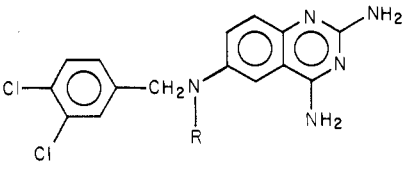
# Folate Antagonists. 20. Synthesis and Antitumor and Antimalarial Properties of Trimetrexate and Related 6-[(Phenylamino)methyl]-2,4-quinazolinediamines[1-3a-c]

Edward F. Elslager, Judith L. Johnson, and Leslie M. Werbel*

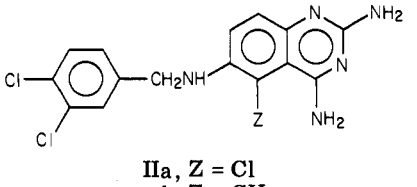
*Chemistry Department, Warner-Lambert/Parke-Davis Pharmaceutical Research, Ann Arbor, Michigan 48105.*
*Received February 4, 1983*

A series of 6-[(arylamino)methyl]-2,4-quinazolinediamines have been prepared by catalytic hydrogenation of the requisite 2,4-diamino-6-quinazolinecarbonitriles in the presence of the appropriate benzenamine. Formylation, acetylation, and nitrosation provided $N^{\omega}$ derivatives of these compounds. A variety of the compounds exhibited potent antimalarial, antibacterial, and antitumor activity. In particular, 5-methyl-6-[[(3,4,5-trimethoxyphenyl)-amino]methyl]-2,4-quinazolinediamine (trimetrexate, **15**) has shown a broad spectrum of antitumor effects and is undergoing preclinical toxicology evaluation prior to trial in man.

Various nonclassical, lipophilic quinazoline-2,4,6-triamine antifols, exemplified by Ia, exhibit potent antimalarial effects against both sensitive and cycloguanil- and pyrimethamine-resistant plasmodia.[3-5] The antimalarial potency of this class is generally enhanced by the introduction of formyl, nitroso, or methyl groups at N-6 (i.e., Ib–d).[3-7] Enhancement is also achieved by insertion of a chlorine or methyl substituent at position 5 on the quinazoline ring (IIa,b).[4]



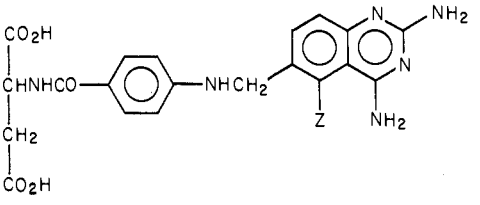
Ia, R = H
b, R = CHO
c, R = NO
d, R = $CH_3$



IIa, Z = Cl
b, Z = $CH_3$

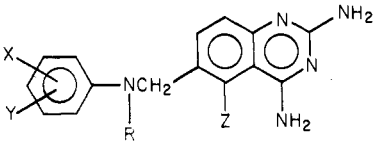
Substitution at both N-6 and C-5 results in a somewhat lower degree of enhancement, possibly as a result of excess bulk at a critical receptor site.[3]

The classical quinazoline antifolates, quinespar (IIIa), methasquin (IIIb), and chlorasquin (IIIc), exhibit potent inhibitory effects against *S. faecalis* R[4] and thymidylate synthetase and dihydrofolate reductase from mammalian and bacterial sources.[8-10] However, they lack appreciable antiprotozoal activity, presumably due to the lack of an active folate transport mechanism in such organisms.[3,8]



IIIa, Z = H
b, Z = $CH_3$
c, Z = Cl

The postulate that replacement of the highly polar *N*-(*p*-aminobenzoyl)-L-aspartic acid moiety of III by more lipophilic substituents might result in improved antimalarial properties and the presence of potent antimalarial activity in the quinazolinetriamines Ia–c and IIa,b, described above spurred the preparation of a series of 6-[(arylamino)methyl]-2,4-quinazolinediamines (IV), which are the subject of this paper.



IV, R = H, NO, CHO
Z = H, $CH_3$, Cl

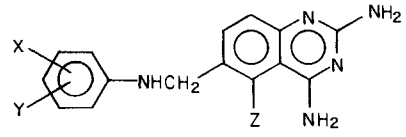
Since certain of the earlier classical analogues III exhibited potent inhibitory effects against thymidylate synthetase from C 1300 mouse neuroblastoma,[11] L1210 mouse leukemia,[9] canine lymphosarcoma,[12] and human leukemia cells,[13] these compounds were also of interest for their potential as antitumor agents.

