Table I—Antimicrobial Activity of Phenolic Constituents of *M. grandiflora* L.

Compound	Zone Diameter, mm						
	B. subtilis	*S. aureus*	*M. smegmatis*	*C. albicans*	*S. cerevisiae*	*A. niger*	*T. mentagrophytes*
I	8	7	15	6	12	6	17
II	9	10	12	6	12	8	20
III	7	6	13	2	15	1	15
IV	1	2	—	—	4	—	4
V	—	—	—	—	3	—	3
Streptomycin sulfate	10	7	17	NT[a]	NT	NT	NT
Amphotericin B	NT	NT	NT	4	5	3	4

[a] Not tested.

Table II—Minimum Inhibitory Concentrations (Micrograms per Milliliter) of Phenolic Constituents of *M. grandiflora* L.[a]

Compound	*B. subtilis*	*S. aureus*	*M. smegmatis*	*C. albicans*	*S. cerevisiae*	*A. niger*	*T. mentagrophytes*
I	5 (5)	5 (5)	5 (5)	30 (30)	10 (10)	30 (30)	2.5 (2.5)
II	5 (5)	10 (10)	7.5 (7.5)	30 (30)	10 (10)	30 (30)	2.5 (2.5)
III	2.5 (2.5)	2.5 (2.5)	2.5 (2.5)	NT[b]	10 (10)	NT	1.25 (1.25)
Streptomycin sulfate	10 (10)	10 (10)	2.5 (1.25)	NT	NT	NT	NT
Amphotericin B	NT	NT	NT	5 (5)	2.5 (2.5)	30 (30)	15 (15)

[a] Numbers in parentheses refer to values obtained on duplicate testing. [b] Not tested.

creased to either 30 or 60 μg/ml.

The MIC was taken as the lowest concentration that inhibited growth after 24 or 48 hr of incubation. Tubes inoculated with *B. subtilis* and *S. aureus* were incubated at 37° for 24 hr, while tubes inoculated with *M. smegmatis* were incubated at 37° for 48 hr. Tubes inoculated with fungi and yeasts were incubated at 30° for 48 hr. Streptomycin sulfate[1] and amphotericin B[2] were used as standard antibiotics for comparison with the phenolic compounds.

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[1] Chas. Pfizer & Co., Groton, Conn.
[2] Calbiochem, San Diego, Calif.

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Preparation and Antidiabetic Activity of Cyclic Sulfonylthiourea Derivatives

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Received September 29, 1980, from the **Department of Pharmaceutical Chemistry and the* ‡*Department of Pharmacology, Faculty of Pharmacy, and the* §*Department of Chemistry, Faculty of Science, University of Alexandria, Alexandria, Egypt.* Accepted for publication January 21, 1981.

Abstract □ 3-Substituted 5-methyl-1-{*p*-[(3,5-dimethyl)pyrazol-1-yl]-, 5-methyl-1-{*p*-[(5-methyl-3-carboxy)pyrazol-1-yl]-, 1-{*p*-[(3-methyl-5-phenyl)pyrazol-1-yl]-, and 1-{*p*-[(3-methyl-4-bromo-5-phenyl)pyrazol-1-yl]benzenesulfonyl}-2-thiohydantoin and their 5-methyl-2-thiohydantoin and 5,6-dihydro-4(3*H*)-oxo-2(1*H*)-pyrimidinethione derivatives were prepared for evaluation as hypoglycemic agents. Biological testing showed that some of these compounds possessed antidiabetic activity.

Keyphrases □ Cyclic sulfonylthiourea derivatives—preparation and evaluation for antidiabetic activity, IR and PMR spectroscopy □ IR spectroscopy—identification of cyclic sulfonylthiourea derivatives, antidiabetic activity in mice □ Antidiabetic activity—synthesis and evaluation of cyclic sulfonylthiourea derivatives, identification by IR spectroscopy

In spite of the low hypoglycemic effect of substituted pyrazolesulfonylthiourea derivatives (1–3), their cyclic thio analogs showed potent antidiabetic activity (1). This finding initiated the synthesis of new cyclic pyrazolesulfonylthio analogs[1] for the evaluation of their antidiabetic effect.

