Synthesis and Antimalarial and Antitumor Effects of 2-Amino-4-(hydrazino and hydroxyamino)-6-[(aryl)thio]quinazolines[1,2]

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A variety of analogues of 2,4-diamino-6-[(aryl)thio]quinazolines with known antimalarial properties were prepared wherein the 4-amino group was replaced by hydrazino and hydroxyamino moieties. Such changes were found to reduce markedly the antimalarial and antitumor properties of this series.

A variety of 2,4-diamino heterocycles are useful chemotherapeutic agents with known activity against bacterial and parasitic infections as well as cancer.

Many of these compounds are inhibitors of the folic acid pathway of the invading organisms with the enzyme dihydrofolate reductase being a particular target.

A fair amount of analogue work has attended this area with the aim of producing more effective chemotherapeutic agents. Generally, this effort has concerned the diamino heterocycle itself or the attached substituents. We were interested on the other hand in examining the amino groups themselves to ascertain whether replacement of the amino function by more or less basic groups might alter the enzyme binding sufficiently to provide drastic changes in the biological profile of the compounds.

We therefore examined hydrazine and hydroxylamine analogues of two diaminoquinazolines **1a,b**, which had been shown to have potent antimalarial activity in our earlier work,[3,4] almost certainly by virtue of their inhibition of dihydrofolate reductase.

Synthesis of the target molecules was accomplished according to Scheme I, and their properties are depicted in Table I.

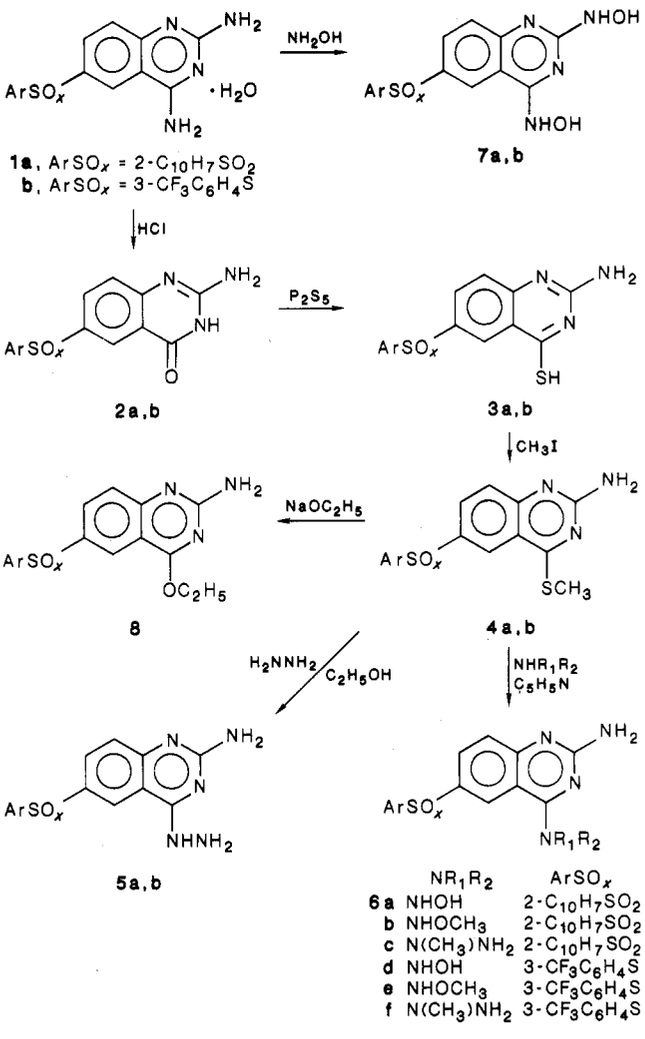
The somewhat more straightforward approach depicted in Scheme II was attempted initially; however, the difficulties with the chlorination step as well as the apparent instability of the chloro intermediate necessitated a more viable route.

