Articles

Synthesis and Antimalarial Effects of N^2-Aryl-N^4-[(dialkylamino)alkyl]- and N^4-Aryl-N^2-[(dialkylamino)alkyl]-2,4-quinazolinediamines[1,2]

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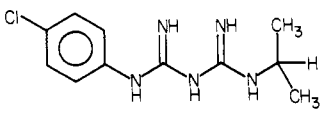
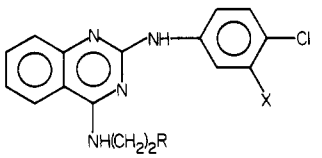
A series of N^2(and N^4)-aryl-N^4(and N^2)-[(dialkylamino)alkyl]-2,4-quinazolinediamines has been synthesized for antimalarial evaluation. Condensation of the appropriate 2,4-dichloroquinazoline (IV) with the requisite *N,N*-dialkylalkylenediamine afforded a series of 2-chloro-*N*-[(dialkylamino)alkyl]-4-quinazolinamines (V) which were condensed with the appropriate arylamine to provide the corresponding N^2-aryl-N^4-[(dialkylamino)alkyl]-2,4-quinazolinediamines (VI). Hydrolysis of 2,4-dichloroquinazoline to 2-chloro-4-quinazolinol was followed by condensation with the appropriate *N,N*-dialkylalkylenediamine to give an array of 2-[[(dialkylamino)alkyl]amino]-4-quinazolinols (IXa). Chlorination with phosphorus oxychloride and condensation with a requisite arylamine provided the N^2-[(dialkylamino)alkyl]-N^4-phenyl-2,4-quinazolinediamines (X). Antimalarial activity was general among the N^2-aryl-N^4-[(dialkylamino)alkyl]-2,4-quinazolinediamines (VI), while the reverse isomers were of lower activity. Phototoxic liability precluded clinical evaluation of a member of the series.

During the evolutionary process that led to the development of chlorguanide (I),[3,4] it was discovered that certain



I

N^4-[(dialkylamino)alkyl]-N^2-phenyl-2,4-quinazolinediamines possessed strong antimalarial effects against *Plasmodium gallinaceum* in chicks.[5,6] Among them, N^2-(4-chlorophenyl)-N^4-[2-(diethylamino)ethyl]-2,4-quinazolinediamine (IIa) proved to be one of the most

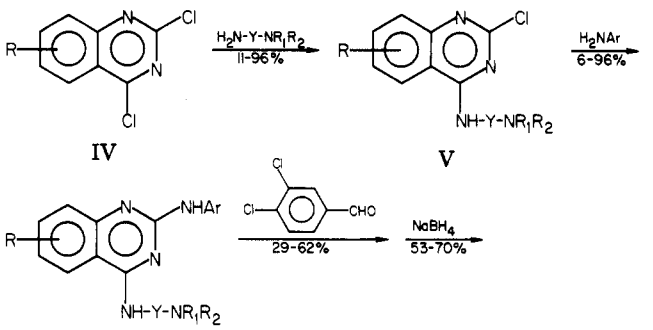


IIa, X = H; R = $-N(C_2H_5)_2$

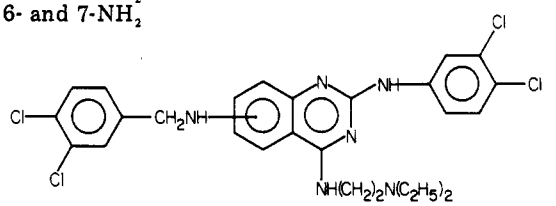
b, X = Cl; R = 

promising members of the series, but the development of chlorguanide and its active metabolite, cycloguanil (III),[4,7] precluded evaluation of this compound and related substances.

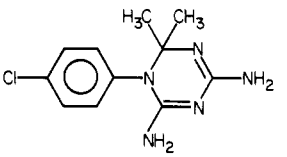
Scheme I



VIa, R = 6- and 7-NO_2
b, R = 6- and 7-NH_2



VIIa, 6-substituted
b, 7-substituted



III

Faced with the problem of developing new agents that might be useful against drug-resistant malarias,[4] IIa and several close analogues were synthesized for evaluation against *Plasmodia* in contemporary test systems.[8-10] Early

(1) This is paper 48 of a series on antimalarial drugs. For paper 47, see *J. Heterocycl. Chem.*, 17, 497 (1980).
(2) 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. 1586 to the Army Research Program on Malaria.
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(4) P. E. Thompson and L. M. Werbel, "Antimalarial Agents, Chemistry and Pharmacology", Academic Press, New York, 1972.
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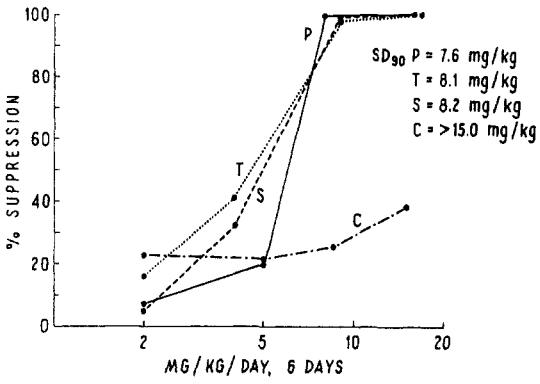


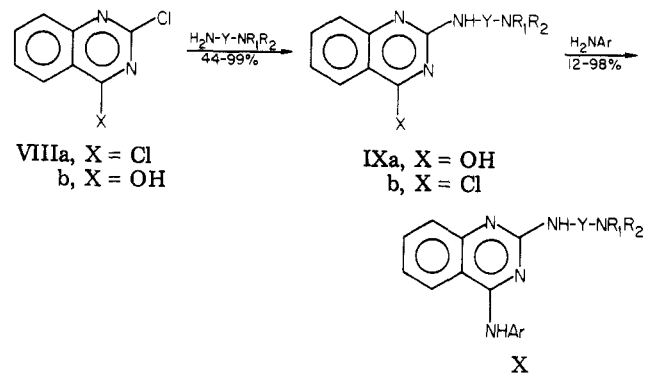
Figure 1. Effects of N^2-(3,4-dichlorophenyl)-N^4-[2-(1-methyl-2-pyrrolidinyl)ethyl]-2,4-quinazolinediamine against drug-resistant lines of *P. berghei* in mice.

results revealed that IIa (compound **51**; Table II) was active against *P. berghei* in mice at 80 mg/kg and curative at 160 mg/kg and, moreover, that IIb (compound **19**; Table II) proved to be essentially as active against cycloguanil- and DDS-resistant strains of *P. berghei* as against the sensitive parasite, although some cross-resistance to chloroquine was noted (Figure 1). Therefore a full-scale investigation of this structural class was undertaken, and the present article summarizes the results with the N^4-[(dialkylamino)alkyl]-N^2-phenyl-2,4-quinazolinediamines, as well as the related N^2-[(dialkylamino)alkyl]-N^4-phenyl-2,4-quinazolinediamines.

Chemistry. The synthetic approach utilized for the preparation of the N^4-[(dialkylamino)alkyl]-N^2-phenyl-2,4-quinazolinediamines (VI) involved modifications of previous[5,6] procedures and is depicted in Scheme I. Condensation of the appropriate 2,4-dichloroquinazoline (IV) with the requisite *N,N*-dialkylalkylenediamine in ether, alcohol–ether, alcohol, nitrobenzene, or dilute aqueous sodium hydroxide[5] generated the corresponding 2-chloro-*N*-[(dialkylamino)alkyl]-4-quinazolinamines V (1–17; Table I) in 11–96% yield (procedures A–C). It has been shown[5] that, under the conditions used, only the chlorine in the 4 position is replaced. The cis and trans isomers arising from the reactions of *N,N*-dimethyl- and *N,N*-diethyl-1,4-cyclohexanediamine with 2,4-dichloroquinazoline (compounds **1**, **2** and **4**, **5**; Table I) were separated by fractional crystallization and differentiated on the basis of their R_f values on TLC. Condensation of V with the appropriate arylamine in alcohol either in the presence of or the absence of hydrochloric acid provided the desired N^4-[(dialkylamino)alkyl]-N^2-phenyl- and -heterocyclic-2,4-quinazolinediamines VI (compounds 18–82; Tables II and III) in 6–96% yield (procedure F). Alternatively, VI may be synthesized from IV in one pot (procedures D and E) in ethanol or nitrobenzene by treatment with the appropriate *N,N*-dialkylalkylenediamine, followed by the addition of the desired arylamine after the initial reaction had been shown by TLC to be complete.

Reduction of 6- or 7-nitro-substituted VI (VIa) with Raney nickel in 2-methoxyethanol (procedure G) afforded the corresponding N^2-(3,4-dichlorophenyl)-N^4-[2-(diethylamino)ethyl]-2,4(6 and 7)-quinazolinetriamines (VIb) (compounds **71** and **72**; Table II) in 65 and 74% yield, respectively. Condensation of VIb with 3,4-dichlorobenzaldehyde, followed by reduction of the Schiff base with sodium tetrahydroborate in 2-methoxyethanol (procedure H), gave the desired N^2-(3,4-dichlorophenyl)-N^6- and -N^7-[(3,4-dichlorophenyl)methyl]-N^4-[2-(diethylamino)-ethyl]-2,4(6 and 7)-quinazolinetriamines (VIIa,b) (compounds **73** and **74**; Table II) in 53 and 70% yield, respectively.

Scheme II



VIIIa, X = Cl
b, X = OH

IXa, X = OH
b, X = Cl

X

Scheme II illustrates the approach[11] used for the preparation of the N^2-[(dialkylamino)alkyl]-N^4-phenyl-2,4-quinazolinediamines (X). Hydrolysis of 2,4-dichloroquinazoline (VIIIa) in 2 N sodium hydroxide[12] provided 2-chloro-4-quinazolinol[5,11] (VIIIb), which was allowed to condense with the requisite *N,N*-dialkylalkylenediamine in benzene or ethanol to form the corresponding 2-[[(dialkylamino)alkyl]amino]-4-quinazolinols (IXa) in 44–99% yield (procedures I and J). Chlorination using phosphorus oxychloride, followed by condensation of the crude 4-chloro-*N*-[(dialkylamino)alkyl]-4-quinazolinamine (IXb) with the desired substituted benzenamine, furnished the various N^4-[(dialkylamino)alkyl]-N^2-phenyl-2,4-quinazolinediamines X (compounds **83–116**; Table IV) in 12–98% yield (procedures K–M).