EXPERIMENTAL[2]

Substituted *p*-[(3,5-dimethyl)pyrazol-1-yl]-, *p*-[(5-methyl-3-carboxy)pyrazol-1-yl]-, *p*-[(3-methyl-5-phenyl)pyrazol-1-yl]-, and *p*-[(3-methyl-4-bromo-5-phenyl)pyrazol-1-yl]benzenesulfonylthiourea derivatives were prepared by the treatment of their corresponding *p*-sulfamylphenylpyrazole derivatives with the appropriate isothiocyanates.

[1] Application for a patent was made for compounds described in this report.
[2] Melting points were determined on a Kofler block and are uncorrected. IR spectra were determined as Nujol mulls with a Beckman IR-4210 spectrometer. PMR spectra was recorded on a Varian A-60 A spectrometer. Microanalyses were performed by the Microanalytical Unit, Faculty of Science, University of Cairo, Cairo, Egypt.

0022-3549/81/0800-0952$01.00/0

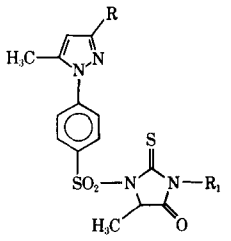
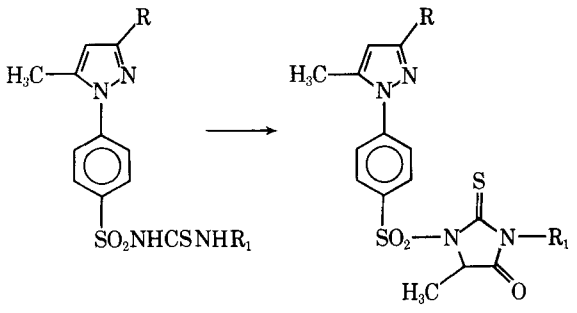


Table I—3-Substituted 5-Methyl-1-{*p*-[(3,5-dimethyl)pyrazol-1-yl]- and [(5-Methyl-3-carboxy)pyrazol-1-yl]benzenesulfonyl}-2-thiohydantoins

Compound	R	R_1	Yield, %	Melting Point	Formula	Analysis, % Calc.	Found
IIa	CH_3	CH_2=$CHCH_2$	70	165°	$C_{18}H_{20}N_4O_3S_2$	C 53.5	53.5
						H 5.0	5.3
						N 13.9	14.0
						S 15.8	15.6
IIb	CH_3	$CH_3(CH_2)_2$	65	216°	$C_{18}H_{22}N_4O_3S_2$	C 53.2	53.4
						H 5.4	5.2
						N 13.8	13.7
						S 15.8	16.0
IIc	CH_3	C_6H_{11}	75	175°	$C_{21}H_{26}N_4O_3S_2$	C 56.5	56.8
						H 5.8	6.0
						N 12.6	12.6
						S 14.3	14.0
IId	CH_3	p-$CH_3C_6H_4$	65	230°	$C_{22}H_{22}N_4O_3S_2$	C 58.1	58.0
						H 4.8	5.0
						N 12.3	12.3
						S 14.1	14.1
IIe	CH_3	$C_6H_5CH_2$	70	140°	$C_{22}H_{22}N_4O_3S_2$	C 58.1	57.9
						H 4.8	4.9
						N 12.3	12.5
						S 14.1	14.1
IIIa	COOH	$CH_3(CH_2)_2$	65	210°	$C_{18}H_{20}N_4O_5S_2$	C 49.5	49.7
						H 4.6	4.6
						N 12.8	13.0
						S 14.7	14.7
IIIb	COOH	$CH_3(CH_2)_3$	70	144°	$C_{19}H_{22}N_4O_5S_2$	C 50.7	51.0
						H 4.9	4.8
						N 12.4	12.5
						S 14.2	14.0
IIIc	COOH	C_6H_{11}	65	171°	$C_{21}H_{24}N_4O_5S_2$	C 52.9	53.1
						H 5.0	5.2
						N 11.8	12.0
						S 13.4	13.1

3-Substituted 5-methyl-1-{*p*-[(3,5-dimethyl)pyrazol-1-yl]- and 5-methyl-1-{*p*-[(5-methyl-3-carboxy)pyrazol-1-yl]benzenesulfonyl}-2-thiohydantoins (II and III, Scheme I) were prepared by refluxing an alcoholic solution of the appropriate thiourea derivative with ethyl α-bromopropionate. The intermediate pseudothio derivatives underwent rapid rearrangement with the formation of 2-thiones. Their IR spectra showed a characteristic absorption band at 1120–1140 cm^{-1}, indicative of C=S, and at 1300 cm^{-1}, indicative of C–N (amide III band).

