Folate Antagonists. 16. Antimalarial and Antibacterial Effects of 2,4-Diamino-6-[(heterocyclic)thio, sulfinyl, and sulfonyl]quinazolines (1-3)

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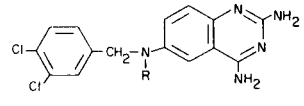
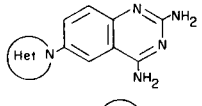
The reaction of 5-chloro-2-nitrobenzonitrile with a variety of mercaptoheterocycles provided the corresponding 2-nitro-5-[(heterocyclic)thio]benzonitriles. Reduction to the amine followed by cyclization with chloroformamidine hydrochloride afforded a series of 2,4-diamino-6-[(heterocyclic)thio]quinazolines. Bromination, oxidation, and amidine formation were accomplished with 2,4-diamino-6-[(4-phenyl-2-thiazolyl)thio]quinazoline (**23**) to provide additional analogs. Several of these compounds exhibited suppressive antimalarial activity against drug-sensitive lines of *Plasmodium berghei* in mice.

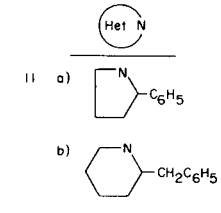
J. Heterocyclic Chem., **17**, 129 (1980).

Previous communications from these laboratories have reported the strong antimalarial activity of a variety of 2,4-diamino-6-{[aralkyl and (heterocyclic)methyl]amino- and nitrosamino}quinazolines, exemplified by 2,4-diamino-6-[(3,4-dichlorobenzyl)amino]quinazoline (**Ia**) (4,5), 2,4-diamino-6-[(3,4-dichlorobenzyl)nitrosamino]quinazoline (**Ib**) (6,7) and 2,4-diamino-6-[(3,4-dichlorobenzyl)-methylamino]quinazoline (**Ic**) (8). Moreover 2,4-diamino-6-(heterocyclic) quinazolines also were shown to have potent antimalarial activity (9). Both 2,4-diamino-6-(2-phenyl-1-pyrrolidinyl)quinazoline (**IIa**) and 2,4-diamino-6-(2-benzylpiperidino)quinazoline (**IIb**) showed activity comparable with that of Ib.



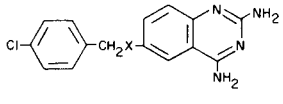
I a) R = H
b) NO
c) CH_3



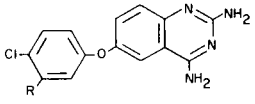


II a)

b)

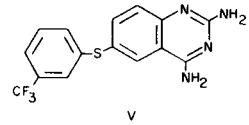


III a) X = O
b) S
c) SO
d) SO_2



IV a) R = H
b) Cl

Although oxygen and sulfur bioisosteres such as 2,4-diamino-6-[(*p*-chlorobenzyl)oxy]quinazoline (**IIIa**)(10) and 2,4-diamino-6-[(*p*-chlorobenzyl)thio, sulfinyl and sulfonyl]quinazolines (**IIIbd**) (11) demonstrated markedly lower antimalarial activity, potent activity was restored when the methylene bridge was extruded. Thus 2,4-diamino-6-(*p*-chlorophenoxy)quinazoline (**IVa**) and 2,4-diamino-6-(3,4-dichlorophenoxy)quinazoline (**IVb**) displayed activity in mice comparable with **Ia**. Extension of this effort to the thio analogs resulted in a series of 2,4-diamino-6-[(phenyl and naphthyl)thio]quinazolines exemplified by **V** which possessed extraordinary antimalarial properties (12). It was considered of interest to investigate other 6-thio analogs and we now report the antimalarial activity of a series of 2,4-diamino-6-[(heterocyclic)thio, sulfinyl, and sulfonyl]quinazolines.



V

Chemistry.

Scheme I outlines the synthetic approach utilized for the preparation of the 2,4-diamino-6-[(heterocyclic)thio]-quinazolines. 5-Chloro-2-nitrobenzonitrile (**VI**) was allowed to react with the requisite mercaptoheterocycles in the presence of potassium carbonate (procedures **I-III**) to afford the 2-nitro-5-[(heterocyclic)thio]benzonitriles (**VII**, Table I: **1-8**) (21-67%). Reduction with stannous chloride-hydrochloric acid in glacial acetic acid (procedure IV) gave the corresponding 2-amino-5-[(heterocyclic)thio]-benzonitriles (**VIII**, Table 2: 9-16) (23-74%) which were cyclized with chloroformamidine hydrochloride (13) in either diglyme (procedure **V**) or dimethyl sulfone (procedure **VI**) to give the desired 2,4-diamino-6-[(heterocyclic)thio]quinazolines (**IX**, Table III: **17-23**) (6-52%). In the cyclization of 2-amino-5-(2-pyrimidinylthio)benzonitrile (**9**), *N,N*-dimethylformamide was added to the mix-