All of the requisite 2,4-dichloroquinazolines (IV) were prepared by chlorination[5] of the corresponding 2,4-(1*H*,3*H*)-quinazolinediones with phosphorus oxychloride or a phosphorus oxychloride–phosphorus pentachloride mixture. Among the intermediate quinazolinediones, 2,4(1*H*,3*H*)-quinazolinedione is commercially available,[13] and the 6- and 7-chloro-2,4(1*H*,3*H*)-quinazolinediones[6] were obtained by cyclization[6] of 4- and 5-chloroanthranilic acid with potassium cyanate. 6,8-Dichloro-2,4(1*H*,3*H*)-quinazolinedione[14] and 7-nitro-2,4(1*H*,3*H*)-quinazolinedione[15] were prepared by cyclization[14,15] of the corresponding anthranilic acids with urea, while 6-nitro-2,4(1*H*,3*H*)-quinazolinedione resulted from the nitration[16] of 2,4(1*H*,3*H*)-quinazolinedione. The majority of the intermediate *N,N*-dialkylalkylenediamine and arylamine side chains employed were commercially available; otherwise, they were prepared by published procedures.[17–20]

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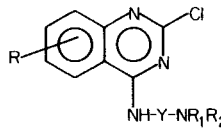
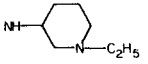
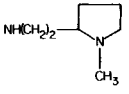
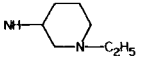
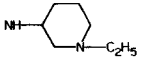
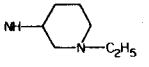
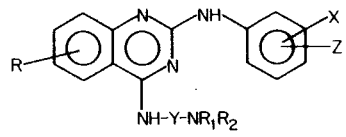
Table I. 2-Chloro-*N*-[(dialkylamino)alkyl]-4-quinazolinamines

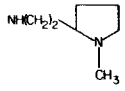
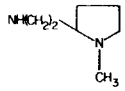
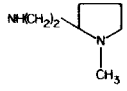
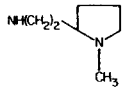
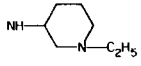
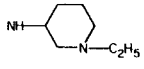


no.	-NH-Y-NR$_1$R$_2$	R	mp, °C	yield purified, %	purifn solvent	procedure	formula	anal.
1	NHCH[(CH$_2$)$_2$]$_2$CHN(CH$_3$)$_2$[a]	H	250–252	28	EtOH–2-PrOH	A	$C_{16}H_{21}ClN_4$·HCl	C, H, N
2	NHCH[(CH$_2$)$_2$]$_2$CHN(CH$_3$)$_2$[b]	H	245–247	9	CH_3CN	A	$C_{16}H_{21}ClN_4$·HCl·H_2O	C, H, N, H_2O
3		H	180–185	24	Et_2O	C	$C_{15}H_{19}ClN_4$·HCl	*c*
4	NHCH[(CH$_2$)$_2$]$_2$CHN(C$_2$H$_5$)$_2$[a]	H	276–279	37	2-PrOH	A	$C_{18}H_{25}ClN_4$·HCl	C, H, N
5	NHCH[(CH$_2$)$_2$]$_2$CHN(C$_2$H$_5$)$_2$[b]	H	233–235	30	CH_3CN	A	$C_{18}H_{25}ClN_4$·HCl·0.3H_2O	C, H, N, H_2O
6	NH(CH$_2$)$_2$N(CH$_2$)$_4$	H	136–138	56	C_6H_{12}	C	$C_{14}H_{17}ClN_4$	C, H, N
7	NH(CH$_2$)$_3$N(CH$_2$)$_4$	H	135–136	26	C_6H_{12}	C	$C_{15}H_{19}ClN_4$	C, H, N
8	NH(CH$_2$)$_2$N(C$_2$H$_5$)$_2$	H	81–82[d]	33	Me_2CO–H_2O	*e*	$C_{14}H_{19}ClN_4$·H_2O	C, H, N, H_2O
9		6-Cl	176–179 dec	55	2-PrOH	B	$C_{15}H_{18}Cl_2N_4$·HCl	*c*
10		6-Cl	295–300 dec	75	2-PrOH	B	$C_{15}H_{18}Cl_2N_4$·HCl	*c*
11		7-Cl	270–275 dec	37	EtOH–2-PrOH	B	$C_{15}H_{18}Cl_2N_4$·HCl	*c*
12		6,8-Cl$_2$	185–192 dec	62	EtOH	B	$C_{15}H_{17}Cl_3N_4$·HCl	*c*
13	NHCH[(CH$_2$)$_2$]$_2$CHN(C$_2$H$_5$)$_2$[f]	6-Cl	143–155	48	EtOH–2-PrOH	B	$C_{15}H_{18}Cl_2N_4$·HCl	*c*
14	NH(CH$_2$)$_3$N(CH$_2$)$_4$	6-Cl	135–140	72	EtOH	B	$C_{15}H_{18}Cl_2N_4$·HCl	*c*
15	NH(CH$_2$)$_2$N(C$_2$H$_5$)$_2$	6-Cl	157–162 dec[g]	96	Et_2O	B	$C_{14}H_{18}Cl_2N_4$·HCl	*c*
16	NH(CH$_2$)$_2$N(C$_2$H$_5$)$_2$	7-Cl	218–222[h]	78	Et_2O	B	$C_{14}H_{18}Cl_2N_4$·HCl	*c*
17	NH(CH$_2$)$_2$N(C$_2$H$_5$)$_2$	7-NO_2	114–116[i]	11	Hexane	C	$C_{14}H_{18}ClN_5O_2$	*c*

[a] Isomer A (see Experimental Section, Procedure A). [b] Isomer B. [c] These compounds were crystallized, spectrally characterized, and used directly in the next step without microanalyses. [d] Lit. (ref 5) mp 96–98 °C for the unhydrated compound. [e] Prepared as described in ref 5. [f] A mixture of isomers A and B. [g] Lit. (ref 6) mp 135–136 °C for the free base. [h] Lit. (ref 6) mp 119 °C for the free base. [i] Lit. (ref 6) mp 125–126 °C.

Table II. N^4-[(Dialkylamino)alkyl]-N^2-phenyl-2,4-quinazolinediamines



no.	-NH-Y-NR$_1$R$_2$	X, Z	R	mp, °C	yield purified, %	purifn solvent	procedure	formula	anal.
18		4-Cl	H	268–272 dec	45	2-PrOH-EtOH	D	$C_{21}H_{24}ClN_5 \cdot 2HCl \cdot 1.4H_2O$	C, H, N, H_2O
19		3,4-Cl_2	H	268–272 dec	35	2-PrOH-EtOH	D	$C_{21}H_{23}Cl_2N_5 \cdot 2HCl \cdot 1.6H_2O$	C, H, N, H_2O
20		3-Br	H	269–274 dec	24	EtOH-MeOH	D	$C_{21}H_{24}BrN_5 \cdot 2HCl \cdot 0.8H_2O$	C, H, N, H_2O
21		4-CF_3	H	268–270 dec	12	2-PrOH	D	$C_{22}H_{24}F_3N_5 \cdot 2HCl \cdot 2.2H_2O$	C, H, N, H_2O
22	NHCH[$(CH_2)_2$]$_2$CHN$(CH_3)_2$[a]	3,4-Cl_2	H	311–313 dec	57	EtOH	F	$C_{22}H_{25}Cl_2N_5 \cdot 2HCl \cdot 2.2H_2O$	C, H, N, H_2O
23	NHCH[$(CH_2)_2$]$_2$CHN$(CH_3)_2$[b]	3,4-Cl_2	H	326–336 dec	78	2-PrOH	F	$C_{22}H_{25}Cl_2N_5 \cdot 2HCl$	C, H, N
24	NHCH[$(CH_2)_2$]$_2$CHN$(CH_3)_2$[c]	3,4-Cl_2	H	168–172 dec	6	2-PrOH	D	$C_{22}H_{25}Cl_2N_5 \cdot 2HCl \cdot 1.9H_2O$	C, H, N, H_2O
25	NHCH[$(CH_2)_2$]$_2$CHN$(CH_3)_2$[a]	3,5-Cl_2	H	292–294 dec	75	MeOH	F[d]	$C_{22}H_{25}Cl_2N_5 \cdot 2HCl \cdot 1.3H_2O$	C, H, N, H_2O
26	NHCH[$(CH_2)_2$]$_2$CHN$(CH_3)_2$[b]	3,5-Cl_2	H	328–338 dec	49	MeOH	F	$C_{22}H_{25}Cl_2N_5 \cdot 2HCl$	C, H, N
27	NHCH[$(CH_2)_2$]$_2$CHN$(CH_3)_2$[c]	4-OCH_3, 3-$CH_2NHC_2H_5$	H	275–280 dec	55	EtOH	F	$C_{26}H_{36}N_6O \cdot 3HCl \cdot 2.4H_2O$	C, H, N, Cl; H_2O[f]
28	NHCH[$(CH_2)_2$]$_2$CHN$(CH_3)_2$	4-OCH_3, 3-$CH_2N(C_2H_5)_2$	H	265–268	46	EtOH	F	$C_{28}H_{40}N_6O \cdot 3HCl \cdot 1.1H_2O$	C, N, H_2O; H[g]
29		4-Cl	H	181–183	34	CH_3CN	F[e]	$C_{21}H_{24}ClN_5 \cdot 2HCl \cdot 0.7H_2O$	C, H, N, H_2O
30		3,4-Cl_2	H	249–251	71	CH_3CN	E	$C_{21}H_{23}Cl_2N_5 \cdot 2HCl \cdot 1.5H_2O$	C, H, N, H_2O
31	$NHCH_2CH[(CH_2)_2]_2NC_2H_5$	3,4-Cl_2	H	339–342	41	MeOH	E	$C_{22}H_{25}Cl_2N_5 \cdot 2HCl \cdot 0.4H_2O$	C, H, N, Cl, H_2O
32	NHCH[$(CH_2)_2$]$_2$CHN$(C_2H_5)_2$[a]	3,4-Cl_2	H	277–279 dec	74	EtOH-MeOH	F	$C_{24}H_{29}Cl_2N_5 \cdot 2HCl \cdot 1.6H_2O$	C, H, N, H_2O
33	NHCH[$(CH_2)_2$]$_2$CHN$(C_2H_5)_2$[b]	3,4-Cl_2	H	331–336 dec	42	MeOH	F	$C_{24}H_{29}Cl_2N_5 \cdot 2HCl$	C, H, N
34	NHCH[$(CH_2)_2$]$_2$CHN$(C_2H_5)_2$[a]	3,5-Cl_2	H	290–291 dec	67	MeOH	F[d]	$C_{24}H_{29}Cl_2N_5 \cdot 2HCl \cdot 1.1H_2O$	C, H, N, H_2O
35	NHCH[$(CH_2)_2$]$_2$CHN$(C_2H_5)_2$[b]	3,5-Cl_2	H	332–334 dec	53	MeOH	F	$C_{24}H_{29}Cl_2N_5 \cdot 2HCl \cdot 0.5H_2O$	C, H, N, H_2O