**Chemistry.** The synthetic approach used in preparing the 6-[(arylamino)methyl]-2,4-quinazolinediamines (IVa,

(1) This is part 20 of a series of folate antagonists. For paper 19, see *J. Med. Chem.* **1981**, *24*, 1001.
(2) This investigation was supported in part by U.S. Army Medical Research and Development Command Contract DA 17-72-C-2077. This is contribution number 1676 to the Army Research Program on Malaria.
(3) (a) A preliminary report of a portion of this work was presented by Elslager, E. F.; Davoll, J. In "Lecture in Heterocyclic Chemistry"; Castle, R. N.; Townsend, L. B., Eds.; Hetero Corp.: Orem, UT, 1974; Vol. 2, p S-97. (b) Also see *Med. Chem., Proc. Int. Symp. Med. Chem. 4th, 1974*, 227. (c) Trimetrexate is the USAN approved generic name for 5-methyl-6-[[(3,4,5-trimethoxyphenyl)amino]methyl]-2,4-quinazolinediamine.
(4) Davoll, J.; Johnson, A. M.; Davies, H. J.; Bird, O. D.; Clarke, J.; Elslager, E. F. *J. Med. Chem.* **1972**, *15*, 812.
(5) Thompson, P. E.; Bayles, A.; Olszewski, B. *Exp. Parasitol.* **1969**, *25*, 32.
(6) Thompson, P. E.; Bayles, A.; Olszewski, B. *Am. J. Trop. Med. Hyg.* **1970**, *19*, 12.
(7) Elslager, E. F.; Bird, O. D.; Clarke, J.; Perricone, S. C.; Worth, D. F.; Davoll, J. *J. Med. Chem.* **1972**, *15*, 1138.
(8) Bird, O. D.; Vaitkus, J. W.; Clarke, J. *Mol. Pharmacol.* **1970**, *6*, 573.
(9) Hutchison, D. J.; Sirotnak, F. M.; Albrecht, A. M. *Proc. Am. Assoc. Cancer Res.* **1969**, *10*, 41.
(10) Hutchison, D. J. *Cancer Chemother. Rep. Part 1* **1968**, *52*, 697.
(11) Carlin, S. C.; Rosenberg; R. N.; Vandeventer, L.; Friedkin, M. *Mol. Pharmacol.* **1974**, *10*, 194–203.
(12) Folsch, E.; Abboud, G.; Gralla, E.; Bertino, J. R. *Ann. N.Y. Acad. Sci.* **1971**, *186*, 501.
(13) Johns, D. G.; Capizzi, R. L.; Nahos, A.; Cashmore, A. R.; Bertino, J. R. *Biochem. Pharmacol.* **1970**, *19*, 1528.

0022-2623/83/1826-1753$01.50/0 

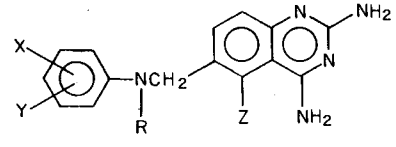
Table I. 6-[(Arylamino)methyl]-2,4-quinazolinediamines



| no. | X, Y | Z | mp, °C | yield purified, % | recrystn solvent, % HOAc/$H_2O$ | formula | anal. |
|---|---|---|---|---|---|---|---|
| 1 | 3,4-$Cl_2$ | Cl | 233–236 dec w/ps[a] | 29 | 25 | $C_{15}H_{12}Cl_3N_5 \cdot C_2H_4O_2 \cdot 1.2H_2O$ | C, H, N, Cl, $H_2O$ |
| 2 | 3-Br | Cl | 203–207 dec[b] | 15 | 20 | $C_{15}H_{13}BrClN_5 \cdot C_2H_4O_2 \cdot 1.1H_2O$ | C, H, N, $H_2O$ |
| 3 | 4-Cl | Cl | 229–231 dec | 13 | 20 | $C_{15}H_{13}Cl_2N_5 \cdot 0.2C_2H_4O_2 \cdot 0.3H_2O$ | C, H, N, Cl, $H_2O$ |
| 4 | 3,4-$Cl_2$ | H | 204–208 | 57 | 20 | $C_{15}H_{13}Cl_2N_5 \cdot C_2H_4O_2 \cdot 2H_2O$ | C, H, N, $H_2O$ |
| 5 | 3,5-$Cl_2$ | H | 220–223 | 50 | 20 | $C_{15}H_{13}Cl_2N_5 \cdot C_2H_4O_2 \cdot 2H_2O$ | C, H, N, $H_2O$ |
| 6 | 3-Br | H | 179–181 dec w/ps | 18 | 20 | $C_{15}H_{14}BrN_5 \cdot C_2H_4O_2$ | C, H, N |
| 7 | 2-Cl | H | 210–213 w/ps | 38 | 20 | $C_{15}H_{14}ClN_5 \cdot C_2H_4O_2 \cdot H_2O$ | C, H, N, Cl, $H_2O$ |
| 8 | 3-Cl | H | 172–175 | 44 | 20 | $C_{15}H_{14}ClN_5 \cdot C_2H_4O_2 \cdot 2.1H_2O$[c] | C, H, N, Cl, $H_2O$ |
| 9 | 4-Cl | H | 192–195 | 47 | 20 | $C_{15}H_{14}ClN_5 \cdot C_2H_4O_2 \cdot 2.1H_2O$ | C, H, N, $H_2O$ |
| 10 | 3-$CF_3$, 4-Cl | H | 196–198 w/ps | 41 | 20 | $C_{16}H_{13}ClF_3N_5 \cdot C_2H_4O_2 \cdot 2H_2O$ | C, H, N, $H_2O$ |
| 11 | 3,4-$Cl_2$ | $CH_3$ | 237–240 dec | 20 | 20 | $C_{16}H_{15}Cl_2N_5 \cdot C_2H_4O_2$ | C, H, N |
| 12 | 3-Br | $CH_3$ | 233–235 w/ps | 35 | 20 | $C_{16}H_{16}BrN_5 \cdot C_2H_4O_2 \cdot H_2O$ | C, H, N, Br, $H_2O$ |
| 13 | 4-Cl | $CH_3$ | 223–225 w/ps | 13 | 20 | $C_{16}H_{16}ClN_5 \cdot C_2H_4O_2$ | C, H, N |
| 14 | 3,4,5-$(OCH_3)_3$ | H | 184–186 w/ps | 43 | 4 | $C_{18}H_{21}N_5O_3 \cdot C_2H_4O_2 \cdot 1.1H_2O$ | C, H, N, $H_2O$ |
| 15 | 3,4,5-$(OCH_3)_3$ | $CH_3$ | 215–217 w/ps | 26 | 10 | $C_{19}H_{23}N_5O_3 \cdot C_2H_4O_2 \cdot H_2O$ | C, H, N, $H_2O$ |
| 16 | 6-Cl-2-$C_{10}H_6$ | H | 270–274 w/ps | 35 | 20 | $C_{19}H_{16}ClN_5 \cdot C_2H_4O_2 \cdot 2.2H_2O$ | C, H, N, $H_2O$ |
| 17 | 4-Cl-1-$C_{10}H_6$ | H | 228–231 | 27 | 20 | $C_{19}H_{16}ClN \cdot 1.5C_2H_4O_2 \cdot H_2O$ | C, H, N, Cl, $H_2O$ |

