **36** (8.8 g, 22 mmol) were added to DMF (50 mL) and the mixture was chilled to 0 °C. A solution of allenyl compound **35**[11] (8.3 g, 48 mmol) in DMF (20 mL) was added and the mixture was stirred at 0 °C for 3.5 h. The solvent was removed, the residue was taken up in EtOAc, and the solution was extracted with H_2O. The organic layer was dried ($MgSO_4$) and evaporated. Flash chromatography (25% EtOAc/hexane) of the residue gave 7.9 g of a thick oil (**37**): NMR ($CDCl_3$), δ 5.05 (m, 2 H), 4.7 (m, 4 H) 3.75 (m, 4 H), 3.15 (m, 8 H) 1.75 (m, 4 H), and 1.4 (s, 27 H).

To a solution of **37** (7.9 g, 0.02 mol) in ethanol (35 mL) was added a solution of anhydrous HCl in ether (120 mL, 2 N). The mixture was stirred for 18 h at ambient temperature. The solid that precipitated was filtered and dried at reduced pressure over P_2O_5 to give 50 mg (0.66% from **36**) of **38**: mp 273–275 °C dec; IR (KBr) 2800, 1960, 1580, and 1450 cm^{-1}; NMR (D_2O) δ 5.3 (m, 2 H), 5.0 (m, 4 H), 4.75 (m, 8 H), 3.75 (m, 4 H), and 2.15 (m, 4 H): MS (CI/CH_4) 236 (M + H). Anal. ($C_{22}H_{42}N_4 \cdot 6HCl$) C, H, N, Cl.

N,N'-Bis(3-hydroxylpropyl)-N,N'-bis(phenylmethyl)-1,8-diaminooctane (39). *N,N'*-Dibenzyl-1,8-diaminooctane (**30**, 32.4 g, 0.1 mol), sodium carbonate (50.4 g, 0.475 mol), sodium iodide (1.19 g, 0.008 mol), and 3-chloro-1-hydroxypropane (16.7 mL, 0.2 mol) were combined in *n*-butanol (40 mL), and the mixture was heated at reflux for 20 h. The mixture was then partitioned between ethyl acetate (900 mL) and water (200 mL). The organic layer was separated, dried ($MgSO_4$), and evaporated in vacuo. Bulb-to-bulb distillation yielded 35.0 g (80%) of **39**: $bp_{0.1}$ 250 °C; NMR ($CDCl_3$) δ 7.20 (s, 10 H), 4.45 (b m, 2 H), 3.65 (t, J = 4.5 Hz, 4 H), 3.50 (s, 4 H), 2.65–2.25 (m, 8 H), and 1.85–1.05 (m, 16 H).

1,18-Bis(2,3-butadienyl)-1,5,14,18-tetrakis(*tert*-butoxycarbonyl)-1,5,14,18-tetaazaoctadecane (41). Compound **39** (35.0 g, 0.078 mol) and palladium oxide (4.0 g) were combined in acetic acid (300 mL) and treated with hydrogen on a Parr hydrogenation apparatus until uptake ceased. The catalyst was removed by filtration and the solvent was evaporated at reduced pressure to yield 20.0 g of viscous oil. The oil was dissolved in dichloromethane (700 mL) containing triethylamine (30 mL) and treated with di-*tert*-butyl dicarbonate (35.0 g, 0.15 mol) with stirring for 16 h. The mixture was then washed with water and the organic layer was dried ($MgSO_4$) and evaporated in vacuo. Flash chromatography (75% EtOAc/hexane) yielded 9.9 g of bis-Boc compound **40** (28% for the two steps) as a viscous oil: R_f = 0.31 (75% EtOAc/hexane); NMR ($CDCl_3$) δ 3.55 (t, J = 6 Hz, 4 H), 3.35 (t, J = 6 Hz, 4 H), 3.15 (t, J = 6 Hz, 6 H), 1.95–1.60 (m, 4 H), 1.55 (s, 18 H), 1.35 (m, 12 H). Treatment of this oil at 0 °C with triethylamine (9.65 mL, 0.069 mol) and methanesulfonyl chloride (3.66 mL, 0.046 mol) in dichloromethane (210 mL) yielded after aqueous workup and flash chromatography (eluted with 60% EtOAc/hexane) 9.4 g (73%) of bis-methylate, a clear oil: R_f = 0.39 (60% EtOAc/hexane); NMR ($CDCl_3$) δ 4.20 (t, J = 6 Hz, 4 H), 3.35–3.05 (m, 8 H), 3.00 (s, 6 H), 2.00 (m, 4 H), 1.45 (s, 18 H), and 1.30 (m, 12 H). To a solution of the bis-mesylate (9.4 g, 0.015 mol), sodium hydride (60% in oil, 2.11 g, 0.053 mol), and sodium iodide (4.5 g, 0.03 mol) in DMF (24 mL) cooled to 0 °C was added a solution of **35** (8.24 g, 0.04 mol) in DMF (12 mL). When the addition was completed the mixture was warmed to ambient temperature and allowed to stir for 5 h. The solvent was removed in vacuo and the thick residue was partitioned between EtOAc (1 L) and water (500 mL). The organic layer was washed with water (2 × 500 mL), dried ($MgSO_4$), and evaporated in vacuo. Flash chromatography (25% EtOAc/hexane) yielded 7.6 g (67%) of **41** as a clear oil: R_f = 0.39 (25% EtOAc/hexane). NMR ($CDCl_3$) δ 5.15 (m, 2 H), 4.75 (m, 4 H), 3.75 (m, 4 H), 3.15 (m, 12 H), 1.6 (m, 4 H), 1.45 (s, 36 H), and 1.30 (m, 8 H).