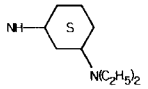
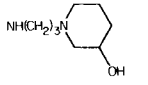
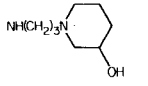
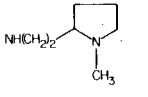
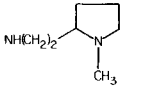
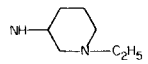
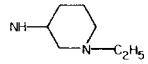
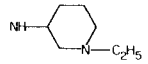
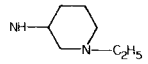
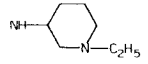
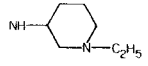
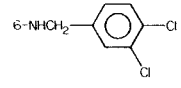
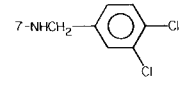
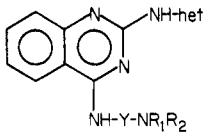
36	$NHCH[(CH_2)_2]_2CHN(C_2H_5)_2$[a]	3,5-Br_2	H	298–300 dec	59	2-PrOH–EtOH	F	$C_{24}H_{29}Br_2N_5 \cdot 2HCl \cdot 1.3H_2O$	C, H, N, H_2O
37		3,4-Cl_2	H	197 dec	24	2-PrOH	E	$C_{24}H_{29}Cl_2N_5 \cdot 1.9HCl \cdot 1.3H_2O$	C, H, N, Cl^-, H_2O
38	$NH(CH_2)_2N(CH_2)_6$	4-Cl	H	297–300[h]	66	MeOH	F[e]	$C_{20}H_{22}ClN_5 \cdot 2HCl$	C, H, N
39	$NH(CH_2)_2N(CH_2)_4$	3,4-Cl_2	H	296–298	48	MeOH	F[e]	$C_{20}H_{21}Cl_2N_5 \cdot 2HCl$	C, H, N
40	$NH(CH_2)_2N(CH_2)_4$	3,5-Cl_2	H	> 300	87	MeOH	F[e]	$C_{20}H_{21}Cl_2N_5 \cdot 2HCl$	C, H, N
41	$NH(CH_2)_2N(CH_2)_4$	3-Br	H	271–275 dec	28	EtOH–MeOH	D	$C_{20}H_{22}BrN_5 \cdot 2HCl$	C, H, N
42	$NH(CH_2)_2N(CH_2)_4$	3-Cl	H	260–265	74	EtOH–MeOH	F[e]	$C_{20}H_{22}ClN_5 \cdot 2HCl$	C, H, N
43	$NH(CH_2)_2N(CH_2)_4$	4-CF_3	H	270–273 dec	80	2-PrOH–EtOH	F[e]	$C_{21}H_{22}F_3N_5 \cdot 2HCl \cdot 1.2H_2O$	C, H, N, H_2O
44	$NH(CH_2)_2N(CH_2)_4$	3,5-$(CF_3)_2$	H	260–263 dec	67	2-PrOH	F[e]	$C_{22}H_{21}F_6N_5 \cdot 2HCl \cdot 0.5H_2O$	C, H, N, H_2O
45	$NH(CH_2)_2N(CH_2)_4$	4-SCH_3	H	292–294	61	EtOH	F[e]	$C_{21}H_{25}N_5S \cdot 2HCl \cdot 0.4H_2O$	C, H, N, H_2O
46	$NH(CH_2)_2N(CH_2)_4$	4-OH, 3-$CH_2N(C_2H_5)_2$	H	75–100	6	Et_2O	F	$C_{25}H_{34}N_6O$	C, H, N
47	$NH(CH_2)_3N(CH_2)_4$	3,4-Cl_2	H	297–299	55	MeOH–EtOAc	F[e]	$C_{21}H_{23}Cl_2N_5 \cdot 2HCl$	C, H, N
48	$NH(CH_2)_3N(CH_2)_4$	4-SCH_3	H	264–265	62	EtOH	F[e]	$C_{22}H_{27}N_5S \cdot 2HCl \cdot 0.5H_2O$	C, H, N, H_2O
49		4-Cl	H	271–276 dec	44	EtOH–MeOH	D	$C_{22}H_{26}ClN_5O \cdot 2HCl \cdot 1.5H_2O$	C, H, N, H_2O
50		4-I	H	258–260 dec	28	2-PrOH–EtOH	D	$C_{22}H_{26}IN_5O \cdot 2HCl \cdot H_2O$	C, H, N, H_2O
51	$NH(CH_2)_2N(C_2H_5)_2$	4-Cl	H	264–265[i]	20	2-PrOH	j	$C_{20}H_{24}ClN_5 \cdot 2HCl \cdot 0.1H_2O$	C, H, N, Cl, H_2O
52	$NH(CH_2)_2N(C_2H_5)_2$	3,4-Cl_2	H	280–282	69	MeOH–Et_2O	F[e]	$C_{20}H_{23}Cl_2N_5 \cdot 2HCl$	C, H, N
53	$NH(CH_2)_2N(C_2H_5)_2$	3,5-Cl_2	H	298–300	66	EtOH	F	$C_{20}H_{23}Cl_2N_5 \cdot 2HCl$	H, N; C[k]
54	$NH(CH_2)_2N(C_2H_5)_2$	2,4,5-Cl_3	H	268–272 dec	12	EtOH	F	$C_{20}H_{22}Cl_3N_5 \cdot 2HCl$	C, H, N
55	$NH(CH_2)_2N(C_2H_5)_2$	4-CF_3	H	243–245	76	EtOH–Et_2O	l	$C_{21}H_{24}F_3N_5 \cdot 2HCl \cdot 1.5H_2O$	C, H, N, Cl, F; O,[m] H_2O[n]
56	$NH(CH_2)_2N(C_2H_5)_2$	4-$N[(CH_2)_2]_2$-NCH_3	H	269–275 dec	62	EtOH	F[e]	$C_{25}H_{35}N_7 \cdot 3HCl \cdot 2H_2O$	C, H, N, Cl; H_2O[o]
57	$NH(CH_2)_2N(C_2H_5)_2$	4-OCH_3, 3-$CH_2N(C_2H_5)_2$	H	233–234	45	2-PrOH	F	$C_{26}H_{38}N_6O \cdot 3HCl \cdot 1.2H_2O$	C, H, N, Cl, H_2O
58	$NH(CH_2)_2N(C_2H_5)_2$	3,4-Cl_2-C_6H_3-CH_2[p]	H	169–172	22	MeOH–EtOAc	F[e]	$C_{21}H_{25}Cl_2N_5 \cdot 2HCl \cdot 0.7H_2O$	C, H, N, H_2O
59		3,4-Cl_2	6-Cl	306–312 dec	51	MeOH	F	$C_{21}H_{22}Cl_3N_5 \cdot 2HCl \cdot 1.4H_2O$	C, H, N, H_2O
60		3,5-Cl_2	6-Cl	315–320 dec	73	MeOH	F	$C_{21}H_{22}Cl_3N_5 \cdot 2HCl$	C, H, N

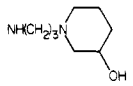
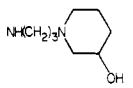
Table II (*Continued*)

no.	-NH-Y-NR_1R_2	X, Z	R	mp, °C	yield purified, %	purifn solvent	procedure	formula	anal.
61		3,4-Cl_2	6-Cl	316–319 dec	37	EtOH–MeOH	F	$C_{21}H_{22}Cl_3N_5 \cdot 2HCl \cdot 1.2H_2O$	C, H, N, Cl^-, H_2O
62		3,4-Cl_2	7-Cl	289–295 dec	51	MeOH	F	$C_{21}H_{22}Cl_3N_5 \cdot 2HCl \cdot 2.1H_2O$	C, H, N, Cl^-, H_2O
63		3,5-Cl_2	6-Cl	287–293 dec	52	2-PrOH–MeOH	F	$C_{21}H_{22}Cl_3N_5 \cdot 2HCl \cdot 0.9H_2O$	C, H, N, H_2O
64		3,5-Cl_2	7-Cl	240–250 dec	72	EtOH–MeOH	F	$C_{21}H_{22}Cl_3N_5 \cdot 2HCl \cdot 1.9H_2O$	C, H, N, Cl^-, H_2O
65		3,4-Cl_2	6,8-Cl_2	256–259	38	EtOH	F[e]	$C_{21}H_{21}Cl_4N_5 \cdot 2HCl \cdot 0.6H_2O$	C, H, N, H_2O
66		3,4-Cl_2	6-NO_2	273–276 dec	78	EtOH	E	$C_{21}H_{22}Cl_2N_6O_2 \cdot 2HCl \cdot 2H_2O$	C, H, N, Cl^-, H_2O
67	$NHCH[(CH_2)_2]_2CHN(C_2H_5)_2$[c]	3,4-Cl_2	6-Cl	320–322 dec	24	2-PrOH	F	$C_{24}H_{28}Cl_3N_5 \cdot 2HCl$	C, H, N
68	$NH(CH_2)_3N(CH_2)_4$	4-CF_3	6-Cl	297–299	48	EtOH	F[e]	$C_{22}H_{23}ClF_3N_5 \cdot 2HCl$	C, H, N
69	$NH(CH_2)_2N(C_2H_5)_2$	3,4-Cl_2	6-NO_2	270–272 dec	87	EtOH	E	$C_{20}H_{22}Cl_2N_6O_2 \cdot 2HCl \cdot H_2O$	C, H, N, Cl^-, H_2O
70	$NH(CH_2)_2N(C_2H_5)_2$	3,4-Cl_2	7-NO_2	293–296	96	2-PrOH	F[d]	$C_{20}H_{22}Cl_2N_6O_2 \cdot 1.8HCl \cdot 0.2H_2O$	C, H, N, Cl^-, H_2O
71	$NH(CH_2)_2N(C_2H_5)_2$	3,4-Cl_2	6-NH_2	287–289 dec	65	EtOH–MeOH	G	$C_{20}H_{24}Cl_2N_6 \cdot 2.8HCl \cdot 1.7H_2O$	C, H, N, Cl^-, H_2O
72	$NH(CH_2)_2N(C_2H_5)_2$	3,4-Cl_2	7-NH_2	310–313 dec	74	EtOH	G	$C_{20}H_{24}Cl_2N_6 \cdot 2HCl \cdot 1.1H_2O$	C, H, N, Cl^-, H_2O
73	$NH(CH_2)_2N(C_2H_5)_2$	3,4-Cl_2		136–137	70	CH_3CN	H	$C_{27}H_{28}Cl_4N_6$	C, H, N
74	$NH(CH_2)_2N(C_2H_5)_2$	3,4-Cl_2		162–165	53	CH_3CN	H	$C_{27}H_{28}Cl_4N_6$	C, H, N
75	$NH(CH_2)_2N(C_2H_5)_2$	4-OC_2H_5, 3-$CH_2N(C_2H_5)_2$	6-Cl	125–128	14	CH_3CN	F	$C_{27}H_{39}ClN_6O \cdot 3HCl \cdot 2H_2O$	C, H, N, Cl^-, H_2O
76	$NH(CH_2)_2N(C_2H_5)_2$	4-OC_2H_5, 3-$CH_2N(C_2H_5)_2$	7-Cl	216–218	34	CH_3CN	F	$C_{27}H_{39}ClN_6O \cdot 3HCl \cdot 0.5H_2O$	C, H, N, Cl^-, H_2O
77	$NH(CH_2)_2N(C_2H_5)_2$	4-OC_2H_5, 3-$CH_2N(CH_2)_4$	6-Cl	207–210 dec	20	CH_3CN	F	$C_{27}H_{37}ClN_6 \cdot 3.1HCl \cdot 1.2H_2O$	C, H, N, Cl^-, H_2O
78	$NH(CH_2)_2N(C_2H_5)_2$	4-OC_2H_5, 3-$CH_2N(CH_2)_4$	7-Cl	125–127 dec	41	CH_3CN	F	$C_{27}H_{37}ClN_6O \cdot 3.1HCl \cdot 2.8H_2O$	C, H, N, Cl^-, H_2O

[a] Isomer A (see Experimental Section, procedure A). [b] Isomer B. [c] A mixture of isomers A and B. [d] One equivalent of hydrogen chloride as a 28% solution of hydrogen chloride in 2-propanol was added to the reaction mixture. [e] One equivalent of concentrated hydrochloric acid was added to the reaction mixture. [f] H_2O: calcd, 7.19; found 6.56. [g] H: calcd, 7.32; found, 7.80. [h] Lit. (ref 5) mp 283–285 °C for the dihydrochloride 2.5-hydrate. [i] Lit. (ref 5) mp 253–254 °C for the dihydrochloride dihydrate. [j] Prepared as described in ref 5. [k] C: calcd, 50.33; found, 50.87. [l] Prepared using procedure of ref 5. [m] O: calcd, 5.07; found, 5.58. [n] Water in this compound could not be satisfactorily determined by microanalytical techniques. [o] H_2O: calcd, 6.23; found, 5.51. [p] N^2-[(3,4-Dichlorophenyl)methyl]-N^4-[2-(diethylamino)ethyl]-2,4-quinazolinediamine.