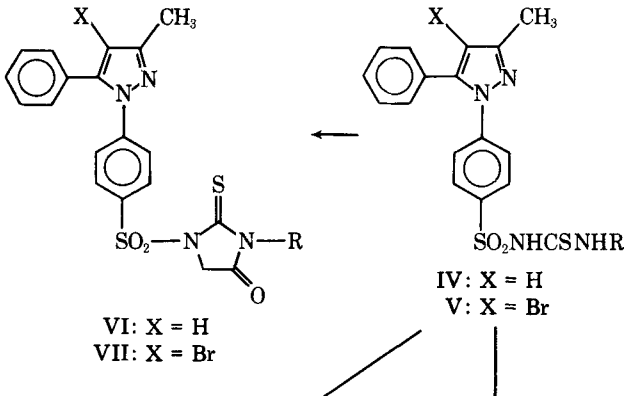
3-Substituted 1-{*p*-[(3-methyl-5-phenyl)pyrazol-1-yl]- and 1-{*p*-[(3-methyl-4-bromo-5-phenyl)pyrazol-1-yl]benzenesulfonyl}-2-thiohydantoin (VI and VII, Scheme II) and their 5-methyl-2-thiohydantoin (VIII and IX, Scheme II) and 5,6-dihydro-4(3*H*)-oxo-2(1*H*)-pyrimidinethione (X and XI, Scheme II) derivatives were prepared by refluxing an alcoholic solution of the appropriate thiourea derivative with ethyl bromoacetate, ethyl α-bromopropionate, and ethyl β-bromopropionate, respectively. The intermediate pseudothio derivatives underwent rapid rearrangement with the formation of the 2-thiones.



I

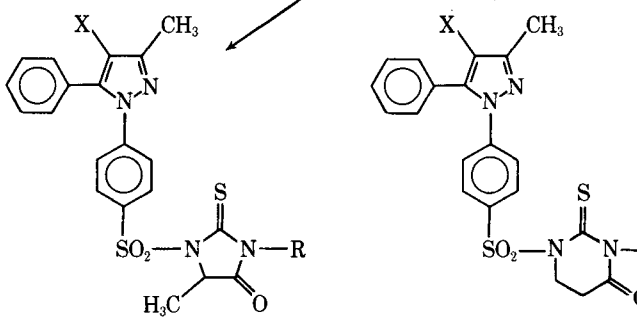
II: R = CH_3
III: R = COOH

Scheme I



VI: X = H
VII: X = Br

IV: X = H
V: X = Br



VIII: X = H
IX: X = Br

X: X = H
XI: X = Br

Scheme II

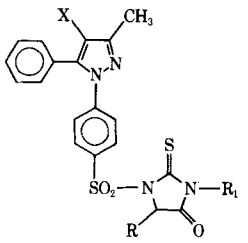


Table II—3-Substituted 1-{*p*-[(3-Methyl-5-phenyl)pyrazol-1-yl] and [(3-Methyl-4-bromo-5-phenyl)pyrazol-1-yl]benzenesulfonyl}-2-thiohydantoins