1,18-Bis(2,3-butadienyl)-1,5,14,18-tetraazaoctadecane Tetrahydrochloride (42). To a solution of **41** (7.6 g, 0.01 mol) in ethanol (5 mL) was added 80 mL of 2 N HCl in ether. After stirring for 18 h, the mixture was filtered. The solid was slurried with hot methanol (200 mL), and the mixture was cooled to ambient temperature and filtered to yield 3.02 g (60%) of **42** as a white solid: mp 286–287 °C; NMR (D_2O) δ 5.35 (m, 2 H), 5.05

(m, 4 H), 3.65 (m, 4 H), 3.20–3.00 (m, 12 H), 2.10 (m, 4 H), 1.70 (m, 4 H), and 1.35 (m, 8 H); IR (KBr) 3420, 2940, 1910, and 1450 cm^{-1}; MS (CI/CH_4) 363 (M + H). Anal. ($C_{22}H_{42}N_4 \cdot 4HCl$) C, H, N, Cl.

***N,N'*-Bis(3-aminopropyl)-*N,N'*-dimethyl-1,8-octanediamine Tetrahydrochloride (46).** A solution of compound **16** (1 g, 4 mmol), sodium hydroxide (0.32 g, 8 mmol), and acrylonitrile (0.43 g, 8 mmol) in ethanol (16 mL) was stirred for 72 h at ambient temperature. The mixture was filtered and the filtrate was evaporated. The residue was stirred with ether (50 mL) and filtered. The filtrate was evaporated to give compound **45** (1 g, 90%) as a clear oil: NMR ($CDCl_3$) δ 2.8–2.35 (m, 12 H), 2.2 (s, 6 H), and 1.30 (m, 12 H). Compound **45** was taken up in a mixture of acetic acid (26 mL) and concentrated HCl (1.3 mL); the solution was hydrogenated in a Parr apparatus in the presence of PtO_2 (0.2 g). The catalyst was removed and the solution was evaporated. The residue was recrystallized from 2-propanol to give **46** (130 mg, 7.4%) as a white solid: mp >300 °C; IR (KBr) 2950, 1610, and 1460 cm^{-1}; NMR (Me_2SO-d_6/D_2O, 1/1) δ 3.05 (m, 8 H), 2.88 (t, J = 7.0 Hz, 4 H), 2.65 (s, 6 H), 1.95 (m, 4 H), 1.6 (m, 4 H), and 1.3 (m, 8 H); MS (EI) 286 (M). Anal. ($C_{16}H_{38}N_4 \cdot 4HCl \cdot {}^1/_2H_2O$) C, H, N, Cl.

Similarly prepared was **21**: NMR (Me_2SO-d_6/D_2O) 3.50 (t, J = 6 Hz, 4 H), 2.90 (m, 12 H), and 2.00 (m, 8 H); IR (KBr) 3480, 2520, 1600, and 1525, cm^{-1}; MS (CI/CH_4) 247 (M + H). Anal. ($C_{12}H_{30}N_4O \cdot 4HCl \cdot {}^1/_2H_2O$) C, H, N; Cl: calcd, 35.45; found, 34.04.