Thus, **1a,b** were hydrolyzed in acid to the corresponding 2-amino-4(3*H*)-quinazolinones **2a,b**, which were warmed with phosphorus pentasulfide in pyridine to produce the respective 4-thiols **3a,b**. Methylation with iodomethane then provided the 4-methylthio compounds **4a,b**. Treatment with hydrazine or hydroxylamine then afforded target compounds **5a, 6a, 5b,** and **6d**. Hydrazine **5b** could also be prepared directly from thiol **3b** by treatment with hydrazine. The 2,4-bis(hydroxyamino) compounds **7a,b** were prepared directly from the diamines **1a,b** with excess hydroxylamine in pyridine.

An initial attempt to replace the methylthio group of **4a** with methoxyamine hydrochloride in ethanol in the presence of sodium methoxide led instead to the 4-ethoxy analogue **8**. The desired **6b** was obtained upon treatment of **4a** with methoxyamine hydrochloride in pyridine.

Confirmation of the products with methylhydrazine as **6c** and **6f** as expected rather than the isomeric 2-methylhydrazino materials was provided by NMR spectroscopy. Both **6c** and **6f** exhibited singlets at 5.45 and 6.6 ppm, respectively, for the primary amino groups. In addition, **6f** when treated with 4-nitrobenzaldehyde formed a hydrazone, again confirming the presence of the NH_2 function.

Scheme I



	NR_1R_2	$ArSO_x$
6a	NHOH	2-$C_{10}H_7SO_2$
b	$NHOCH_3$	2-$C_{10}H_7SO_2$
c	$N(CH_3)NH_2$	2-$C_{10}H_7SO_2$
d	NHOH	3-$CF_3C_6H_4S$
e	$NHOCH_3$	3-$CF_3C_6H_4S$
f	$N(CH_3)NH_2$	3-$CF_3C_6H_4S$

Suppressive Antimalarial Screening in Mice. The compounds were tested against a normal drug-sensitive strain of *Plasmodium berghei* in mice by the parenteral route.[7,8] These results are summarized in Table II. The

(1) This is paper 63 of a series on antimalarial drugs. For paper 62, see: Werbel, L. M.; Elslager, E. F.; Newton, L. S. *J. Heterocycl. Chem.* **1987**, *24*, 345.

(2) This investigation was supported by U.S. Army Medical Research and Development Command Contract DADA-17-72-C-2077. This is contribution 1814 to the U.S. Army Drug Development Program.

(3) Elslager, E. F.; Jacob, P.; Johnson, J.; Werbel, L. M.; Worth, D. F. *J. Med. Chem.* **1978**, *21*, 1059.

(4) Elslager, E. F.; Hutt, M. P.; Jacob, P.; Johnson, J.; Temporelli, B.; Werbel, L. M.; Worth, D. F.; Rane, L. *J. Med. Chem.* **1979**, *22*, 1247.

(5) Ashton, W. T.; Hynes, J. B. *J. Med. Chem.* **1973**, *16*, 1233.

(6) Hynes, J. B.; Ashton, W. T.; Merriman, H. G., III; Walker, F. C., III *J. Med. Chem.* **1974**, *17*, 682.

(7) The parenteral antimalarial screening in mice was carried out in the laboratory of Dr. Leo Rane of the University of Miami. Test results were provided through the courtesy of Drs. T. R. Sweeney, E. A. Steck, M. Musallam, and D. Davidson of the Walter Reed Army Institute of Research.

(8) For a description of the test method, see: Osdene, T. S.; Russell, R. R.; Rane, L. *J. Med. Chem.* **1967**, *10*, 431.

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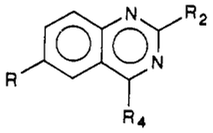
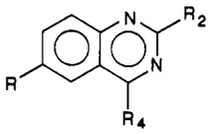
Table I. Physical Properties of 2-Amino-4-(hydrazino and hydroxyamino)-6-[(aryl)thio]quinazolines