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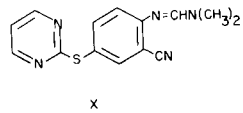
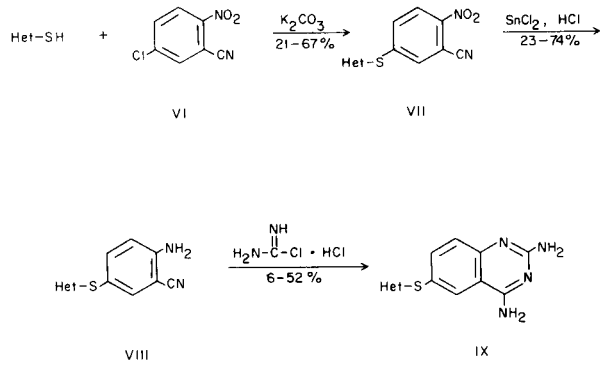
ture and the resulting product was *N'*-[2-cyano-4-(2-pyrimidinylthio)phenyl]-*N,N*-dimethylformamidine (**X**), instead of the desired diaminoquinazoline.



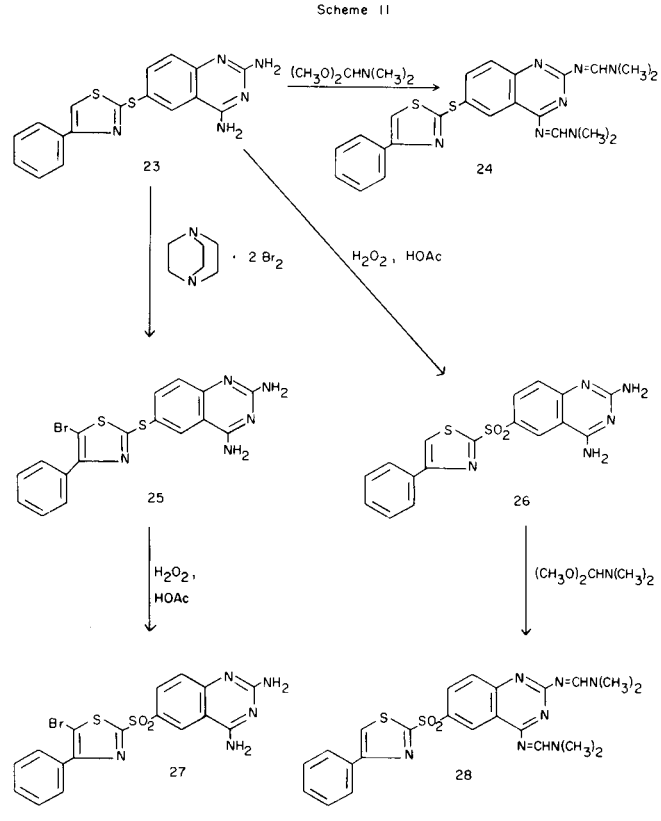
X

Scheme I



Further chemical manipulations of 2,4-diamino-6-[(4-phenyl-2-thiazolyl)thio]quinazoline (**23**, Table III) are outlined in Scheme II. Treatment of **23** with the bromine complex of 1,4-diazabicyclo[2.2.2]octane (14), an oxidizing agent, afforded 2,4-diamino-6-[(5-bromo-4-phenyl-2-thiazolyl)thio]quinazoline (**25**) (68%) instead of the expected sulfinylquinazoline. Both 2,4-diamino-6-[(4-phenyl-2-thiazolyl)thioquinazoline (**23**) and its bromo analog **25** were oxidized with hydrogen peroxide in acetic acid to give the corresponding 2,4-diamino-6-[(4-phenyl-2-thiazolyl)-sulfonyl]quinazoline (**26**) (63%) and 2,4-diamino-6-[(5-bromo-4-phenyl-2-thiazolyl)sulfonyl]quinazoline (**27**) (50%). Finally, treatment of **23** and its oxidized derivative **26** with *N,N*-dimethylformamide dimethylacetal afforded *N',N'''*-{6[(4-phenyl-2-thiazolyl)thio]-2,4-quinazolinediyl}-bis[*N,N*-dimethylformamidine] (**24**) (79%) and *N',N'''*-{6-[4-phenyl-2-thiazolyl)sulfonyl]-2,4-quinazolinediyl}bis-[*N,N*-dimethylformamidine] (**28**) (78%), respectively.