Compound	R	R_1	X	Yield, %	Melting Point	Formula	Analysis, %	Calc.	Found
VI*a*	H	C_2H_5	H	70	167°	$C_{21}H_{20}N_4O_3S_2$	C	57.3	57.4
							H	4.5	4.3
							N	12.7	12.6
							S	14.5	14.6
VI*b*	H	CH_2=$CHCH_2$	H	50	175°	$C_{22}H_{20}N_4O_3S_2$	C	58.4	58.2
							H	4.4	4.4
							N	12.4	12.5
							S	14.2	14.0
VI*c*	H	$CH_3(CH_2)_3$	H	60	115°	$C_{23}H_{24}N_4O_3S_2$	C	59.0	59.1
							H	5.1	5.2
							N	12.0	12.2
							S	13.7	13.4
VI*d*	H	C_6H_{11}	H	70	215°	$C_{25}H_{26}N_4O_3S_2$	C	60.7	60.8
							H	5.3	5.1
							N	11.3	11.4
							S	13.0	13.2
VI*e*	H	*p*-$CH_3C_6H_4$	H	65	168°	$C_{26}H_{22}N_4O_3S_2$	C	62.2	62.3
							H	4.4	4.5
							N	11.2	11.2
							S	12.7	12.8
VI*f*	H	$C_6H_5CH_2$	H	55	222°	$C_{26}H_{22}N_4O_3S_2$	C	62.2	62.4
							H	4.4	4.2
							N	11.2	11.2
							S	12.7	12.9
VII*a*	H	C_2H_5	Br	65	175°	$C_{21}H_{19}BrN_4O_3S_2$	C	48.6	48.7
							H	3.7	3.5
							Br	15.4	15.2
							N	10.8	11.0
							S	12.3	12.5
VII*b*	H	$CH_3(CH_2)_3$	Br	60	162°	$C_{23}H_{23}BrN_4O_3S_2$	C	50.5	50.5
							H	4.2	4.1
							Br	14.6	14.2
							N	10.2	10.4
							S	11.7	11.8
VII*c*	H	C_6H_{11}	Br	70	208°	$C_{25}H_{25}BrN_4O_3S_2$	C	52.4	52.5
							H	4.4	4.2
							Br	14.0	14.1
							N	9.8	9.6
							S	11.2	11.3
VII*d*	H	*p*-$CH_3C_6H_4$	Br	70	240°	$C_{26}H_{21}BrN_4O_3S_2$	C	53.7	53.6
							H	3.6	3.4
							Br	13.8	13.7
							N	9.6	10.0
							S	11.0	11.2
VII*e*	H	$C_6H_5CH_2$	Br	60	168°	$C_{26}H_{21}BrN_4O_3S_2$	C	53.7	53.6
							H	3.6	4.0
							Br	13.8	14.0
							N	9.6	9.5
							S	11.0	11.3
VIII*a*	CH_3	C_2H_5	H	60	194°	$C_{22}H_{22}N_4O_3S_2$	C	58.1	58.2
							H	4.8	4.7
							N	12.3	12.1
							S	14.1	14.2
VIII*b*	CH_3	$CH_3(CH_2)_3$	H	55	178°	$C_{24}H_{26}N_4O_3S_2$	C	59.8	60.0
							H	5.4	5.2
							N	11.6	11.4
							S	13.3	13.1
VIII*c*	CH_3	C_6H_{11}	H	65	198°	$C_{26}H_{28}N_4O_3S_2$	C	61.4	61.3
							H	5.5	5.6
							N	11.0	11.2
							S	12.6	12.5
VIII*d*	CH_3	*p*-$CH_3C_6H_4$	H	65	218°	$C_{27}H_{24}N_4O_3S_2$	C	62.8	62.4
							H	4.7	4.5
							N	10.9	11.0
							S	12.4	12.2
IX*a*	CH_3	C_2H_5	Br	65	215°	$C_{22}H_{21}BrN_4O_3S_2$	C	49.5	49.4
							H	3.9	4.1
							Br	15.0	15.1
							N	10.5	10.3
							S	12.0	12.3

Table II—*Continued*

Compound	R	R_1	X	Yield, %	Melting Point	Formula	Analysis, % Calc.	Found
IX*b*	CH_3	$CH_3(CH_2)_3$	Br	55	135°	$C_{24}H_{25}BrN_4O_3S_2$	C 51.3	51.4
							H 4.5	4.3
							Br 14.3	14.2
							N 10.0	10.2
							S 11.4	11.1
IX*c*	CH_3	C_6H_{11}	Br	65	225°	$C_{26}H_{27}BrN_4O_3S_2$	C 53.2	53.4
							H 4.6	4.4
							Br 13.6	13.7
							N 9.5	9.3
							S 10.9	11.2
IX*d*	CH_3	*p*-$CH_3C_6H_4$	Br	70	245°	$C_{27}H_{23}BrN_4O_3S_2$	C 54.5	54.3
							H 3.9	3.7
							Br 13.4	13.1
							N 9.4	9.7
							S 10.8	11.0

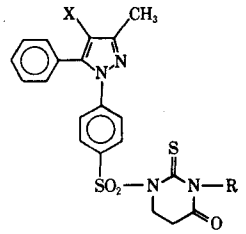


Table III—3-Substituted 1-{*p*-[(3-Methyl-5-phenyl)pyrazol-1-yl] and 3-Methyl-4-bromo-5-phenyl)pyrazol-1-yl]benzenesulfonyl}-5,6-dihydro-4(3*H*)-oxo-2(1*H*)-pyrimidinethiones