no.	R	R_2	R_4	mp, °C	% yield	recrystn solvent	formula	anal.
2a	2-$C_{10}H_7SO_2$	NH_2	OH	318–9 dec[5]	61	DMF/H_2O		
3a	2-$C_{10}H_7SO_2$	NH_2	SH	318 dec[6]	45	DMF		
4a	2-$C_{10}H_7SO_2$	NH_2	SCH_3	235–237	43	DMF/EtOAc	$C_{19}H_{15}N_3O_2S_2$	C, H, N
8	2-$C_{10}H_7SO_2$	NH_2	OC_2H_5	178–181	40	EtOH	$C_{20}H_{17}N_3O_3S$	C, H, N, S
5a	2-$C_{10}H_7SO_2$	NH_2	$NHNH_2$	315–318 dec	32	DMF	$C_{18}H_{15}N_5O_2S$	C, H, N
6a	2-$C_{10}H_7SO_2$	NH_2	NHOH	286–288 dec	97	–	$C_{18}H_{14}N_4O_3S$	C, H, N
6b	2-$C_{10}H_7SO_2$	NH_2	$NHOCH_3$	292–294 dec	89	–	$C_{19}H_{16}N_4O_3S$	C, H, N, S
6c	2-$C_{10}H_7SO_2$	NH_2	$N(CH_3)NH_2$	280–284	80	–	$C_{19}H_{17}N_5O_2S$	C, H, N
7a	2-$C_{10}H_7SO_2$	NHOH	NHOH	268–270 dec	53	DMF	$C_{18}H_{14}N_4O_4S{\cdot}0.5Me_2NCHO$	C, H, N
2b	3-$CF_3C_6H_4S$	NH_2	OH	273–277 dec	93	–	$C_{15}H_{10}F_3N_3OS$	C, H, N, S
3b	3-$CF_3C_6H_4S$	NH_2	SH	238–242 dec	70	–	$C_{15}H_{10}F_3N_3S_2$	C, H, N
4b	3-$CF_3C_6H_4S$	NH_2	SCH_3	125–127	53	EtOH	$C_{16}H_{12}F_3N_3S_2$	C, H, N
5b	3-$CF_3C_6H_4S$	NH_2	$NHNH_2$	188–189	73	MeCN	$C_{15}H_{12}F_3N_5S$	C, H, N
6d	3-$CF_3C_6H_4S$	NH_2	NHOH	244–245 dec	92	–	$C_{15}H_{11}F_3N_4OS$	C, H, N
6e	3-$CF_3C_6H_4S$	NH_2	$NHOCH_3$	227–229 dec	24	MeOH	$C_{16}H_{13}F_3N_4OS$	C, H, N
6f	3-$CF_3C_6H_4S$	NH_2	$N(CH_3)NH_2$	203–204	30	EtOAc	$C_{16}H_{14}F_3N_5S$	C, H, N
7b	3-$CF_3C_6H_4S$	NHOH	NHOH	220 dec	61	EtOH/H_2O	$C_{15}H_{11}F_3N_4O_2S$	C, H, N

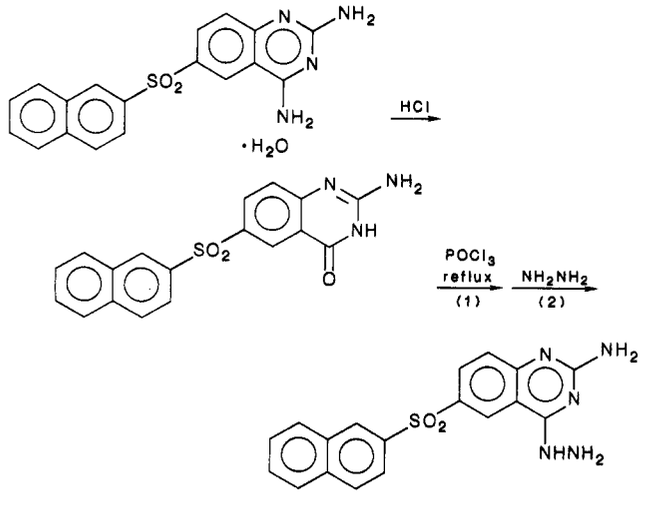
Table II. Parenteral Antimalarial Effects of 2-Amino-4-(hydrazino and hydroxyamino)-6-[(aryl)thio]quinazolines against *Plasmodium berghei* in Mice