Scheme II



Biological Results.

Antimalarial Effects.

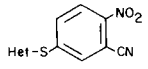
The 2,4-diamino-6-[(heterocyclic)thio]quinazolines (**17-23**) were administered subcutaneously in a single dose to mice infected with a normal drug-sensitive strain of *Plasmodium berghei* (15,16) (Table IV). Four (compounds **17,18,22,23**) (Table IV) cured mice at one or more dose levels ranging from 160 to 640 mg./kg. None of the compounds tested were toxic at the highest level tested, 640 mg./kg. 2,4-Diamino-6-[(4-phenyl-2-thiazolyl)thio]quinazoline (**23**), the most active of the series, proved to be almost as potent as the reference drug 2,4-diamino-6-[(3,4-dichlorobenzyl)amino]quinazoline (**Ia**) (4,5) and considerably more potent than 2,4-diamino-6-[(*p*-chlorobenzyl)thio]quinazoline (**IIIb**), the thiobioisostere of **Ia**, but not as potent, however as the corresponding arylthio analogs such as **V**. None of the derivatives (**24-26**) of **23** was as active as the parent (Table V).

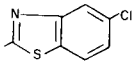
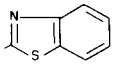
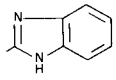
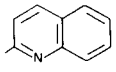
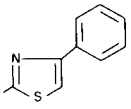
Antibacterial Activity.

The 2,4-diamino-6-[(heterocyclic)thio]quinazolines (**17, 19-23**) and the 2,4-diamino-6-[(4-phenyl-2-thiazolyl)thio and sulfonyl]quinazolines (**23-28**) were tested *in vitro* against the following pathogenic bacteria: *Streptococcus faecalis* (MGH-2), normal (UC-76) and drug-resistant (S18713) *Staphylococcus aureus, Pseudomonas aeruginosa* (28), *Escherichia coli* (Vogel) and *Shigella sonnei* (C-10) (Tables VI and VII). A modification of the gradient plate procedure of Szybalski (17) and Webb and Washington (18) was employed. Most of the compounds tested inhibited the growth of *S. faecalis* MGH-2, *S. aureus* UC-76, and *S. aureus* S18713 at concentrating of <0.25 μg./ml. 2,4-Diamino-6-[(1-methylimidazol-2-yl)thio]quinazoline (**17**) was in addition highly active (<0.25 μg./ml.) against *E. coli* and the only compound active (2.5 μg./ml.) against *S. sonnei*. None of the compounds tested was active against *P. aeruginosa* (28) at 25 μg./ml., and 2,4-diamino-6-(2-benzimidazolylthio)quinazoline (**21**) was not active against any of the bacteria tested.

Table I

2-Nitro-5-[(heterocyclic)thio]benzonitriles



No.	Het	M.p., °C	Yield purified %	Purification solvent	Procedure	Formula	Analyses Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1		162-163	66	2-PrOH	III	$C_{11}H_6N_4O_2S$ (a)	51.15	51.24	2.34	2.55	21.69	21.90
2		130-131.5	46	2-PrOH	II	$C_{11}H_8N_4O_2S$	50.76	50.46	3.10	3.11	21.53	21.20
3		103-106	67	EtOH	II	$C_{12}H_7N_3O_2S$	56.02	55.81	2.74	2.85	16.33	15.94
4		159.5-162	34	EtOAc	I	$C_{14}H_6ClN_3O_2S_2$	48.35	48.59	1.74	1.85	12.08	12.93
5		136.5-139.5	21	EtOAc	II	$C_{14}H_7N_3O_2S_2$	53.66	53.89	2.25	2.57	13.41	13.55
6		195-197	31	EtOH	II	$C_{14}H_8N_4O_2S$	56.75	57.01	2.72	2.87	18.91	18.91
7		161-163	41	EtOH	I	$C_{16}H_9N_3O_2S$	62.53	62.65	2.95	3.23	13.67	13.84
8		129-133	40	EtOAc	I	$C_{16}H_9N_3O_2S_2$	56.62	56.51	2.67	2.96	12.38	12.08

(a) S: Calcd., 12.41; Found, 12.39.

EXPERIMENTAL

Melting points (corrected) were taken on a Thomas-Hoover capillary melting point apparatus. The starting materials, 5-chloro-2-nitrobenzonitrile and the heterocyclic mercaptans, were commercially available (19).