Table III. N^4-[(Dialkylamino)alkyl]-N^2-heterocyclic-2,4-quinazolinediamines



no.	-NH-Y-NR$_1$R$_2$	het	mp, °C[a]	yield purified, %	purifn solvent	procedure	formula	anal.
79	$NH(CH_2)_3N(CH_2)_4$	2-thiazolyl	226–228	14	EtOH	F[b]	$C_{18}H_{22}N_6S\cdot 2HCl\ 1.3H_2O$	C, H, N, Cl, H_2O
80	$NH(CH_2)_3N(CH_2)_4$	4-pyridyl	287–295	28	2-PrOH–EtOH	F[b]	$C_{20}H_{24}N_6\cdot 2.1HCl\cdot 0.3H_2O$	C, H, N, Cl, H_2O
81		2,1,3-benzothiadiazol-4-yl	275–280	14	EtOH–MeOH	D	$C_{22}H_{25}N_7OS\cdot 2HCl\cdot 0.5H_2O$	C, H, N, Cl, H_2O
82		4-phenyl-2-thiazolyl	258–260	10	2-PrOH–EtOH	D	$C_{25}H_{28}N_6OS\cdot 2HCl\cdot 2.1H_2O$	C, H, N, H_2O

[a] All compounds melted with decomposition. [b] See footnote *d*, Table II.

Suppressive Antimalarial Screening in Mice. The N^2-aryl-N^4-[(dialkylamino)alkyl]-2,4-quinazolinediamines VI (compounds **18–78**; Table II), the related quinazolinetriamine derivatives VII (compounds **79–82**; Table III), and the N^4-[(dialkylamino)alkyl]-N^2-phenyl-2,4-quinazolinediamines X (compounds, **83–116**, Table IV) were tested initially against a normal drug-sensitive strain of *P. berghei* in mice by the parenteral route.[21,22] The compounds were dissolved or suspended in sesame or peanut oil and were administered to mice in a single subcutaneous dose 72 h postinfection. Extension of the mean survival time of the treated mice is interpreted as evidence of antimalarial activity.[10] Insufficient amount of compounds **66** and **78** obtained precluded their evaluation in this screen. The data are summarized in Tables V–VII.

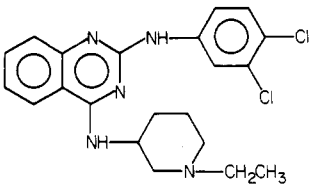
The vast majority of the N^2-aryl-N^4-[(dialkylamino)alkyl]-2,4-quinazolinediamines VI and related quinazolinetriamine derivatives VII were also evaluated orally against another normal drug-sensitive strain of *P. berghei* in mice.[23,24] The drugs were given continuously in the diet of mice for 6 consecutive days, and all drug doses were calculated as the free base equivalent. Results (Tables V and VI) are expressed both in terms of the SD_{90} and the quinine equivalent *Q*.

Both oral and parenteral base-line data for cycloguanil hydrochloride (III), quinine, and pyrimethamine are included for comparison purposes (Table V).

Results

Structure–Activity Relationships in Mice. Among the N^4-[(dialkylamino)alkyl]-N^2-phenyl-2,4-quinazolinediamines, VI, activity is retained over a range of N^4-[(dialkylamino)alkyl] side chains, provided that the N^2-phenyl ring contains either the 4-(trifluoromethyl), 3,4-dichloro, or 3,5-dichloro substituent. Thirteen analogues (compounds **21–24, 26, 31–35, 37, 47,** and **71**; Table II) possessed greater activity against *P. berghei* infections and were less toxic for mice when administered subcutaneously than the lead compound IIA (compound **51**; Table V). Comparison of the subcutaneous data with that of cycloguanil hydrochloride or pyrimethamine indicates that the instant compounds are better tolerated in mice while demonstrating only slightly lowered potency (cures at 80 and 160 mg/kg vs. cures at 40 mg/kg). Although all 56 of the compounds tested by the oral route were less active than cycloguanil hydrochloride or pyrimethamine, 29 exhibited antimalarial activity comparable with or superior to the lead compound IIa (compound **51**; Table V), and compound **43** proved to be as active or more active than quinine. In general, there was good agreement between subcutaneous and oral test results in mice.

In view of the overall promise of N^2-aryl-N^4-[(dialkylamino)alkyl]-2,4-quinazolinediamines and the activity of these compounds against drug-resistant strains of *P. berghei* (vide infra), N^2-(3,4-dichlorophenyl)-N^4-(1-ethyl-3-piperidinyl)-2,4-quinazolinediamine, XI (compound **30**;

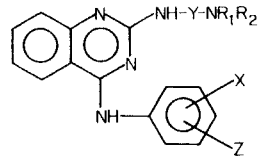


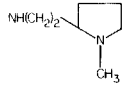
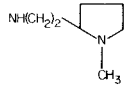
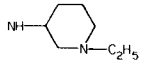
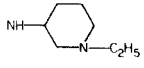
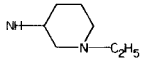
XI

Table II) was selected for preclinical toxicity studies. The drug exhibits strong suppressive and curative activity against *P. berghei* when administered to mice in a single subcutaneous dose of 160–640 mg/kg and is nontoxic for mice. When administered to mice in the diet for 6 days, it proved to be approximately 34 times as active as quinine against *P. berghei* (Table V). Unfortunately, XI and several related compounds were subsequently shown to be phototoxic,[25] and plans to study XI in man were abandoned.

(20) E. F. Elslager, L. M. Werbel, A. Curry, N. Headen, and J. Johnson, *J. Med. Chem.*, 17, 1915 (1974).
(21) 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 Drs. David P. Jacobus, T. R. Sweeney, and E. A. Steck of the Walter Reed Army Institute of Research.
(22) For a description of the test method, see ref 10.
(23) The oral antimalarial screening against P. *berghei* in mice was carried out by Dr. Paul E. Thompson and co-workers, Department of Pharmacology, Parke-Davis and Co., Ann Arbor, Mich.
(24) For a description of the test method, see ref 8 and 9.
(25) Private communication from the Walter Reed Army Institute for Research.

Table IV. N^2-[(Dialkylamino)alkyl]-N^4-phenyl-2,4-quinazolinediamines



no.	-NH-Y-NR$_1$R$_2$	X, Z	mp, °C	yield purified, %	purifn solvent	procedure	formula	anal.
83		3,4-Cl_2	272–274	61	EtOH	K	$C_{21}H_{23}Cl_2N_5 \cdot 2HCl \cdot 1.6H_2O$	C, H, N, Cl^-, H_2O
84		4-CF_3	265–267	40	2-PrOH–EtOH	K	$C_{22}H_{24}F_3N_5 \cdot 2HCl \cdot 1.8H_2O$	C, N, Cl^-, H_2O; H[a]
85	$NHCH[(CH_2)_2]_2CHN(CH_3)_2$	3,4-Cl_2	250–265	61	2-PrOH	K	$C_{22}H_{25}Cl_2N_5 \cdot 2HCl \cdot 1.8H_2O$	C, H, N, Cl^-, H_2O
86	$NHCH[(CH_2)_2]_2CHN(CH_3)_2$	4-CF_3	205 dec	75	EtOAc	L	$C_{23}H_{26}F_3N_5 \cdot 2HCl \cdot 1.8H_2O$	C, H, N, Cl^-, F, H_2O
87	$NHCH[(CH_2)_2]_2CHN(CH_3)_2$	3-Br	165 dec	87	EtOAc	L	$C_{22}H_{26}BrN_5 \cdot 1.8HCl \cdot H_2O$	C, H, N, Br, Cl^-, H_2O
88	$NHCH[(CH_2)_2]_2CHN(CH_3)_2$	3,5-Cl_2	165 dec	44	EtOAc	L	$C_{22}H_{25}Cl_2N_5 \cdot 1.9HCl \cdot 1.7H_2O$	C, H, N, Cl, Cl^-, H_2O
89	$NHCH[(CH_2)_2]_2CHN(CH_3)_2$	4-$N(CH_3)_2$	85–89	43	Et_2O	M	$C_{24}H_{32}N_6 \cdot 0.7H_2O$	C, H, N, H_2O
90		4-CF_3	274	34	2-PrOH	K	$C_{22}H_{24}F_3N_5 \cdot 2HCl \cdot 0.3H_2O$	C, H, N, Cl^-, F, H_2O
91		3,4-Cl_2	332–334	50	2-PrOH	K	$C_{21}H_{23}Cl_2N_5 \cdot 2HCl \cdot 0.5H_2O$	C, H, N, Cl, Cl^-, H_2O
92		3,5-Cl_2	308–309	31	2-PrOH	K	$C_{21}H_{23}Cl_2N_5 \cdot 2.4HCl \cdot 1.5H_2O$	C, H, N, Cl, Cl^-[b]
93	$NHCH_2CH[(CH_2)_2]_2NC_2H_5$	3,4-Cl_2	298–300 dec	67	2-PrOH	K	$C_{22}H_{25}Cl_2N_5 \cdot 2HCl \cdot 0.7H_2O$	C, H, N, Cl^-, H_2O
94	$NHCH_2CH[(CH_2)_2]_2NC_2H_5$	3,5-Cl_2	295–297 dec	91	2-PrOH	K	$C_{22}H_{25}Cl_2N_5 \cdot 2HCl \cdot 1.1H_2O$	C, H, N, Cl^-, H_2O
95	$NHCH_2CH[(CH_2)_2]_2NC_2H_5$	4-CF_3	>300	47	2-PrOH	K	$C_{23}H_{26}F_3N_5 \cdot 2HCl$	C, H, N
96	$NHCH[(CH_2)_2]_2CHN(C_2H_5)_2$	3,4-Cl_2	273–275	35	2-PrOH	K	$C_{24}H_{29}Cl_2N_5 \cdot 2HCl \cdot 1.1H_2O$	C, H, N, Cl^-, H_2O
97	$NHCH[(CH_2)_2]_2CHN(C_2H_5)_2$	3,5-Cl_2	206–207	17	2-PrOH	K	$C_{24}H_{29}Cl_2N_5 \cdot 2HCl \cdot 2.7H_2O$	C, H, N, Cl^-, H_2O
98	$NHCH[(CH_2)_2]_2CHN(C_2H_5)_2$	3-Br	245–275	59	2-PrOH–EtOH	K	$C_{24}H_{30}BrN_5 \cdot 2HCl \cdot 1.4H_2O$	C, H, N, Cl^-, H_2O
99	$NHCH[(CH_2)_2]_2CHN(C_2H_5)_2$	4-I	264–267 dec	55	2-PrOH	K	$C_{24}H_{30}IN_5 \cdot 2HCl \cdot 1.9H_2O$	C, N, Cl^-; H,[c] H_2O[d]
100	$NHCH[(CH_2)_2]_2CHN(C_2H_5)_2$	4-CF_3	295–300 dec	32	2-PrOH	K	$C_{25}H_{30}F_3N_5 \cdot 2HCl \cdot H_2O$	C, H, N, Cl^-, H_2O
101	$NHCH[(CH_2)_2]_2CHN(C_2H_5)_2$	4-SCH_3	260–265 dec	56	2-PrOH	K	$C_{25}H_{33}N_5S \cdot 2HCl \cdot 1.6H_2O$	C, H, N, Cl^-, H_2O
102	$NH(CH_2)_3N(CH_2)_4$	3,5-Cl_2	215–220	83	2-PrOH–EtOH	L	$C_{21}H_{23}Cl_2N_5 \cdot 2HCl \cdot 1.9H_2O$	C, H, N, Cl, Cl^-, H_2O