Compound	R	X	Yield, %	Melting Point	Formula	Analysis, % Calc.	Found
X*a*	$CH_3(CH_2)_3$	H	60	165°	$C_{24}H_{26}N_4O_3S_2$	C 59.8	59.8
						H 5.4	5.4
						N 11.6	11.2
						S 13.3	13.3
X*b*	C_6H_{11}	H	70	228°	$C_{26}H_{28}N_4O_3S_2$	C 61.4	61.4
						H 5.5	5.3
						N 11.0	11.2
						S 12.6	12.2
X*c*	*p*-$CH_3C_6H_4$	H	65	255°	$C_{27}H_{24}N_4O_3S_2$	C 62.8	62.6
						H 4.7	4.7
						N 10.9	10.7
						S 12.4	12.3
X*d*	$C_6H_5CH_2$	H	65	220°	$C_{27}H_{24}N_4O_3S_2$	C 62.8	62.5
						H 4.7	4.4
						N 10.9	11.1
						S 12.4	12.6
XI*a*	C_2H_5	Br	70	222°	$C_{22}H_{21}BrN_4O_3S_2$	C 49.5	49.4
						H 3.9	4.1
						Br 15.0	15.1
						N 10.5	10.4
						S 12.0	12.3
XI*b*	C_6H_{11}	Br	65	230°	$C_{26}H_{27}BrN_4O_3S_2$	C 53.2	53.3
						H 4.6	4.5
						Br 13.6	13.4
						N 9.5	9.6
						S 10.9	11.2
XI*c*	*p*-$CH_3C_6H_4$	Br	70	198°	$C_{27}H_{23}BrN_4O_3S_2$	C 54.5	54.2
						H 3.9	3.7
						Br 13.4	13.2
						N 9.4	9.3
						S 10.8	10.5
XI*d*	$C_6H_5CH_2$	Br	65	225°	$C_{27}H_{23}BrN_4O_3S_2$	C 54.5	54.3
						H 3.9	3.6
						Br 13.4	13.7
						N 9.4	9.2
						S 10.8	10.7

In addition to the two bands of the $-SO_2N<$ group at 1330–1355 and 1155–1180 cm^{-1}, the IR spectra of VI and VII revealed a secondary carbonyl amide absorption at 1740–1755 cm^{-1} and a C=S band at 1100–1120 cm^{-1}.

The IR spectra of VIII and IX revealed, in addition to the two bands of the $-SO_2N<$ group at 1330–1350 and 1160–1190 cm^{-1}, a secondary carbonyl amide absorption at 1740–1752 cm^{-1} and a C=S band at 1090–1110 cm^{-1}.

The IR spectra of X and XI revealed a secondary carbonyl amide absorption at 1640–1665 cm^{-1} and a C=S band at 1080–1100 cm^{-1} in addition to the two bands of the $-SO_2N<$ group at 1330–1350 and 1160–1180 cm^{-1}.

Synthesis of II and III—A mixture of *p*-[(3,5-dimethyl)- or *p*-[(5-methyl-3-carboxy)pyrazol-1-yl]benzenesulfonylthiourea (I, 0.01 mole) and ethyl α-bromopropionate (0.011 mole) in absolute ethanol (50 ml) was refluxed with stirring for 4–6 hr, concentrated, and allowed to crystallize. The products obtained were recrystallized from ethanol (Table I).

Synthesis of VI and VII—A mixture of *p*-[(3-methyl-5-phenyl)- or *p*-[(3-methyl-4-bromo-5-phenyl)pyrazol -1- yl]benzenesulfonylthiourea

Table IV—Antidiabetic Activity of Substituted Cyclic Sulfonylthiourea Derivatives

Compound	Reduction in Plasma Glucose Level Compared with Control, %	Statistical Significance Value of p
Phenformin	10	<0.01[a]
IIc	1.5	0.05
IIIc	4.5	<0.05[a]
VI*d*	3.0	<0.01[a]
VIIc	2.0	0.05
VIIIc	8.0	<0.01[a]
IXc	4.0	<0.01[a]
X*b*	2.0	0.05
XI*a*	4.0	<0.01[a]

[a] Statistically significant.

(IV or V, 0.01 mole) and ethyl bromoacetate (0.011 mole) in absolute ethanol (50 ml) was refluxed with stirring for 4–6 hr, concentrated, and allowed to crystallize. The products obtained were recrystallized from ethanol (Table II).