2-Nitro-5-[(heterocyclic)thio]benzonitriles **(VII)** (1-8, Table I). Procedure 1.

A mixture of 19.3 g. (0.1 mole) of 2-mercapto-4-phenylthiazole, 18.3 g. (0.1 mole) of 5-chloro-2-nitrobenzonitrile, and 7.6 g. (0.555 mole) of potassium carbonate in 250 ml. of acetone was stirred at room temperature for 20 hours. The mixture was filtered and the filtrate was concentrated to dryness *in vacuo*. The residue was recrystallized once from acetonitrile and once from ethyl acetate to give 13.7 g. (40%) of 2-nitro-5-[(4-phenyl-2-thiazolyl)thio]benzonitrile **(8)**, m.p. 129-133°.

Procedure II.

A mixture of 8.5 g. (0.075 mole) of 2-mercapto-1-methylimidazole, 13.7 g. (0.075 mole) of 5-chloro-2-nitrobenzonitrile, and 11.3 g. of anhydrous potassium carbonate in 400 ml. of acetone was stirred under reflux for 10 hours, cooled, and filtered. The filtrate was concentrated to a dark oil which crystallized on cooling. The solid was recrystallized once from ethanol and once from 2-propanol to give 9.0 g. (46%) of 2-nitro-5-[(1-methylimidazol-2-yl)thio]benzonitrile **(2)**, m.p. 130-131.5°.

Procedure III.

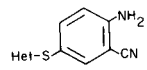
A mixture of 1.1 g. (0.01 mole) of 2-mercaptopyrimidine, 1.8 g. (0.01 mole) of 5-chloro-2-nitrobenzonitrile, and 1.5 g. (0.01 mole) of anhydrous potassium carbonate in 60 ml. of *N,N*-dimethylformamide was stirred at room temperature for 21 hours and filtered to remove inorganic material. The filtrate was poured into rapidly stirred cold water. The bright yellow solid which precipitated was collected, washed with water, and recrystallized from 2-propanol to give 1.7 g. (66%) of 2-nitro-5-(2-pyrimidinylthio)benzonitrile **(1)**, m.p. 162-163°.

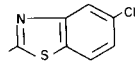
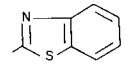
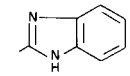
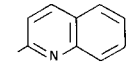
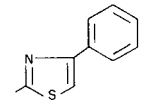
2-Amino-5-[(heterocyclic)thio]benzonitriles **(VIII)** (9-16, Table **II**). Procedure IV.

To a stirred solution of 29.7 g. (0.132 mole) of stannous chloride dihydrate in 55 ml. of concentrated hydrochloric acid was added in small portions a warm solution of 13.6 g. (0.04 mole) of 2-nitro-5-[4-phenyl-2-thiazolyl)thio]benzonitrile **(8)** in 90 ml. of glacial acetic acid. The temperature of the mixture was maintained at 25-30° during the addition with a cold water bath. After 0.75 hours, when addition was almost complete, a solid precipitated from the solution. The mixture was stirred at room temperature for 18 hours and filtered. The filter cake was suspended in cold water, and filtered. The solid was dissolved in 225 ml. of hot

Table II

2-Amino-5-[(heterocyclic)thio]benzonitriles



No.	Het	M.p., °C	Yield purified %	Purification solvent	Procedure	Formula	Analyses Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
9		163-164	74	2-PrOH-petroleum ether	IV	$C_{11}H_8N_4S$	57.86	58.06	3.53	3.64	24.55	24.68
10		153.5-155	72	EtOH	IV	$C_{11}H_{10}N_4S$	57.37	57.15	4.38	4.55	24.33	24.49
11		125-129	62	EtOH-H_2O	IV	$C_{12}H_9N_3S$	63.41	63.15	3.99	4.09	18.49	18.67
12		206-209	50	Me_2CO-H_2O	IV	$C_{14}H_8ClN_3S_2$	52.90	53.06	2.54	2.80	13.23	12.78
13		176-179.5	44	EtOAc	IV	$C_{14}H_9N_3S_2$	59.34	59.46	3.20	3.33	14.83	14.83
14		230-233	61	EtOH-H_2O	IV	$C_{14}H_{10}N_4S$	63.14	62.60	3.79	3.92	21.04	20.94
15		155-157	23	EtOH-H_2O	IV	$C_{16}H_{11}N_3S$	69.29	69.12	4.00	4.13	15.15	15.27
16		147-149.5	66	EtOH-H_2O	IV	$C_{16}H_{11}N_3S_2$	62.11	61.88	3.58	3.69	13.58	13.41