				ΔMST, C after single sc dose, mg/kg[a]				
no.	R	R_2	R_4	640	320	160	80	40
1a	2-$C_{10}H_7SO_2$	NH_2	NH_2	5C	5C	5C	5C	5C
1b	3-$CF_3C_6H_4S$	NH_2	NH_2	5C	5C	5C	5C	3C
5a	2-$C_{10}H_7SO_2$	NH_2	$NHNH_2$	4.5	3.5	2.3	1.3	0.5
6a	2-$C_{10}H_7SO_2$	NH_2	NHOH	15.3	14.1	11.1	8.9	6.1
6b	2-$C_{10}H_7SO_2$	NH_2	$NHOCH_3$	4C	12.7	9.1	5.7	3.9
6c	2-$C_{10}H_7SO_2$	NH_2	$N(CH_3)NH_2$	10.7	7.1	4.3	2.3	0.5
7a	2-$C_{10}H_7SO_2$	NHOH	NHOH	10.7	8.1	5.9	3.3	1.1
5b	3-$CF_3C_6H_4S$	NH_2	$NHNH_2$	15.7	11.9	6.9	3.1	0.5
6d	3-$CF_3C_6H_4S$	NH_2	NHOH	5C	10.3	8.1	5.1	3.5
6e	3-$CF_3C_6H_4S$	NH_2	$NHOCH_3$	–	3C	9.7	6.9	5.7
6f	3-$CF_3C_6H_4S$	NH_2	$N(CH_3)NH_2$	5C	4C	12.3	8.9	5.7
7b	3-$CF_3C_6H_4S$	NHOH	NHOH	1C	10.7	9.7	3.1	1.7

[a] ΔMST is the change in mean survival time of the treated mice, in days, calculated by subtracting the mean survival time of the control mice (an average of 6.2 days in these experiments) from the mean survival time of the treated mice. In calculating the mean survival time of the treated mice, 60-day survivors are not included. C indicates the number of mice surviving at 60 days postinfection and termed "cured". Each compound was administered as a single sc dose 72 h postinfection. Each entry at each dose represents results with a five-animal group.

Scheme II



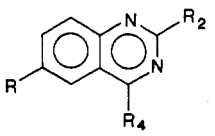
test compounds were dissolved or suspended in peanut oil, and a single dose was administered subcutaneously 72 h after the mice had been infected with *P. berghei*. In the present study the mean survival time of the control mice (MSTC) was 6.2 days. Extension of the mean survival time of the treated mice (MSTT) is interpreted as evidence of antimalarial activity. An increase of 100% in the MSTT is considered the minimum effective response for activity. Mice that survive 60 days postinfection are termed "cured".

Clearly, antimalarial activity is dramatically reduced by the structural modifications on the quinazoline amino groups.

Antitumor Activity. The target compounds were also evaluated against the L1210 leukemia in tissue culture.[9]

(9) In vitro antitumor data was obtained in the laboratory of Dr. Joan Shillis, Warner-Lambert/Parke-Davis Pharmaceutical Research, Ann Arbor, MI, and we thank her for providing this data.

Table III. Effects of 2-Amino-4-(hydrazino and hydroxyamino)-6-[(aryl)thio]quinazolines against L1210 Leukemia in Tissue Culture[a]



no.	R	R_2	R_4	in vitro, L1210: ID_{50}[b]
1a	$2\text{-}C_{10}H_7SO_2$	NH_2	NH_2	1.1×10^{-7}
	$3,4,5\text{-}(OCH_3)_3C_6H_2\text{-}NHCH_2$	NH_2	NH_2 (5-Me)	2.4×10^{-9}
5a	$2\text{-}C_{10}H_7SO_2$	NH_2	$NHNH_2$	2.7×10^{-6}
6b	$2\text{-}C_{10}H_7SO_2$	NH_2	$NHOCH_3$	1.7×10^{-5}
7a	$2\text{-}C_{10}H_7SO_2$	NHOH	NHOH	2×10^{-5}
6c	$2\text{-}C_{10}H_7SO_2$	NH_2	$N(CH_3)NH_2$	1.1×10^{-5}
5b	$3\text{-}CF_3C_6H_4S$	NH_2	$NHNH_2$	1.3×10^{-6}
6d	$3\text{-}CF_3C_6H_4S$	NH_2	NHOH	3.5×10^{-5}
6e	$3\text{-}CF_3C_6H_4S$	NH_2	$NHOCH_3$	2.4×10^{-5}
6f	$3\text{-}CF_3C_6H_4S$	NH_2	$N(CH_3)NH_2$	3.8×10^{-6}
7b	$3\text{-}CF_3C_6H_4S$	NHOH	NHOH	1×10^{-6}