103	$NH(CH_2)_3N(CH_3)_2$	3,4-Cl_2	>320[e]	85	2-PrOH	K	$C_{22}H_{25}Cl_2N_5 \cdot 2HCl \cdot H_2O$	C, H, N, Cl, Cl^-; H_2O[f]
104	$NH(CH_2)_3N(CH_3)_2$	3,5-Cl_2	285–288	98	2-PrOH	K	$C_{22}H_{25}Cl_2N_5 \cdot 2HCl \cdot 0.2H_2O$	C, H, N, Cl, Cl^-, H_2O
105	$NH(CH_2)_3N(CH_3)_2$	4-CF_3	143–150	89	EtOAc	L	$C_{23}H_{26}F_3N_5 \cdot 2HCl \cdot 1.8H_2O$	C, H, N, Cl^-, F, H_2O
106	$NH(CH_2)_2N(C_2H_5)_2$	3,4-Cl_2	300	43	2-PrOH	K	$C_{20}H_{23}Cl_2N_5 \cdot 2HCl \cdot H_2O$	C, H, N, Cl, Cl^-[b]
107	$NH(CH_2)_2N(C_2H_5)_2$	4-CF_3	126–127	12	petr ether	M	$C_{21}H_{24}F_3N_5$	C, H, N
108	$NH(CH_2)_3N(C_2H_5)_2$	3,4-Cl_2	232	62	2-PrOH	K	$C_{21}H_{25}Cl_2N_5 \cdot 2HCl \cdot 1.6H_2O$	C, H, N, Cl, Cl^-, H_2O
109	$NH(CH_2)_3N(C_2H_5)_2$	3,5-Cl_2	256–259	66	2-PrOH	K	$C_{21}H_{25}Cl_2N_5 \cdot 2.25HCl \cdot 2.6H_2O$	C, H, N, Cl, Cl^-, H_2O
110	$NH(CH_2)_3N(C_2H_5)_2$	4-CF_3	224–228	67	2-PrOH	K	$C_{22}H_{26}F_3N_5 \cdot 2.1HCl \cdot 0.4H_2O$	C, H, N, Cl^-, F, H_2O
111	$NHCH(CH_3)(CH_2)_3N(C_2H_5)_2$	3,4-Cl_2	105–110	68	2-PrOH	L	$C_{23}H_{29}Cl_2N_5 \cdot 2HCl \cdot 1.8H_2O$	C, H, N, Cl, Cl^-, H_2O
112	$NHCH(CH_3)(CH_2)_3N(C_2H_5)_2$	3,5-Cl_2	105–108	78	EtOAc	L	$C_{23}H_{29}Cl_2N_5 \cdot 2.1HCl \cdot 2.1H_2O$	C, H, N, Cl, Cl^-, H_2O
113	$NHCH(CH_3)(CH_2)_3N(C_2H_5)_2$	3,4,5-$(OCH_3)_3$	45–50	91	Et_2O	M	$C_{26}H_{37}N_5O_3 \cdot 0.9H_2O$	C, H, N, H_2O
114	$NHCH(CH_3)(CH_2)_3N(C_2H_5)_2$	4-OH, 3-$CH_2N(C_2H_5)_2$	132–137	90	Et_2O	M	$C_{28}H_{42}N_6O \cdot 2.7HCl \cdot 2H_2O$	C, H, N, Cl^-, H_2O
115	$NHCH(CH_3)(CH_2)_3N(C_2H_5)_2$	4-NO_2	125–128	84	Et_2O	M	$C_{23}H_{30}N_6O_2 \cdot 2.2HCl \cdot 1.7H_2O$	C, H, N, Cl^-, H_2O
116	$NHCH(CH_3)(CH_2)_3N(C_2H_5)_2$	4-CF_3	115–120	92	Et_2O	M	$C_{24}H_{30}F_3N_5 \cdot 2.2HCl \cdot 2H_2O$	C, H, N, Cl^-, H_2O

[a] H: calcd, 5.73; found, 5.27. [b] Water in this compound could not be satisfactorily determined by microanalytical techniques. [c] H_2O: calcd, 5.80; found, 5.39. [d] H_2O: calcd, 5.50; found, 4.95. [e] Shrinks at 238 °C. [f] H_2O: calcd, 3.46; found, 3.87.

An early report on the "reverse" N^2-[(dialkylamino)alkyl]-N^4-phenyl-2,4-quinazolinediamine analogues (X) indicated that, although related compounds had been reported to be devoid of activity against *P. gallinaceum* infections in the chick, compound **85** (Table VII) exhibited curative activity at sc doses of 160–640 mg/kg and, moreover, was shown not to exhibit phototoxic liability. Therefore, a more thorough exploration of this series was conducted, and the results are reported in Table VII.

Examination of the overall results for the N^2-[(dialkylamino)alkyl]-N^4-phenyl-2,4-quinazolinediamines (Table VII) indicates that, although antimalarial activity is retained, the level of potency is generally inferior to that of the N^2-aryl-N^4-[(dialkylamino)alkyl]-2,4-quinazolinediamines [compare compounds **19**, **22**, **26**, **30**, **31**, **52**, **55** (Table V) vs. **83**, **85**, **88**, **91**, **93**, **106**, **107**, respectively (Table VII)]. However, two members of this series N^2-[dialkylamino)alkyl]-N^4-phenyl-2,4-quinazolinediamines **85** and **93**; Table VII) did possess greater activity and showed less toxicity for the mice than the lead compound, IIA (compound **51**; Table V). Comparison of the activity of the N^2-[(dialkylamino)alkyl]-N^4-phenyl-2,4-quinazolinediamines with that of cycloguanil hydrochloride or pyrimethamine indicates that, although many compounds were better tolerated by mice, none were as active vs *P. berghei* as the two reference drugs.

Drug-Resistance Studies in Mice. To determine whether the diaminoquinazolines represented a unique chemical type with regard to apparent mode of action, one of the more promising members of the series, namely N^2-(3,4-dichlorophenyl)-N^4-[2-(1-methyl-2-pyrrolidinyl)-ethyl]-2,4-quinazolinediamine (compound **19**), was selected for evaluation against representative drug-resistant lines of *P. berghei* in the mouse.[26,27] The drug was administered continuously in the diet at levels of 0.0313, 0.008, 0.004, and 0.002% for 6 days to mice infected with the drug-sensitive parent line P and the following drug-resistant lines: line T, completely (>300-fold) resistant to cycloguanil hydrochloride; line S, completely (>600-fold) resistant to 4,4′-sulfonyldianiline (DDS); and line C, 77-fold resistant to chloroquine. The results (Figure 1) indicate that this material is essentially fully active against the cycloguanil (T) and DDS (S) resistant lines, albeit possessing some cross-resistance against the chloroquine line C. These results provide support for the hypothesis that compound **19** and related diaminoquinazolines have a different mode of action from cycloguanil and pyrimethamine.

Conclusion

The N^4-[(dialkylamino)alkyl]-N^2-phenyl-2,4-quinazolinediamines exhibit antimalarial activity over a wide range of structural variations. The inability to separate phototoxicity from antimalarial activity and the pressure of other structural classes with much greater potency has required that we terminate efforts in this area.

Experimental Section[28,29]

Preparation of 2-Chloro-*N*-[(dialkylamino)alkyl]-4-quinazolinamines, V (1–17; Table I). Procedure A. To a

(26) Testing against resistant strains of *P. berghei* was carried out by Dr. Paul E. Thompson and co-workers, Department of Pharmacology, Parke-Davis Co., Ann Arbor, Mich.
(27) For a description of the test method, see ref 8 and 9.
(28) Melting points (corrected) were taken on a Thomas-Hoover capillary melting point apparatus.
(29) Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

Table V. Parenteral and Oral Suppressive Antimalarial Effects of N^4-[(Dialkylamino)alkyl]-N^2-phenyl-2,4-quinazolinediamines against Trophozoite-Induced *P. berghei* in Mice