95% ethanol and 2 *N* ammonium hydroxide was added until the mixture was weakly basic. The precipitate was collected, washed with water, and dried in air. The solid was treated with 300 ml. of hot ethanol and filtered. The filtrate was concentrated to 150 ml. and refiltered. The filtrate on cooling yielded 7.3 g. of 2-amino-5-[(4-phenyl-2-thiazolyl)-thio]benzonitrile (**16**), m.p. 147-149.5°. Addition of water to the filtrate afforded an additional 0.9 g. of the product. The total yield was 8.2 g. (66%).

2,4-Diamino-6-[(heterocyclic)thio]quinazolines (**IX**) (**17-23**, Table III). Procedure V.

A stirred suspension of 5.3 g. (0.0165 mole) of 2-amino-5-[(5-chloro-2-benzothiazolyl)thio]benzonitrile (**12**) in 20 ml. of diglyme was heated in an oil bath at 150° to effect solution. When a homogeneous solution formed, 2.0 g. (0.0174 mole) of chloroformamidine hydrochloride (13) was added and the mixture was stirred at 150° (bath temperature) for 1 hour. During this time hydrogen chloride was evolved and a thin oil began to separate. After 1 hour the oil had solidified and the mixture was cooled and filtered. The brown solid which was collected was washed with ethyl acetate and dried. The crude product was reprecipitated from a mixture of *N,N*-dimethylformamide and dilute sodium hydroxide upon addition of water. The dark yellow solid was collected and dried *in vacuo* at 50° to give 2.6 g. (44%) of the desired 2,4-diamino-6-[(5-chloro-2-benzothiazolyl)thio]quinazoline (**19**), m.p. 305-307°.

Procedure VI.

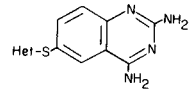
A mixture of 7.5 g. (0.0242 mole) of 2-amino-5-[(4-phenyl-2-thiazolyl)-thio]benzonitrile (**16**), 5.6 g. (0.0487 mole) of chloroformamidine hydrochloride (13) and 23 g. of dimethyl sulfone was ground together and heated in an oil bath at 160° (external temperature) for 20 minutes. Upon cooling, the solid was triturated with water and dried. The crude product (7.4 g.) was dissolved in 125 ml. of hot *N,N*-dimethylformamide containing 8 ml. of concentrated ammonium hydroxide, the hazy solution was filtered through Supercell, and water was added to the cloud point. Upon cooling, the product that crystallized was collected and dried *in vacuo* at 60° for 24 hours and then at 100° for 5 hours (weight, 5.8 g.). Recrystallization from 450 ml. of ethanol containing 4 ml. of water gave 4.3 g. of yellow crystals, which upon drying at 100° for 48 hours afforded 4.0 g. (48%) of anhydrous 2,4-diamino-6-[(4-phenyl-2-thiazolyl)thio]quinazoline (**23**), m.p. 217-220°.

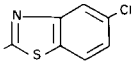
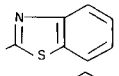
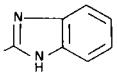
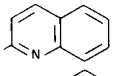
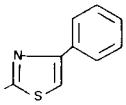
N'-(2-Cyano-4-(2-pyrimidinylthio)phenyl]-*N,N*-dimethylformamidine.

A mixture of 6.9 g. (0.0258 mole) of 2-amino-5-(2-pyrimidinylthio)-benzonitrile (**9**), 3.4 g. (0.0296 mole) of chloroformamidine hydrochloride (13), 15 ml. of diglyme, and 5 ml. of *N,N*-dimethylformamide was heated in an oil bath to 130°. Before solution of the starting materials was complete, a new solid began to precipitate. The mixture was heated at 140° (external temperature) for 1 hour, cooled to room temperature, and filtered. The sticky solid was triturated with ethanol and dissolved in water. The filtered solution was added to dilute aqueous ammonium