[a] For a description of the assay, see: Baguley, B. C.; Nash, R. *Eur. J. Cancer* **1981**, *17*, 671. [b] ID_{50} = the molar concentration of test drug required to reduce the number of L1210 cells by 50% after incubation for 2 days. The average ID_{50} of the reference drug, mithramycin, is 8.1×10^{-8} M.

The data are shown in Table III. Once again, it is clear that these structural changes drastically diminish antitumor potential for this structural class, presumably by reducing rather than enhancing inhibition of dihydrofolate reductase, the apparent primary target for such compounds.

Experimental Section

Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. ^1H NMR 90-MHz spectra were obtained with a Bruker spectrometer. IR spectra were obtained on a Beckman IR-9 or Digilab IR-14 spectrometer. The NMR and IR spectra of all compounds and intermediates were consistent with the assigned structures. Where analyses are indicated only by symbols of the elements, analytical results obtained were within ±0.4% of the theoretical values.

2-Amino-6-(2-naphthalenylsulfonyl)-4(3*H*)-quinazolinone (2a). In 290 mL of bis(2-methoxyethyl) ether, 10.0 g (0.0272 mol) of 6-(2-naphthalenylsulfonyl)-2,4-quinazolinediamine and 145 mL of 2 N hydrochloric acid were heated under reflux for 5 h. The resulting solution was chilled and made weakly basic by addition of concentrated ammonium hydroxide. Water was added to precipitate a beige solid, which was recrystallized from *N,N*-dimethylformamide/water, with a few drops of 5 N NH_4OH added, to give 5.8 g of the product.

2-Amino-6-(2-naphthalenylsulfonyl)-4-quinazolinethiol (3a). A mixture of 3.0 g (0.008 55 mol) of 2-amino-6-(2-naphthalenylsulfonyl)-4(3*H*)-quinazolinone and 6.7 g (0.0301 mol) of phosphorus pentasulfide in 60 mL of pyridine was heated at 80–82 °C for 22 h under protection from moisture. The two-phase mixture (dark solution and yellow solid) was poured into 1000 mL of stirred boiling water. After being boiled for 2 h, the mixture was filtered hot to collect a yellow-brown solid. This was heated in 130 mL of ethyl Cellosolve, with filtering to remove insoluble brown material. Water was added to the cloud point, and the orange precipitate was filtered. Water and ice were added to the filtrate to precipitate a yellow solid. This was recrystallized from *N,N*-dimethylformamide containing 2 drops of water to give 1.4 g of the desired product as yellow crystals.

4-(Methylthio)-6-(2-naphthalenylsulfonyl)-2-quinazolinamine (4a). A mixture of 1.4 g (0.003 81 mol) of 2-amino-6-(2-naphthalenylsulfonyl)-4-quinazolinethiol and 0.39 mL (0.60 g, 0.0042 mol) of methyl iodide in 15 mL of *N,N*-dimethylformamide was stirred at ambient temperature for 45 min. The yellow solution was poured into 150 mL of stirred cold water, giving an unfilterable yellow precipitate. The suspension was warmed to coagulate the particles, then chilled, and filtered to collect 1.0 g of yellow powder. Recrystallization from *N,N*-dimethylformamide/ethyl acetate (1:1) and drying at 80 °C in vacuo gave 0.63 g of the title compound as tan crystals.