Synthesis of VIII and IX—A mixture of IV or V (0.01 mole) and ethyl α-bromopropionate (0.011 mole) in absolute ethanol (50 ml) was refluxed with stirring for 6–8 hr, concentrated, and allowed to crystallize. The products obtained were recrystallized from ethanol as colorless needles (Table II).

Synthesis of X and XI—A mixture of IV or V (0.01 mole) and ethyl β-bromopropionate (0.011 mole) in absolute ethanol (50 ml) was refluxed with stirring for 6–8 hr, concentrated, and allowed to crystallize. The products were recrystallized from 95% ethanol as colorless needles (Table III).

In addition to the aromatic protons at δ 7.0–8.1, the PMR spectra of VIc showed a multiplet at δ 0.8–1.7 for the $(CH_2)_3$ protons of the butyl group together with the methylene group of the cyclic ring, a singlet at δ 2.4 characteristic of the methyl group at C-3 of the pyrazole ring, a singlet at δ 1.3 for the CH_3 of the butyl group, and a singlet at δ 6.4 for the proton at C-4 of the pyrazole ring.

In addition to the aromatic protons at δ 6.8–7.9, the PMR spectra of XIc showed a singlet at δ 2.3 for the two methyl groups together with the two methylene groups of the cyclic ring.

DISCUSSION

Biological Testing—Compounds IIc, IIIc, VI*d*, VIIc, VIIIc, IX*c*, X*b*, and XI*a* were tested for hypoglycemic activity using alloxanized female albino mice weighing 20–25 g. Alloxan, 100 mg/kg of body weight, was injected into the tail vein in saline solution (10 mg/ml). Three days later, the mice were given the test compounds orally in suspension in 1% carboxymethylcellulose sodium at the rate of 0.2 mmole/kg of body weight.

Each day, four mice were used as a control group and one group of four mice was given the standard drug phenformin in a dose of 100 mg (0.4 mmole)/kg of body weight. Up to six groups of four mice received test compounds. Blood samples were taken at 0, 1, and 3 hr.

Blood was collected into 0.04% NaF solution. Glucose was determined by the microcolorimetric copper reduction technique of Haslewood and Strookman (4). Results are expressed as a percentage reduction of plasma glucose level compared to the control value.

Statistical Significance—Statistical significance was assessed using the Student t test. Statistical significance was accepted where the calculated t value exceeded the tabulated t value at the 0.05 level.

From the data presented in Table IV, it is obvious that VIII possesses marked hypoglycemic activity. While IIIc, IX*c*, and XI*a* possess only moderate hypoglycemic activity, the potency of these compounds is more than their corresponding thiourea analogs.

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Synthesis of New Polyamine Derivatives for Cancer Chemotherapeutic Studies

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Abstract □ Selected homologs, analogs, and acylated derivatives of spermine and spermidine, together with several heterocyclic and aromatic compounds containing a novoldiamine side chain, were prepared and evaluated biologically. Several compounds possessed activity against B-16 melanoma and human epidermoid carcinoma of the nasopharynx.

Keyphrases □ Polyamines—synthesis of derivatives, cancer chemotherapy □ Chemotherapy—synthesis of polyamine derivatives for cancer chemotherapy □ Derivatives—polyamines, synthesis, cancer chemotherapy

The importance of many naturally occurring polyamines, such as putrescine, spermidine, and spermine, to the growth of living cells is well established (1–4). It was reported recently that increased amounts of certain polyamines were found in rapidly proliferating biological systems (*e.g.*, chick embryo cells, rat regenerating liver cells, and wound-healing tissues) (5–10), as well as in neoplastic cells of animals and humans (11–16). The higher polyamine levels are believed to be contributed by ornithine decarboxylase activity in these tissues (17). Elevated polyamine levels also were detected in the urine of cancer patients (18–20). The high excretion level of polyamines declined when the patients were in remission, and chemotherapy treatment with methotrexate, cytosine arabinoside, 5-azacitidine, or fluorouracil resulted in polyamine depletion in tumor cells (21–23).

Since cellular protein synthesis is affected by polyamines at the transcription and translation level (24) and at least one role of polyamines is to organize the structure and activity of tRNA (25), it was postulated that properly designed analogs of polyamines could be useful in oncology studies. This concept was substantiated by previous reports (26–29) that some spermine and spermidine analogs of both synthetic and plant origin demonstrated inter-

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