Table III

2,4-Diamino-6-[(heterocyclic)thio]quinazolines



No.	Het	M.p., °C	Yield purified, %	Purification solvent	Procedure	Formula	Analyses Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
17		300 dec.	35	EtOH-H_2O	V	$C_{12}H_{12}N_6S$	52.92	52.69	4.45	4.57	30.86	30.53
18		260-262	6	EtOH	V	$C_{13}H_{11}N_5S \cdot 0.5C_2H_6O$(a)	57.51	57.61	4.83	4.93	23.96	23.85
19		305-307	44	DMF-aq. NaOH	V	$C_{15}H_{10}ClN_5S_2$	50.06	50.19	2.80	3.00	19.46	19.57
20		300-302	52	DMF-H_2O	V	$C_{15}H_{11}N_5S_2 \cdot C_3H_7NO$(b)	54.25	54.40	4.56	4.42	21.09	20.87
21		>310	26	DMF	V	$C_{15}N_{12}N_6S \cdot C_3H_7NO$(b)	56.67	56.67	5.02	5.16	25.70	26.06
22		269.5-272.5	28	EtOH-H_2O	V	$C_{17}H_{13}N_5S \cdot 0.33C_2H_6O \cdot 0.5H_2O$ (a,c)	61.74	61.84	4.69	4.69	20.38	20.33
23		217-220	48	EtOH-H_2O	VI	$C_{17}H_{13}N_5S_2$	58.10	57.87	3.73	4.01	19.93	20.00

(a) The nmr spectrum confirmed the presence of ethanol. (b) The nmr spectrum confirmed the presence of *N,N*-dimethylformamide. (c) H_2O: Calcd., 2.62; Found, 2.78.

hydroxide and filtered. The sticky solid was dried, dissolved in ethyl acetate, filtered, and petroleum ether added to the cloud point. Scratching with a glass rod induced crystallization of a pale yellow solid which was collected and dried to give 1.4 g. (19%) of the product, m.p. 120-123°.

Anal. Calcd. for $C_{14}H_{13}N_5S$: C, 59.34; H, 4.62; N, 24.72. Found: C, 59.13; H, 4.86; N, 24.57.

2,4-Diamino-6-[(5-bromo-4-phenyl-2-thiazolyl)thio]quinazoline (**25**).

A mixture of 2.9 g. (0.00826 mole) of 2,4-diamino-6-[(4-phenyl-2-thiazolyl)thio]quinazoline (**23**), 1.8 g. (0.00413 mole) of the bromine complex of 1,4-diazabicyclo[2.2.2]octane (14), and 60 ml. of 70% aqueous acetic acid was stirred at room temperature for 24 hours, and then poured into a mixture of ice and 60 ml. of 50% aqueous sodium hydroxide. The precipitate was collected, washed with water, recrystallized from ethanol-1 *N* sodium hydroxide, washed with water, and dried *in vacuo* at 100° for 18 hours to give 2.4 g. (68%) of the product, m.p. 217-220°.

Anal. Calcd. for $C_{17}H_{12}BrN_5S_2$: C, 47.45; H, 2.81; N, 16.28; Br, 18.57; Br^-, 0.0. Found: C, 47.72; H, 3.00; N, 16.57; Br, 18.54; Br^-, 0.0.

2,4-Diamino-6-[(4-phenyl-2-thiazolyl)sulfonyl]quinazoline (**26**).

A mixture of 0.5 g. (0.00145 mole) of 2,4-diamino-6-[(4-phenyl-2-thiazolyl)thio]quinazoline (**23**), 3.5 ml. (0.035 mole) of 30% hydrogen peroxide, and 6.5 ml. of glacial acetic acid was stirred at room temperature for 48 hours. The resulting solution was poured into a mixture of ice and 10 ml. of 50% aqueous sodium hydroxide. The solid that formed was collected, washed with water, recrystallized from *N,N*-dimethylformamide-water, and dried *in vacuo* at 100° for 18 hours to give 0.35 g. (63%) of the product, m.p. 278-279° dec.

Anal. Calcd. for $C_{17}H_{13}N_5O_2S_2$: C, 53.25; H, 3.42; N, 18.27. Found: C, 52.96; H, 3.52; N, 18.27.

2,4-Diamino-6-[(5-bromo-4-phenyl-2-thiazolyl)sulfonyl]quinazoline (**27**).

A mixture of 1.0 g. (0.00232 mole) of 2,4-diamino-6-[(5-bromo-4-phenyl-2-thiazolyl)thio]quinazoline (**25**), 6.7 ml. of 30% hydrogen peroxide, and 15 ml. of glacial acetic acid was stirred at room temperature for 18 hours and then poured into a mixture of ice and 22 ml. of 50% aqueous sodium hydroxide. The precipitate that formed was collected and washed with water to give 0.95 g. of crude product. This material was combined with 0.25 g. of crude product obtained similarly from 0.3 g. (0.007 mole) of starting material in a prior run and recrystallized from ethanol containing a few drops of 1 *N* sodium hydroxide to give 0.95 g., m.p. 255-258° dec. with softening at 120-130° and at 240-255°. Infrared spectroscopy indicated a mixture of sulfone (1160 cm^{-1} and 1365 cm^{-1}) and sulfoxide (1060 cm^{-1}). The material in 18 ml. of glacial acetic acid and 7 ml. of 30% hydrogen peroxide was stirred for 18 hours at room temperature, poured into a mixtue of ice and 25 ml. of 50% sodium hydroxide, and filtered. The filter cake was washed with water and recrystallized from *N,N*-dimethylformamide-1 *N* ammonium hydroxide to give 0.70 g. (50%) of the product, m.p. 288-290° dec.