4-Hydrazino-6-(2-naphthalenylsulfonyl)-2-quinazolinamine (5a). A solution of 2.32 g (0.006 09 mol) of 4-(methylthio)-6-(2-naphthalenylsulfonyl)-2-quinazolinamine and 0.71 mL (0.706 g, 0.022 mol) of anhydrous hydrazine in 200 mL of absolute ethanol was heated under reflux for 25.5 h. The reaction mixture was filtered hot to collect the yellow precipitate, which was recrystallized from *N,N*-dimethylformamide and dried to yield 0.7 g of the title compound.

4-Ethoxy-6-(2-naphthalenylsulfonyl)-2-quinazolinamine (8). To a mixture of 0.70 g (0.008 38 mol) of methoxyamine hydrochloride and 0.48 g (0.008 38 mol) of 95% sodium methoxide in 200 mL of absolute ethanol was added 3.0 g (0.007 86 mol) of 4-(methylthio)-6-(2-naphthalenylsulfonyl)-2-quinazolinamine, and the mixture was stirred and warmed at 45 °C for 6 h. TLC (Si; EtOAc/MeOH/Et_3N, 75:25:1) indicated mostly starting material. The mixture was allowed to remain for 72 h at room temperature, and to it was added 1.3 g (0.0156 mol) of methoxyamine hydrochloride treated with 0.88 g (1 equiv) of 95% sodium methoxide in 50 mL of absolute ethanol. Warming at 45 °C for 7 h afforded no change according to thin-layer chromatography. Again 1.3 g (0.0156 mol) of methoxyamine hydrochloride treated with 0.88 g (1 equiv) of 95% sodium methoxide in 50 mL of absolute ethanol was added to the reaction mixture, and it was heated at 100 °C for 5 h in a bomb. The mixture was evaporated to about 150 mL and filtered hot to remove salt, and the filtrate was chilled. The yellow material that crystallized was collected and dried. It was indistinguishable from starting material in several thin-layer chromatography systems but had a 50 °C lower melting point, at 178–181 °C. Analytical and spectroscopic data was consistent with the proposed 4-ethoxy structure. The yield was 1.2 g of the title compound.

***N*⁴-Methoxy-6-(2-naphthalenylsulfonyl)-2,4-quinazolinediamine (6b).** A solution of 1.35 g (0.003 54 mol) of 4-(methylthio)-6-(2-naphthalenylsulfonyl)-2-quinazolinamine and 0.85 g (0.012 mol) of methoxyamine hydrochloride in 20 mL of pyridine was stirred at 45 °C for 22 h. TLC (Si; EtOAc/MeOH/Et_3N, 75:25:1) indicated incomplete reaction, so an additional 0.5 g (0.006 mol) of methoxyamine hydrochloride was added and warming at 45 °C was continued. After a total of 47 h of warming, starting material was still present. Warming was discontinued, an additional 0.5 g (0.006 mol) of methoxyamine hydrochloride was added, and the mixture was allowed to stand at room temperature for 70 h. The reaction mixture was poured into 350 mL of ice water; and the yellow precipitate was collected, washed with water, and dried to give 1.2 g of the title compound.

4-(1-Methylhydrazino)-6-(2-naphthalenylsulfonyl)-2-quinazolinamine (6c). A mixture of 1.5 g (0.003 94 mol) of 4-(methylthio)-6-(2-naphthalenylsulfonyl)-2-quinazolinamine and 1.0 mL of methylhydrazine in 20 mL of pyridine was warmed at 65 °C for 24 h. The cooled reaction mixture was poured into 300 mL of ice water, and the precipitate was collected and dried to give 1.2 g of the title compound as a yellow solid.

***N*⁴-Hydroxy-6-(2-naphthalenylsulfonyl)-2,4-quinazolinediamine (6a).** A mixture of 1.4 g (0.003 67 mol) of 4-(methylthio)-6-(2-naphthalenylsulfonyl)-2-quinazolinamine and 0.255 g (0.003 67 mol) of hydroxylamine hydrochloride in 10 mL of pyridine was stirred at room temperature for 24 h. The reaction mixture was poured into 250 mL of ice water. The white precipitate was collected, washed with water, and dried to give 1.3 g of the title compound.