	MST; C or T[a] after single sc dose, mg/kg						diet, 6 days		
compd	640	320	160	80	40	20	no. of mice	SD_{90},[b] (mg/kg)/day	Q[c]
18	12.2; C2	14.4	10.7	4.4	1.1	0.8	28	9.8	7.6
	22.3; C3		10.2		0.8				
19	29.8; C4	20.8; C2	13.2	8.0	4.0	3.0	28	10.5	7.1
	28.9; C3		13.9		3.9				
20	20.3; C3	15.0	11.4	7.8	5.2	1.6	21	6	12.4
	21.9; C2		11.7		4.5				
21	25.8; C4	15.5; C2	10.5; C2	3.2	1.2	1.0	21	16	4.7
22	C5	25.9; C4	22.9; C4	11.4; C3	4.5	0.3	14	7.8	9.6
	C5		25.9; C3		4.1				
23	C5	25.9; C4	25.4; C3	10.4; C1	9.7	0.9	14	8.5	8.8
	C5		27.4; C3		9.9				
24	C5	24.3; C3	20.1; C1	6.4	4.8	0.4	28	9.2	8.2
	C5		16.5; C2		3.8				
25	C5	24.9; C4	17.5	10.9	9.7	5.1	21	9.3	8.0
	C5		16.9		9.3				
26	C5	C5	19.1; C2	11.6	4.0	3.6			
	C5	27.8; C4	24.9; C4	9.0	13.3	3.6			
		C5	27.9; C4	23.9; C4	12.7	1.7			
27			3.7	2.7	0.5	0.3	7	>69	<1.1
28	T5	T5	13.0; C3	13.0; C3	7.7	7.5	14	155	0.5
			16.3; C2		7.2				
29	28.3; C3	20.0	10.6	3.0	0.4	0.2	21	38	2.0
	28.8; C3		11.4		0.6				
30	13.8; C3	13.8	6.2	1.0	0.6	0.4	28	2.2	34
	24.2; C2		7.3		0.5				
31	C5	C5	23.9; C4	9.1	7.5	0.7	21	8.4	8.9
			27.9; C4		7.3				
32	C5	C5	25.9; C3	14.1	9.1	7.9	21	8.5	8.8
	C5		25.9; C4		8.5				
33	C5	22.9; C4	13.9; C1	10.4; C1	10.1	0.9	21	8.5	8.8
	C5		13.7; C1		10.5				
34	C5	C5	26.9; C2	13.4; C1	7.7	2.3	14	9.0	8.3
	C5		23.4; C3		7.5				
35	C5	C5	23.9; C4	21.9; C4	9.6; C2	5.5	21	8.5	8.8
	C5		24.9; C3		8.9; C2				
36	C5	26.2; C2	8.7	4.3	1.1	0.3	14	3.3	2.3
	C5		9.1		0.7				
37	C5	C5	22.8; C2	8.0	5.0	1.0	21	17.5	4.2
	C5		23.1; C2		4.8				
38	25.4; C3	18.2; C1	6.1	1.1	0.7	0.1	14	68	1.1
	24.6; C2		6.7		1.1				
39	15.9	9.3	6.5	3.1	2.1	0.3	14	70	1.1
	13.7		7.1		2.3				
40	10.7	5.9	3.5	1.7	0.9	0.5	14	80	0.9
	10.3		4.1		1.3				
41	8.4	5.0	4.4	0.4	0.2	0.2	14	91	0.8
	8.1		4.0		0.8				
42	10.2	4.2	2.8	1.4	0.6	0.4	14	97	0.8
	11.1	4.2	3.5		0.7				
43	16.2	10.2	4.8	2.4	0.4	0.2	21	37	2.0
	13.2		3.4		0.8				
44	1.0		0.2		0.2		14	105	0.5
45	T5	10.3	5.9	3.3	0.9	0.7	21	35	2.1
			4.7		0.3				
46	C1; T2	C1; T2	10.7	2.1	1.7	0.3			
47	C5		C4		5.2		28	12	6.3
48	T5		6.8		1.0		14	47	1.6
49	26.1; C2	17.5; C2	10.4	4.6	2.2	0.2	28	11	6.8
	23.9; C2		11.3		2.5				
50	20.1; C2	13.1; C1	8.0	4.0	1.2	1.0	21	25	3.0
	24.1; C1		5.8		0.8				
51	T5	C3; T2	11.1	6.2	4.1	1.6	21	35	2.1
			C2		4.6				
52	C5		7.0		1.0		21	24	3.1
53	22.1; C2	12.2	8.2	3.2	0.2	0.2	14	120	0.6
	20.8; C3		9.0		2.0				
54	1.2		0.4		0.4				
55	C4	C4	C1	7.3	1.7	0.3	14	91	0.8
	C4		8.9		1.1				
56	6.8; T3	5.2	4.8	3.4	1.0	0.2	14	50	1.5
	6.3; T3		4.2		0.8				
57	C2; T1	C2; T1	8.6	5.6	2.8	0.4	14	40	1.9
	C1; T2		9.1		2.7				

Table V (*Continued*)

compd	MST; C or T[a] after single sc dose, mg/kg						diet, 6 days		
	640	320	160	80	40	20	no. of mice	SD_{90},[b] (mg/kg)/day	Q^c
58	T5		0.9; T1		0.7				
59		14.2; C2	6.1	2.7	1.1	0.5	21	18.5	4.0
		13.6; C2		2.5		0.5			
60	C5	21.1; C1	11.1; C1	5.0	3.6	0.6	21	20	3.8
	C5		10.3; C1		4.0				
61			0.3		0.1	0.1	14	46	1.6
62		0.3		0.3		0.1	14	63	1.2
63	7.8; C3	6.4	1.0	0.6	0.2	0.2	14	36	2.1
	4.8; C3		1.0		0.4				
64	1.6		0.4		0.2		14	73	1.0
65			0.5		0.3	0.3			
66							14	34	2.2
67	12.9; C4	27.2; C2	13.9; C1	14.9	13.3	1.3			
	18.4; C3		12.9; C1		12.9				
68	26.5; C2	14.6; C1	4.6	1.6	0.4	0.2	14	22	3.4
	23.3; C3		4.0		0.4				
69	20.6	10.4	7.0	1.2	0.4	0.2	14	30	2.5
		10.9	7.3	1.5	0.7	0.3			
70	26.9; C3	9.5	0.9	0.9	0.3	0.3	21	9.2	8.1
	21.9; C4		1.1		0.3				
71	C3; T2	C5	29.8; C4	6.8	3.8	1.6	14	47	1.6
		C5	C5	6.8	3.8	2.0			
72	29.8; C4	16.8; C3	13.2	6.0	3.2	0.6	21	30.5	2.4
		16.9; C3	13.5	6.3	3.5	0.9			
73		5.6	3.8	0.4	0.2	0.2	14	69	1.1
			3.8	0.4	0.4	0.2			
74	8.9	1.7	1.3	0.3	0.1	0.1	14	82	0.9
		2.0	1.0	0.6	0.2	0.2			
		2.5	0.7	0.3	0.3	0.3			
75	T5	5.8; T4	4.3; T1	3.2	0.8	0.2	14	45	1.6
	T5		4.3; T1		0.8				
76	T5		0.8		0.6		7	>30	<2.5
77	13.3; T3	7.8; T2	4.8	1.0	0.6	0.2	7	>33	<2.3
	12.8; T3		4.6		0.2				
78							7	>34	<2.2
cycloguanil hydrochloride	T5	C3; T2	C5	21.6; C2	13.4; C1	7.9	40	2.1	35
		C3; T2	C5	21.9; C2	13.4; C1	8.1			
pyrimethamine	C1; T2	C2; T3	C5	C3	C1	7.7	42	0.28	270
quinine[e]	5.4	3.2	2.0	1.4	1.0	0.2	224	74.5	1.0

[a] MST 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 6.5 days. T signifies the number of toxic deaths occurring on days 2–5 after infection which are attributed to drug action. C indicates the number of mice surviving at 60 days postinfection and termed "cured"; data to establish parasitological cure based on subinoculation are unavailable. Each entry at each dose level represents results with a five-animal group. [b] All doses were calculated as the free base equivalent. SD_{90} represents the daily dose (mg/kg) required for 90% suppression of the parasitemia in treated mice relative to control mice. The SD_{90} was estimated graphically using semilog paper. [c] The quinine equiv Q is the ratio for the SD_{90} of quinine hydrochloride to the SD_{90} of the test substance under comparable experimental conditions. [d] N^2-[(3,4-Dichlorophenyl)methyl]-N^4-[2-(diethylamino)ethyl]-2,4-quinazolinediamine. [e] Tested parenterally as the sulfate and by diet as the hydrochloride.

Table VI. Parenteral and Oral Suppressive Antimalarial Effects of N^4-[(Dialkylamino)alkyl]-N^2-heterocyclic-2,4-quinazolinediamines against Trophozoite-Induced *P. berghei* in Mice

no.	MST; C or T[a] after single sc dose, mg/kg						diet, 6 days		
	640	320	160	80	40	20	no. of mice	SD_{90},[b] (mg/kg)/day	Q^c
79	0.9; T3		0.3		0.3				
80	T5		0.9; T2		0.3		7	>37	<2.0
81	0.0		0.0		0.0				
82	0.8		0.4		0.2		7	>147	<0.5

[a–c] See corresponding footnotes in Table V.

stirred solution of 29.0 g (0.014 mol) of 2,4-dichloroquinazoline in 375 mL of nitrobenzene was added dropwise 24.7 g (0.014 mol) of *N,N*-diethyl-1,4-cyclohexanediamine with a concomitant rise in temperature from 27 to 40 °C. The reaction mixture was allowed to stir for 3 h and then to remain at ambient temperature overnight. The precipitate was collected, washed with ether, and boiled twice in 250 mL of *i*-PrOH to give 19.8 g (37%) of N'-(2-chloro-4-quinazolinyl)-*N,N*-diethyl-1,4-cyclohexanediamine hydrochloride (4): mp 276–279 °C dec; TLC (sample dissolved in water, made basic with NaOH, and extracted with $CHCl_3$ and the extract spotted on alumina and eluted with EtOAc) showed a single spot, R_f 0.5, and is designated isomer A (cis or trans isomer).

The combined nitrobenzene–ether wash from above deposited additional precipitate upon standing, which was collected and recrystallized from CH_3CN to give 6.6 g of product, mp 232–236 °C dec. The *i*-PrOH washes from above also deposited precipitates, which were collected, combined, and dried to give an additional 9.8 g of product (5): mp 233–235 °C; TLC (same system

Table VII. Parenteral and Oral Suppressive Antimalarial Effects of N^2-[(Dialkylamino)alkyl]-N^4-phenyl-2,4-quinazolinediamines against Trophozoite-Induced *P. berghei* in Mice

	MST; C or T[a] after single sc dose, mg/kg					
no.	640	320	160	80	40	20
83	C1; T2	C1; T1	6.9	0.5	0.5	0.3
		11.2; T2	7.1	0.7	0.5	0.3
84	7.7	4.1	1.5	0.5	0.3	0.3
		4.3	1.7	0.5	0.3	0.3
85	C3; T2	9.9; C3	12.6; C2	7.9	4.1	0.3
	C3; T1		12.9; C2		3.7	
86	0.7		0.7		1.1	
87	0.7		0.7		−0.1	
88	5T		2.6	1.2	0.0	−0.2
			5.7		1.7	
89	1.1		0.6		−0.2	
90	3.4	0.9	0.2	−0.1	0.2	
	3.1		0.3		−0.1	
91	9.5	2.9	0.9	0.9	0.9	0.9
	10.6		2.2		−0.4	
92	4.4	2.4	0.4	0.2	0.2	0.4
	6.3		0.3		0.1	
93	C5	C5	13.4; C1	6.7	2.1	0.5
		C5		6.9	2.1	0.7
94	C3, T2	C3; T2	5.7	2.5	0.5	0.5
		C3; T2	5.9; T1	2.7	0.5	0.3
95	21.9; C4	8.9; C3	7.3	0.5	0.5	0.3
		9.4; C3	3.9; C1	0.7	0.5	0.3
96	C5	14.4; C3	17.2; C1	2.9	0.5	0.3
		14.9; C3	15.6; C2	3.1	0.5	0.3
97	C5	7.9	0.7	0.5	0.5	0.3
		8.1	0.5	0.5	0.3	0.3
98	C3; T2	12.9	10.3	2.5	0.3	0.3
		12.7	10.1	2.7	0.5	0.5
99	C3; T2	9.4; C2	8.6; C2	0.7	0.5	0.3
		9.9; C3	14.4; C1	0.5	0.5	0.3
100	C3; T2	C5	9.7	0.7	0.5	0.5
		C5	9.5	0.5	0.5	0.3
101		11.7	5.7	1.1	0.7	0.5
			5.7	1.3	0.7	0.7
102	1.2		0.8		0.4	
103	3.0	1.6	0.4	−0.4	−0.4	−0.2
	4.1		0.1		0.1	
104	1.6		0.2		0.2	
105	2.4		−0.2		−0.2	
106	10.3	3.2	0.2; 1T	0.2	0.2	0.2
	5.4		0.9		0.4	
	5.9				−0.1	
107	5.3	2.8	0.2	−0.2	0.2	0.2
	5.5		−0.1		−0.1	
108	9.8; C1	8.4	4.6	2.8	0.8	0.0
	10.5; C1		5.2		0.2	
109	14.5; C2	5.0	3.0	1.4	0.2	0.2
	15.7; C2		2.7		0.9	
110	10.1	9.2	0.6	0.8	−0.2	0.0
	7.5		0.3		0.6	
111	4.7	1.3	1.9	0.3	0.3	0.1
	5.8		−0.2		0.4	
112	4.9	3.1	1.1	−0.1	−0.5	0.1
	4.4		1.2		0.8	
113	3.5	0.5	0.3	0.3	−0.3	0.3
	5.0		0.6		0.2	
114	3.1; C3	7.4	3.8	1.4	0.6	0.0
	5.6		1.6		0.2	
115	5T	5T	2.6	1.4	0.8	0.0
	4.3		3.2		0.6	
116	1.6		0.0		−0.6	

[a] See footnote *a*, Table IV.

as above) showed single spots for both crops, R_f = 0.2, and they are designated isomer B (trans or cis isomer). The yield of isomer B was 16.4 g (30%), and the total yield for both isomers was 36.2 g (67%).