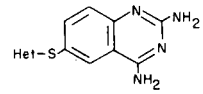
Anal. Calcd. for $C_{17}H_{12}BrN_5O_2S_2$: C, 44.16; H, 2.62; N, 15.15. Found: C, 44.47; H, 2.93; N, 15.11.

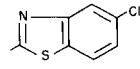
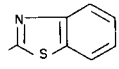
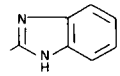
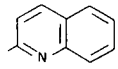
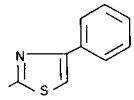
N',N'''-{-6-[(4-Phenyl-2-thiazolyl)sulfonyl]-2,4-quinazolinediyl}bis[*N,N*-dimethylformamidine] (**28**).

To a solution of 1.0 g. (0.0026 mole) of 2,4-diamino-6-[(4-phenyl-2-thiazolyl)sulfonyl]quinazoline (**26**) in 12 ml. of *N,N*-dimethylformamide was

Table IV

Parenteral Antimalarial Effects of 2,4-Diamino-6-[(heterocyclic)thio]quinazolines Against *Plasmodium berghei* in Mice



No.	Het	Single s.c. dose ΔMST; C or T (a) after mg./kg. dose: 640	320	160	80	40	20
17		24.2; C3	21.2; C3 21.9; C3	20.7; Cl 17.2; C2	11.7; Cl 11.7; Cl	5.1 5.7	3.3 3.7
18		14.8; C2	13.8; C2 14.1; C2	7.4 7.6	5.8 6.0	2.2 2.2	2.0 1.8
19		9.7	7.7 7.5	1.1 1.1	0.5 0.5	0.5 0.5	0.3 0.3
20				5.9	4.5	1.5	0.3
21		3.9	1.9 2.1	1.1 1.3	0.3 0.5	0.3 0.3	0.1 0.3
22		C5	14.9; C3	13.7	11.9	6.1	5.1
23		C5	C5 C5	15.6; C2 15.2; C2	5.9 6.1	2.9 2.7	0.3 0.5
Ia·HOAc		C5	C5 C5	9.9; C3 9.9; C3	12.9 13.1	7.1 7.3	2.5 2.7
IIb		25.5; C2 17.3; C3	9.8	4.4 4.2	2.6	0.8 0.8	0.4
V		C5	C5	C5	C5	C3	12.7
Cycloguanil·HCl		T5	C3; T2 C2; T3	C5 C5	21.6; C2 21.6; C2	13.4; Cl 13.4; Cl	7.9 8.1

(a) ΔMST is the mean survival time (days) of treated mice (MSTT) minus the mean survival time (days) of control mice (MSTC). In the present study, the MSTC ranged from 6.1 to 6.2 days. T signifies the number of toxic deaths occurring on days 2-6 after infection which are attributed to drug action. C indicates the number of mice surviving at 60 days post infection and termed "cured", data to establish parasitological cure based on subinoculation are unavailable. Each entry at each dose level represents results with a 5-animal group.

added 6.2 g. (0.052 mole) of *N,N*-dimethylformamide dimethylacetal. The solution was stirred at room temperature for 4 hours. A bright orange precipitate accumulated and the reaction mixture was chilled and filtered to afford 1.0 g. (78%) of the product, m.p. 230-232°.

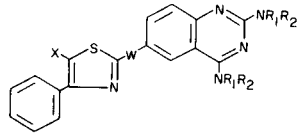
Anal. Calcd. for $C_{23}H_{23}N_7O_2S_2$: C, 55.96; H, 4.70; N, 19.87. Found: C, 55.88; H, 4.84; N, 19.73.

Acknowledgements.

The authors thank Dr. Leo Rane of the University of Miami for the antimalarial testing and Dr. C. L. Heifetz for the antibacterial testing. We also acknowledge Mr. C. E. Childs and associates for the microanalyses, and Dr. J. M. Vandenbelt and co-workers for determination of spectral data.