***N*²,*N*⁴-Dihydroxy-6-(2-naphthalenylsulfonyl)-2,4-quinazolinediamine, Compound with *N,N*-Dimethylformamide (1:0.5) (7a).** A suspension of 1.0 g (0.0027 mol) of 6-(2-naphthalenylsulfonyl)-2,4-quinazolinediamine hydrate and 0.9 g (0.013 mol) of hydroxylamine hydrochloride in 20 mL of pyridine was warmed at 50 °C for 48 h. The resulting solution was cooled and poured into 400 mL of ice water. The white precipitate was collected, recrystallized from *N,N*-dimethylformamide, and dried at 120 °C under reduced pressure to give 0.6 g (53%) of the title compound containing 0.5 mol of *N,N*-dimethylformamide of crystallization. The presence of *N,N*-dimethylformamide was confirmed by NMR spectroscopy.

2-Amino-6-[[3-(trifluoromethyl)phenyl]thio]-4(3*H*)-quinazolinone (2b). In 320 mL of bis(2-methoxyethyl) ether, 20.0 g (0.0594 mol) of 6-[[3-(trifluoromethyl)phenyl]thio]-2,4-quinazolinediamine and 200 mL of 2 N hydrochloric acid were heated under reflux for 6 h. The chilled mixture was made basic by addition of 5 N ammonium hydroxide. The white solid precipitate was collected, washed with water, and dried in a vacuum oven at 50 °C to give 18.7 g (92.7%) of the desired product.

2-Amino-6-[[3-(trifluoromethyl)phenyl]thio]-4-quinazolinethiol (3b). A mixture of 18.7 g (0.0555 mol) of 2-amino-6-[[3-(trifluoromethyl)phenyl]thio]-4(3*H*)-quinazolinone and 50.0 g (0.225 mol) of phosphorus pentasulfide in 200 mL of pyridine was heated at 80 °C for 22 h. The two-phase mixture (dark solution and yellow solid) was poured into 2500 mL of stirred hot water. After being boiled for 2 h, the mixture was filtered hot to collect 18.5 g of yellow-brown solid. This crude product was dissolved in about 500 mL of hot anhydrous ethanol, and water was added to the cloud point. The chilled dark mixture was filtered through several thicknesses of paper to remove a gummy brown precipitate. Water was again added to the warmed filtrate to the cloud point, and a reddish-orange precipitate was removed. The yellow filtrate was poured into 1800 mL of water, and the bright yellow precipitate was collected and dried, yielding 13.7 g of the desired thiol compound.

4-(Methylthio)-6-[[3-(trifluoromethyl)phenyl]thio]-2-quinazolinamine (4b). A mixture of 11.0 g (0.0312 mol) of 2-amino-6-[[3-(trifluoromethyl)phenyl]thio]-4-quinazolinethiol and 3.4 mL (5.2 g, 0.0367 mol) of iodomethane in 50 mL of *N*,*N*-dimethylformamide was stirred at room temperature for 1 h. The resulting amber solution was poured into 600 mL of ice water. The suspension was made weakly acidic (pH 6.5–7.0) by addition of 10% sodium hydroxide. After the mixture was allowed to stand for 1 h, the yellow precipitate was collected and recrystallized from anhydrous ethanol to give 6.1 g of the desired product as tan crystals, which darken slowly with exposure to light.

4-Hydrazino-6-[[3-(trifluoromethyl)phenyl]thio]-2-quinazolinamine (5b). To a solution of 2.0 g (0.0057 mol) of 2-amino-6-[[3-(trifluoromethyl)phenyl]thio]-4-quinazolinethiol in 40 mL of pyridine was added 1.6 mL (0.05 mol) of anhydrous hydrazine. The mixture was stirred at room temperature overnight and poured into 300 mL of iced water. The precipitate that formed was collected and recrystallized from acetonitrile to afford 1.45 g of product.

N^4-Hydroxy-6-[[3-(trifluoromethyl)phenyl]thio]-2,4-quinazolinediamine (6d). A mixture of 2.0 g (0.005 25 mol) of 4-(methylthio)-6-[[3-(trifluoromethyl)phenyl]thio]-2-quinazolinamine and 0.37 g (0.005 32 mol) of hydroxylamine hydrochloride in 10 mL of pyridine was stirred at room temperature for 27 h. The reaction mixture was poured into 300 mL of ice water, and the cream colored precipitate was collected and air-dried to give 1.7 g of the title compound.