Procedure B. To a solution of 12.5 g (0.054 mol) of 2,4,6-trichloroquinazoline in 500 mL of ether was added dropwise a solution of 7.4 g (0.058 mol) of 1-methyl-2-pyrrolidineethanamine in 20 mL of ether. The mixture was stirred for 20 h and concentrated to 150 mL. The precipitate that formed was collected and recrystallized from *i*-PrOH to give 10.8 g (55%) of 2,6-dichloro-*N*-[2-(1-methyl-2-pyrrolidinyl)ethyl]-4-quinazolinamine monohydrochloride (**9**), mp 176–179 °C dec.

Procedure C. To a solution of 8.3 g (0.040 mol) of 2,4-dichloroquinazoline in 100 mL of ether was added dropwise 4.7 g (0.040 mol) of 1-pyrrolidineethanamine. The mixture was stirred for 1.5 h, and the precipitate that formed was collected, added to dilute NaOH solution, and extracted with ether. The extracts were combined, dried (anhydrous $MgSO_4$), and concentrated to a solid in vacuo. Recrystallization from cyclohexane provided 6.2 g (56%) of 2-chloro-*N*-[2-(1-pyrrolidinyl)ethyl]-4-quinazolinamine (**6**), mp 136–138 °C.

The reactions forming compounds **14**, **12**, and **17** were run in ether–ethanol (25:1), ethanol, and methanol, respectively, due to the insolubility of the starting materials in ether.

The free base of **3** could not be crystallized, and the hydrochloride salt was made by bubbling gaseous HCl through an ether solution of **3** and collecting the resulting precipitate.

The other requisite 2-chloro-*N*-[(dialkylamino)alkyl]-4-quinazolinamines not listed in Table I were used directly in the next step without isolation (see procedures D and E).

Preparation of N^4-[(dialkylamino)alkyl]-N^2-phenyl- and -heterocyclic-2,4-quinazolinediamines, VI (18–82; Tables II and III). Procedure D. To a stirred solution of 29.9 g (0.15 mol) of 2,4-dichloroquinazoline in 515 mL of nitrobenzene was added dropwise 19.2 g (0.15 mol) of 1-methyl-2-pyrrolidineethanamine with a concomitant rise in temperature from 25 to 35 °C and formation of a precipitate. The mixture was allowed to cool to room temperature and treated with sufficient *i*-PrOH to dissolve the solid. To one-fifth of the resulting solution[30] was added 4.9 g (0.030 mol) of 3,4-dichlorobenzenamine and the mixture was heated to 180 °C, allowing the *i*-PrOH to boil off. After 1 h the reaction mixture was cooled to 25 °C and the precipitate that accumulated was collected, washed with ether, ground with Me_2CO, and recrystallized from an *i*-PrOH–EtOH (1:5) mixture using decolorizing charcoal to give 5.4 g (35%) of N^2-(3,4-dichlorophenyl)-N^4-[2-(1-methyl-2-pyrrolidinyl)ethyl]-2,4-quinazolinediamine dihydrochloride 1.6 hydrate (**19**), mp 268–272 °C.

Procedure E. A solution of 4.5 g (0.023 mol) of 2,4-dichloroquinazoline and 2.9 g (0.023 mol) of 1-ethyl-3-piperidinamine in 150 mL of EtOH was warmed to 40 °C for 15 min and allowed to stir at room temperature for 15 h. The reaction mixture was treated with 3.7 g (0.023 mol) of 3,4-dichlorobenzenamine and 2 mL of concentrated HCl and heated under reflux for 5 h. The reaction mixture was allowed to cool, and the precipitate that formed was collected and recrystallized from MeCN to give, after drying in vacuo (50 °C), 8.1 g (71%) of N^2-(3,4-dichlorophenyl)-N^4-(1-ethyl-3-piperidinyl)-2,4-quinazolinediamine dihydrochloride 1.5 hydrate (**30**), mp 249–251 °C.

The reactions to provide compounds **66** and **69** were run without using concentrated hydrochloric acid in the final step.

Procedure F. A mixture of 6.2 g (0.017 mol) of *N*-(2-chloro-4-quinazolinyl)-*N*,*N*-diethyl-1,4-cyclohexanediamine monohydrochloride 0.3-hydrate (**4**) and 2.7 g (0.017 mol) of 3,5-dichlorobenzenamine in 50 mL of EtOH was heated under reflux for 3 h and cooled to room temperature. The precipitate that accumulated was collected and recrystallized from MeOH to give 4.7 g (53%) of N^2-(3,5-dichlorophenyl)-N^4-[4-(diethylamino)-cyclohexyl]-2,4-quinazolinediamine dihydrochloride 0.5-hydrate (**35**): mp 332–334 °C; TLC (alumina developed in EtOAc; product spotted as the free base) showed a single spot, R_f 0.4, and is designated isomer B.

Compounds **46**, **58**, and **75–78** could not be induced to crystallize from their reaction mixtures. Therefore, for compound **46**, the mixture was concentrated to a paste in vacuo and triturated with hot MeCN, and the resulting solid was dissolved in H_2O, made basic with 2 N NaOH, and extracted with ether. The extracts were dried ($MgSO_4$) and HCl was bubbled through the solution

(30) The solution was assumed to contain 9.8 g (0.030 mol) of 2-chloro-*N*-[2-(1-methyl-2-pyrrolidinyl)ethyl]-4-quinazolinamine monohydrochloride.

to form a hygroscopic precipitate. The free base was remade as above, and the ether extracts were concentrated in vacuo to give **46** as an amorphous solid.

For compound **58**, the reaction mixture was poured into 600 mL of ether containing 5 mL of a 28% HCl in *i*-PrOH solution, and the resulting oil was dissolved in H_2O, made basic with 2 N NaOH, and extracted with ether. The extracts were dried ($MgSO_4$) and concentrated to an oil in vacuo, and the oil was dissolved in a minimum amount of a 28% HCl in *i*-PrOH solution. The solution was poured into 1 L of ether, and the precipitate was collected and recrystallized to give **58**.

For compounds **75–78**, the reaction mixtures were concentrated in vacuo to dryness and the residues were recrystallized to give the products.

Preparation of N^2-(3,4-Dichlorophenyl)-N^4-[2-(diethylamino)ethyl]-2,4(6 and 7)-quinazolinetriamines, VIb (71–72; Table II). Procedure G. To a suspension of 6.7 g (0.013 mol) of N^2-(3,4-dichlorophenyl)-N^4-[2-(diethylamino)ethyl]-7-nitro-2,4-quinazolinediamine dihydrochloride (**70**) in 400 mL of MeOH was added a slurry of 2.0 g (0.037 mol) of NaOMe in 100 mL of MeOH. Upon heating a solution resulted, which was poured with stirring into 2.5 L of H_2O containing 10 mL of 50% NaOH solution. The resulting precipitate was collected, washed with H_2O, and dried to give 5.5 g (96%) of the free base of **70**. A solution of 4.8 g (0.011 mol) of this material in 100 mL of 2-methoxyethanol was hydrogenated over 0.5 g of Raney nickel at 51 psig and 26 °C for 23.6 h. The mixture was filtered and the filtrate was concentrated to dryness in vacuo. The residue was dissolved in ether and filtered, and an excess of a 28% solution of HCl in *i*-PrOH was added to the filtrate. The precipitate was collected, washed with ether, and recrystallized from EtOH to give 4.0 g (74%) of N^2-(3,4-dichlorophenyl)-N^4-[2-(diethylamino)ethyl]-2,4,7-quinazolinetriamine dihydrochloride 1.1-hydrate (**72**), mp 310–313 °C dec.

Preparation of N^2-(3,4-Dichlorophenyl)-N^6-[(3,4-dichlorophenyl)methyl]-N^4-[2-(diethylamino)ethyl]-2,4(6 and 7)-quinazolinetriamine, VIIa,b (73 and 74; Table II). Procedure H. A suspension of 5.0 g (0.0090 mol) of N^2-(3,4-dichlorophenyl)-N^4-[2-(diethylamino)ethyl]-2,4,6-quinazolinetriamine 2.8 hydrochloride 1.7 hydrate (**71**) in 300 mL of H_2O was made strongly alkaline with a 50% NaOH solution and extracted with 300 mL of $CHCl_3$. The extract was washed with H_2O, dried (anhydrous K_2CO_3), and concentrated to dryness in vacuo. The residue was treated with 1.9 g (0.011 mol) of 3,4-dichlorobenzaldehyde, and the mixture was heated on a steam bath under vacuum for 30 min and triturated in benzene. The yellow solid was collected and the filtrate deposited additional material upon standing. The two crops were combined and recrystallized from MeCN to give 3.2 g (62%) of N^2-(3,4-dichlorophenyl)-N^6-[(3,4-dichlorophenyl)methylene]-N^4-[2-(diethylamino)ethyl]-2,4,6-quinazolinetriamine, mp 159–161 °C.

To a solution of 3.1 g (0.0054 mol) of the above intermediate in 100 mL of 2-methoxyethanol was added 0.8 g (0.021 mol) of sodium tetrahydroborate in small portions over a period of 2 h. The mixture was stirred at room temperature for 1 h and poured into iced H_2O. The precipitate was collected, dried, and recrystallized from MeCN to give 2.2 g (70%) of N^2-(3,4-dichlorophenyl)-N^6-[(3,4-dichlorophenyl)methyl]-N^4-[2-(diethylamino)-ethyl]-2,4,6-quinazolinetriamine (**73**), mp 136–137 °C.

Preparation of 2-[[(Dialkylamino)alkyl]amino]-4-quinazolinols. Procedure I. A mixture of 15.0 g (0.083 mol) of 2-chloro-4-quinazolinol and 10.8 g (0.083 mol) of *N,N*-diethyl-1,3-propanediamine in 85 mL of benzene was heated under reflux for 16 h. The reaction mixture was allowed to cool to room temperature, and the precipitate was collected, dissolved in a minimum amount of EtOH, and poured into 600 mL of H_2O. The resulting suspension was made basic with a saturated Na_2CO_3 solution and stirred for 1.5 h. The precipitate was collected and dried to give 19.5 g (86%) of crude 2-[[3-(diethylamino)-propyl]amino]-4-quinazolinol,[31] which was used directly in the chlorination step.