Table V

Parenteral Antimalarial Effects of 2,4-Diamino-6-[(4-phenyl-2-thiazolyl)thio and sulfonyl]quinazolines Against *Plasmodium berghei* in Mice

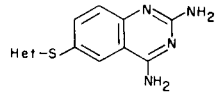


				Single s.c. dose ΔMST; C or T (a) after mg./kg. dose:					
No.	W	X	NR_1R_2	640	320	160	80	40	20
23	-S-	H	NH_2	C5	C5	15.6; C2	5.9	2.9	0.3
					C5	15.2; C2	6.1	2.7	0.5
24	-S-	H	$N{=}CHN(CH_3)_2$	7.3	3.9	2.1	1.9	0.5	0.5
				7.1		1.9		0.7	
25	-S-	Br	NH_2	9.9; C3	6.3	5.7	4.3	0.9	0.5
				9.4; C3		5.9		0.7	
26	$-SO_2-$	H	NH_2		10.7	8.3	2.7	1.3	0.7
					10.9		2.9		0.7
27	$-SO_2-$	Br	NH_2	—	—	—	—	—	—
28	$-SO_2-$	H	$N{=}CHN(CH_3)_2$	—	—	0.9	—	0.5	—

(a) See footnote a, Table IV.

Table VI

In vitro Antibacterial Effects of 2,4-Diamino-6-[(heterocyclic)thio]quinazolines



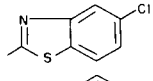
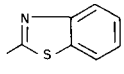
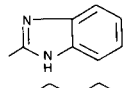
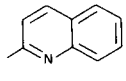
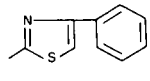
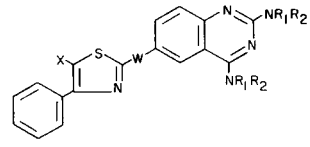
		Minimum inhibitory concentration, μg./ml.					
Number	Heterocycle	*Streptococcus faecalis* MGH-2	*Staphylococcus aureus* UC-76	*Staphylococcus aureus* S18713	*Pseudomonas aeruginosa* 28	*Escherichia coli* Vogel	*Shigella sonnei* C-10
17		<0.25	<0.25	<0.25	>25	<0.25	2.5
19		15	10	10	>25	>25	>25
20		15	<0.25	15	>25	20	>25
21		>25	>25	>25	>25	>25	>25
22		<0.25	<0.25	<0.25	>25	2.0	>25
23		<0.25	<0.25	<0.25	>25	>25	>25

Table VII

In vitro Antibacterial Effects of 2,4-Diamino-6-[(4-phenyl-2-thiazolyl)thio and sulfonyl]quinazolines



				Minimum inhibitory concentration, μg./ml.					
No.	W	X	NR_1R_2	*Streptococcus faecalis* MGH-2	*Staphylococcus aureus* UC-76	*Staphylococcus aureus* S18713	*Pseudomonas aeruginosa* 28	*Escherichia coli* Vogel	*Shigella sonnei* C-10
23	-S-	H	NH_2	<0.25	<0.25	<0.25	>25	>25	>25
24	-S-	H	$N{=}CHN(CH_3)_2$	<0.25	2.0	2.0	>25	>25	>25
25	-S-	Br	NH_2	<0.25	<0.25	<0.25	>25	>25	>25
26	$-SO_2-$	H	NH_2	<0.25	<0.25	<0.25	>25	>25	>25
27	$-SO_2-$	Br	NH_2	<0.25	<0.25	<0.25	>25	>25	>25
28	$-SO_2-$	H	$N{=}CHN(CH_3)_2$	<0.25	<0.25	<0.25	>25	>25	>25

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(1) For previous paper on folate antagonists see E. F. Elslager, M. P. Hutt, P. Jacob, J. Johnson, B. Temporelli, L. M. Werbel, D. F. Worth and L. Rane, *J. Med. Chem.*, **22**, 1247 (1979).

(2) This is communication 45 of a series on antimalarial drugs. For paper 44, see (1).

(3) This investigation was supported by U.S. Army Medical Research and Development Command Contracts DA-49-193-MD-2754 and DADA-17-72-C-2077. This is contribution No. 1544 to the Army Research Progam on Malaria.

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(15) The parenteral antimalarial screening was carried out by Dr. Leo Rane of the University of Miami and test results were supplied through the courtesy of Dr. David P. Jacobus, Dr. T. R. Sweeney, and Dr. E. A. Steck of the Walter Reed Army Institute of Research.

(16) For a description of the test method, see T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).

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