N^4-Methoxy-6-[[3-(trifluoromethyl)phenyl]thio]-2,4-quinazolinediamine (6e). A mixture of 1.0 g (0.002 72 mol) of 4-(methylthio)-6-[[3-(trifluoromethyl)phenyl]thio]-2-quinazolinamine and 1.0 g (0.012 mol) of methoxyamine hydrochloride in 7 mL of pyridine was warmed at 40–45 °C for 6 h. The reaction mixture was poured into 150 mL of cold water and the yellow gum that formed recrystallized twice from anhydrous ethanol and once from methanol to obtain 0.3 g of the title compound containing methanol (1:1). This product was combined with 0.4 g of the title compound containing methanol (1:1) obtained similarly from 1.5 g (0.004 08 mol) of 4-(methylthio)-6-[[3-(trifluoromethyl)-phenyl]thio]-2-quinazolinamine and heated at 100 °C under high vacuum for 24 h. The solvent-free product (0.6 g) was obtained as white needles.

4-(1-Methylhydrazino)-6-[[3-(trifluoromethyl)phenyl]-thio]-2-quinazolinamine (6f). A mixture of 3.6 g (0.0098 mol) of 4-(methylthio)-6-[[3-(trifluoromethyl)phenyl]thio]-2-quinazolinamine in 20 mL of pyridine and 3.0 mL of methylhydrazine was warmed at 50 °C for 20 h. The cooled reaction mixture was poured into 400 mL of water, and the yellow precipitate was collected and recrystallized twice from ethyl acetate to give 0.6 g of the title compound.

N^2,N^4-Dihydroxy-6-[[3-(trifluoromethyl)phenyl]thio]-2,4-quinazolinediamine (7b). A mixture of 1.2 g (0.003 56 mol) of 6-[[3-(trifluoromethyl)phenyl]thio]-2,4-quinazolinediamine and 1.5 g (0.0216 mol) of hydroxylamine hydrochloride in 10 mL of pyridine was stirred and warmed at 50 °C for 24 h. After standing at room temperature (ca. 23 °C) for an additional 48 h, the reaction mixture was poured into 250 mL of cold water to precipitate a white solid. Recrystallization from ethanol/water, followed by trituration with cold ethanol, yielded 0.8 g of the title compound as a white powder, which darkens on exposure to light.

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Acetylenic Nucleosides. 4.[1] 1-β-D-Arabinofuranosyl-5-ethynylcytosine. Improved Synthesis and Evaluation of Biochemical and Antiviral Properties[2]

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5-Ethynyl-1-β-D-arabinofuranosylcytosine (EAC) was prepared from 1-(2,3,5-tri-*O*-acetyl-β-D-arabinofuranosyl)cytosine by iodination followed by coupling with (trimethylsilyl)acetylene and deblocking. At 50 μM, EAC was found to inhibit the in vitro replication of herpes simplex virus type 1 and type 2 by >99%. EAC also showed activity against a strain of HSV-1 resistant to (*E*)-5-(2-bromovinyl)-2′-deoxyuridine which has an alteration of the virus-induced thymidine kinase (TK). At 100 μM, EAC did not inhibit the in vitro growth of leukemia L1210 and HeLa cells. EAC was resistant to the action of dCR-CR deaminase, its rate of deamination being approximately 2% that of dCR. The compound was a poor substrate for dCR kinase, but it was phosphorylated by HSV-1- and HSV-2-induced TKs at 50% and 30%, respectively, the rate of thymidine.

The 5-ethynyl derivative of araC (**4**) was previously synthesized[3] in our laboratory as a potential anticancer and/or antiviral agent. The original synthetic method entailed difficult separation of the α- and β-anomers of **4** and was not, therefore, suitable for a "scale-up" preparation

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(1) For part 3 of this series, see: Sharma, R. A.; Kavai, I.; Hughes, R. G., Jr.; Bobek, M. *J. Med. Chem.* **1984**, *27*, 410.

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