Procedure J. A mixture of 10.8 g (0.060 mol) of 2-chloro-4-quinazolinol, 10.2 g (0.060 mol) of *N,N*-diethyl-1,4-cyclohexanediamine, and 1 mL of a 25% solution of HCl in *i*-PrOH in 40 mL of EtOH was heated under reflux for 6 h, treated while hot with additional HCl in *i*-PrOH until the solution was acidic, and allowed to cool to room temperature overnight. The precipitate that formed was collected and the filtrate was poured into 500 mL of ether. The gum that formed was triturated with additional ether to give a second solid. The two solids were combined and dissolved in a minimum amount of H_2O. The solution was made basic with a saturated Na_2CO_3 solution and extracted with $CHCl_3$. The extracts were combined, dried (anhydrous Na_2SO_4), and concentrated in vacuo to give 10.0 g (53%) of crude 2-[[4-(diethylamino)cyclohexyl]amino]-4-quinazolinol, which was used directly in the chlorination step: TLC (alumina plates developed in EtOH) indicated the presence of cis and trans isomers, R_f 0.30 and 0.48.

2-[[4-(Diethylamino)-1-methylbutyl]amino]-4-quinazolinol. A mixture of 15.0 g (0.083 mol) of 2-chloro-4-quinazolinol and 25.5 g (0.16 mol) of N^1,N^1-diethyl-1,4-pentanediamine was heated with stirring on a steam bath for 14 h, dissolved in 75 mL of EtOH, and added to 500 mL of H_2O. The aqueous mixture was made basic with a saturated Na_2CO_3 solution and extracted with EtOAc. The extracts were combined, dried (anhydrous Na_2SO_4), and concentrated in vacuo to give 26.9 g (97%) of the product as a brown oil, which was used directly in the chlorination step: ^1H NMR and IR were consistent with the structure; VPC showed the material to contain 92.8% of a major component.

The other requisite 2-[[(dialkylamino)alkyl]amino]-4-quinazolinols were prepared in a manner similar to procedures I–J above, with the intermediates being partially purified and chlorinated directly to the corresponding 4-chloro-*N*-[(dialkylamino)alkyl]-2-quinazolinamines without microanalyses.

Preparation of N^2-[(Dialkylamino)alkyl]-N^4-phenyl-2,4-quinazolinediamines, X (83–116; Table IV). Procedure K. A mixture of 3.0 g (0.010 mol) of 2-[[3-(diethylamino)propyl]-amino]-4-quinazolinol and 50 mL of $POCl_3$ was heated under reflux for 1.5 h, concentrated in vacuo to a thick syrup, and poured into stirred ice–water. The mixture was chilled, made basic with a 50% NaOH solution, and poured into ether. The layers were separated and the aqueous phase was extracted twice with ether. The extracts were combined, dried (anhydrous K_2CO_3), and concentrated in vacuo to give 1.7 g (0.0057 mol, 52%) of *N'*-(4-chloro-2-quinazolinyl)-*N,N*-diethyl-1,3-propanediamine as a brown oil. This residue was combined with 0.9 g (0.0057 mol) of 3,4-dichlorobenzenamine, 3.0 mL of a 25% solution of HCl in *i*-PrOH, and 50 mL of *i*-PrOH, and the mixture was heated under reflux for 3 h. The red solution was chilled, and the precipitate that formed was collected, washed with cold *i*-PrOH, and dried in vacuo (90 °C) to give 1.7 g (62%) of N^4-(3,4-dichlorophenyl)-N^2-[3-(diethylamino)propyl]-2,4-quinazolinediamine dihydrochloride 1.6 hydrate (**108**), mp 232 °C.

Procedure L. A mixture of 8.2 g (0.029 mol) of 2-[[4-(dimethylamino)cyclohexyl]amino]-4-quinazolinol and 100 mL of $POCl_3$ was heated under reflux for 2 h, concentrated in vacuo to a thick syrup, and poured into stirred ice–water. The mixture was chilled, made basic with a 50% NaOH solution, and poured into ether. The mixture was filtered to remove NaCl, the layers of the filtrate were separated, and the aqueous phase was extracted twice with ether. The extracts were combined, dried (anhydrous K_2CO_3), and concentrated in vacuo to give 8.0 g (87%) of 94% pure (by VPC) *N'*-(4-chloro-2-quinazolinyl)-*N,N*-dimethyl-1,4-cyclohexanediamine as a paste. A mixture of 4.0 g (0.12 mol) of this residue, 2.3 g (0.13 mol) of 3-bromobenzenamine, 4.0 mL of a 25% solution of HCl in *i*-PrOH, and 70 mL of *i*-PrOH was heated under reflux for 3 h and then chilled. The cold solution was poured into 5 volumes of ether, and the hygroscopic precipitate was collected and immediately triturated with EtOAc. The solid was filtered and dried for 24 h in vacuo over P_2O_5 and for an additional 24 h in vacuo at 80 °C to give 5.7 g (87%) of N^4-(3-bromophenyl)-N^2-[4-(dimethylamino)cyclohexyl]-2,4-quinazolinediamine 1.8-hydrochloride hydrate (**87**), mp dec from 165 °C.

Procedure M. A mixture of 26.9 g (0.082 mol) of 92.8% pure (by VPC) 2-[[4-(diethylamino)-1-methylbutyl]amino]-4-quinazolinol and 700 mL of $POCl_3$ was heated under reflux for 2 h, concentrated in vacuo to a thick syrup, and poured into stirred ice–water. The mixture was chilled, made basic with 50% NaOH

(31) Literature (ref 11) reports a melting point of 96–97 °C for the hydrate of this compound.

solution, and poured into ether. The mixture was filtered to remove NaCl, the layers were separated, and the aqueous phase was extracted with ether. The extracts were combined, dried (anhydrous K_2CO_3), and concentrated in vacuo to give 25.1 g (91%) of 95.6% pure (by VPC) N^4-(4-chloro-2-quinazolinyl)-N^1,N^1-diethyl-1,4-pentanediamine as a brown oil. A mixture of 4.1 g (0.012 mol) of this residue, 1.7 g (0.012 mol) of 4-nitrobenzenamine, 4.0 mL of a 25% solution of HCl in *i*-PrOH, and 60 mL of *i*-PrOH was heated under reflux for 6.25 h, concentrated in vacuo to a paste, and added to 1.5 L of H_2O. The mixture was made basic with 2 N NaOH and extracted with ether. The extracts were combined, dried (anhydrous K_2CO_3), and concentrated in vacuo to an oil. The crude product was dissolved in 200 mL of ether, and HCl was bubbled through the solution for 15 min. The solid which formed was collected and dried to give 5.6 g (84%) of N^2-[4-(diethylamino)-1-methylbutyl]-N^4-(4-nitrophenyl)-2,4-quinazolinediamine 2.2-hydrochloride 1.7-hydrate (**115**), mp 125–128 °C with preliminary softening.

Compounds **89**, **107**, and **113** were of sufficient stability and purity after concentration of the ethereal solution to avoid formation of the hydrochloride salt.

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Folate Antagonists. 18. Synthesis and Antimalarial Effects of N^6-(Arylmethyl)-N^6-methyl-2,4,6-pteridinetriamines and Related N^6,N^6-Disubstituted 2,4,6-Pteridinetriamines[1-3]

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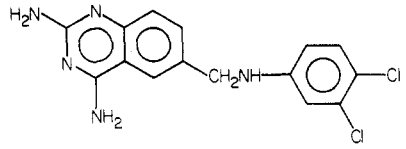
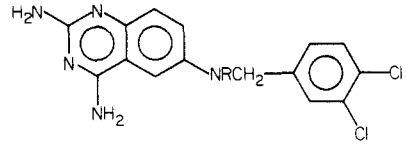
N^6-(Arylmethyl)-N^6-methyl-2,4,6-pteridinetriamines (**1–15**) and related N^6-substituted 2,4,6-pteridinetriamines (**16–20**) were obtained by the condensation of 6-chloro-2,4-pteridinediamine with *N*-methylarylmethanamine and other selected secondary amines. The requisite *N*-methylarylmethanamines (**21–32**) were prepared by the hydrogenation over Pt/C of the corresponding arylcarboxaldehyde in the presence of methanamine. Several of the N^6-(arylmethyl)-N^6-methyl-2,4,6-pteridinetriamines exhibited exceptional suppressive antimalarial activity against a drug-sensitive line of *Plasmodium berghei* in mice. N^6-Methyl-N^6-(1-naphthalenylmethyl)-2,4,6-pteridinetriamine (**9**), the most active of these compounds, was also shown to be curative at 3.16 mg/kg in a single oral dose against *P. cynomolgi* in the rhesus monkey. This compound was also shown to be effective against a chloroquine-resistant line of *P. berghei* in the mouse but showed cross-resistance to a pyrimethamine-resistant strain. Most of the 2,4,6-pteridinetriamines showed strong antibacterial action against *Streptococcus faecalis* and *Staphylococcus aureus*.

Members of a series of 6-[(phenylamino)methyl]-2,4-quinazolinediamines represented by I were reported to be



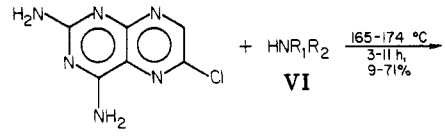
I



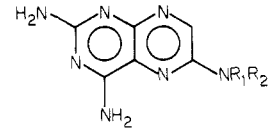
IIa, R = H
b, R = CH_3

even more potent as antimalarial agents than the corresponding 6-[(phenylmethyl)amino]-2,4-quinazolinediamines represented by II.[4]

Scheme I

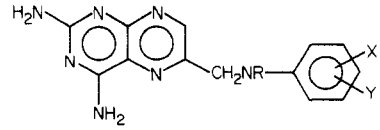


V



VII

We have recently reported[4] that the corresponding 6-[(arylamino)methyl]-2,4-pteridinediamines (IIIa–c) pre-



III

R	X, Y
a C_2H_5	4-OCH_3
b $(CH_2)_2CH_3$	3,4-Cl_2
c $CH(CH_3)_2$	4-Cl

pared as nonclassical analogues of aminopterin and methotrexate, while displaying potent prophylactic effects against *Plasmodium gallinaceum* infections, were generally poorly active against trophozoite-induced *P. berghei* infections in mice.

(1) This is paper 49 of a series on antimalarial drugs. For paper 48, see E. F. Elslager, C. Hess, J. Johnson, D. Ortwine, V. Chu, and L. M. Werbel, *J. Med. Chem.*, preceding paper in this issue.
(2) This investigation was supported by the U.S. Army Medical Research and Development Command Contract DA 17-72-C-2077. This is contribution no. 1587 to the Army Research Program on Malaria.
(3) A preliminary report of the work appeared in *Med. Chem., Proc. Int. Symp. Med. Chem., 4th, 1974*, 227 (1974).
(4) D. F. Worth, J. Johnson, E. F. Elslager, and L. M. Werbel, *J. Med. Chem.* **21**, 331, 1978.

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