Registry No. **8**, 39801-32-6; **9**, 125763-67-9; **10**·2HCl, 51920-08-2; **10** (free base), 13643-20-4; **11**·2HCl, 51920-09-3; 11 (free base), 102203-35-0; **13**·2HCl, 125763-68-0; **13** (free base), 86108-46-5; **14**·2HCl, 89990-48-7; **14** (free base), 2157-24-6; **15**, 105-83-9; **16**·2HCl, 63869-19-2; **16** (free base), 33563-54-1; **17**·3HCl, 125763-69-1; **17** (free base), 75403-53-1; **18**·3HCl, 82958-56-3; **18** (free base), 6711-48-4; **19**·3HCl, 82958-51-8; **19** (free base), 53774-74-6; **20**, 54443-83-3; **21**·4HCl, 102203-40-7; **21** (free base), 102203-41-8; **22**, 117654-82-7; **23b**, 122560-29-6; **25b**·4HCl, 122560-26-3; **25b** (free base), 122560-20-7; **26a**·4HCl, 122560-24-1; **26a** (free base), 122560-19-4; **26b**·4HCl, 122560-25-2; **26b** (free base), 122560-21-8; **26c**·4HCl, 125763-79-3; **26c** (free base), 122560-23-0; **26d**·4HCl, 117654-75-8; **26d** (free base), 125763-86-2; **26e**·4HCl, 117654-74-7; **26e** (free base), 117654-73-6; **27**·4HCl, 125763-70-4; **27** (free base), 125763-82-8; **28**, 125763-71-5; **29**·4HCl, 125763-72-6; **29** (free base), 125763-83-9; **31**, 122560-30-9; **32**, 122560-31-0; **33**, 122560-32-1; **34**·4HCl, 125763-73-7; **34** (free base), 122560-22-9; **35**, 92136-43-1; **36**, 125763-74-8; **37**, 125781-08-0; **38**·3HCl, 125763-75-9; **38** (free base), 125763-81-7; **39**, 117654-97-4; **40**, 117654-99-6; **41**, 117655-01-3; **42**·4HCl, 117681-74-0; **43** (free base), 125763-84-0; **43**, 82409-00-5; **44**, 125763-76-0; **45**, 125763-77-1; **46**·4HCl, 125781-09-1; **46** (free base), 125763-85-1; **47**, 99207-33-7; **48**, 63344-92-3; **49**, 125763-78-2; $PhCH_2NH(CH_2)_8NHCH_2Ph$, 39624-13-0; $H_2N(CH_2)_3NH(CH_2)_8NH(CH_2)_3NH_2$, 54443-83-3; $Me_2NCH_2CH_2CN$, 1738-25-6; $H_2N(CH_2)_8NH_2$, 373-44-4; $H_3CC{-}H{=}CHCN$, 4786-20-3; $MeCOCH{=}CH_2$, 78-94-4; $(BOC)N[(CH_2)_3OH]_2$, 125763-80-6; $HN[(CH_2)_3OH]_2$, 14002-33-6; $HO(CH_2)_3NH(CH_2)_8NH(CH_2)_3OH$, 117654-98-5; $MeSO_3(CH_2)_3N(BOC)(CH_2)_8N(BOC)(CH_2)_3OSO_2Me$, 117655-00-2; $H_2C{=}CHCN$, 107-13-1; $Cl(CH_2)_3OH$, 627-30-5; *N*-(3-bromopropyl)phthalimide, 5460-29-7.

Potential Antitumor Agents. 60. Relationships between Structure and in Vivo Colon 38 Activity for 5-Substituted 9-Oxoxanthene-4-acetic Acids

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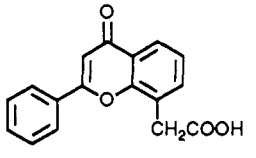
Received June 29, 1989

9-Oxoxanthene-4-acetic acids are a class of antitumor agents effective against the mouse colon adenocarcinoma 38 in vivo. Within this class, 5-substituents on the xanthenone are known to enhance potency. To extend structure–activity relationships for the class, a series of derivatives bearing a wide variety of substituents at the 5-position have been prepared and evaluated. The results suggest that activity correlates better with the lipophilic properties of substituents rather than with their electronic properties. Generally, lipophilic substituents result in more active compounds, but there may be a size limitation on such substituents. The 5-methyl derivative is the most dose-potent of the analogues studied.

The recent discovery[1-5] of the unusual antitumor profile of flavoneacetic acid (1, FAA, NSC 347512) has sparked interest in the development of related compounds of similar activity. While FAA has not yet shown clinical activity,[6,7] its unique effects against experimental colon tumors make it an important lead. Although it has been shown to act as a biological response modifier, inducing natural killer cell activity,[4] and to have marked effects on tumor blood flow,[8,9] its mode of action is not yet known. In the absence of this information new drug development is of necessity slow and relies on the determination of structure–activity relationships (SAR) among related compounds.



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We have recently reported SAR for in vivo colon 38 activity among analogues of FAA itself[10] and also[11] for a

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