[a] w/ps = with preliminary shrinkage. [b] This compound melts at 140–148 °C, resolidifies, and remelts at 203–207 °C. [c] $H_2O$: calcd, 9.52; found, 8.97.

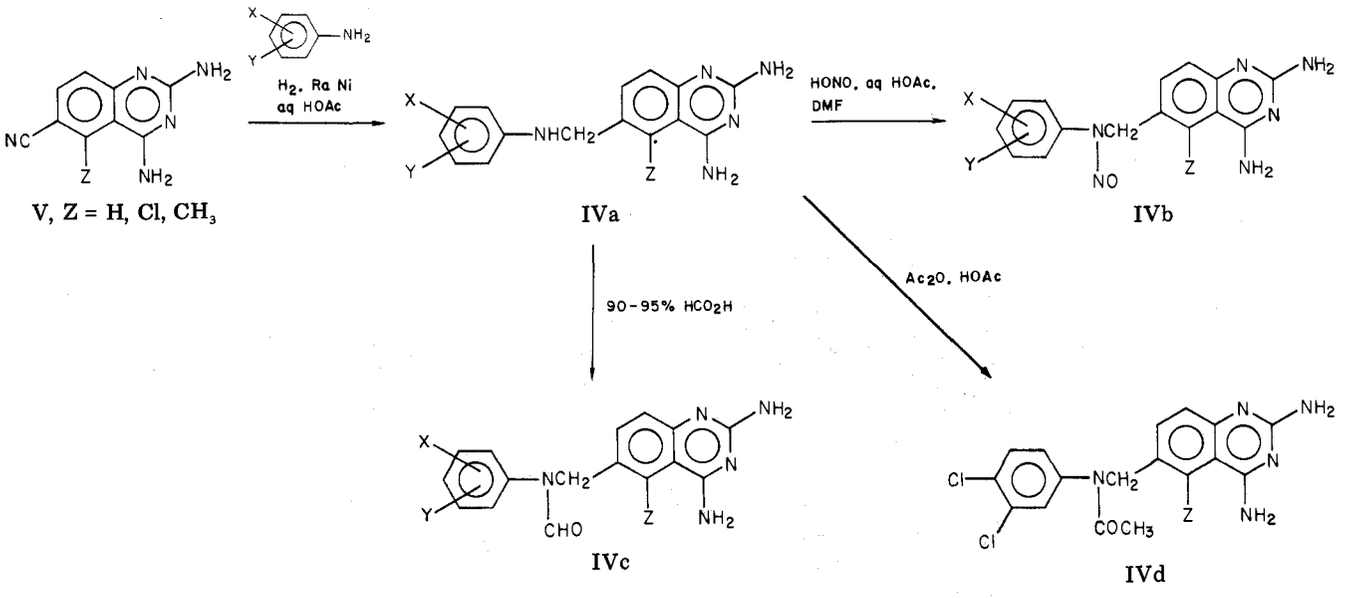
Table II. 6-[(Arylnitrosoamino)methyl]-2,4-quinazolinediamines and *N*-Aryl-*N*-[(2,4-diamino-6-quinazolinyl)methyl]formamides and -acetamides



| no. | X, Y | R | Z | mp, °C | yield purified, % | purification solvent | procedure | formula | anal. |
|---|---|---|---|---|---|---|---|---|---|
| 18 | 3,4-$Cl_2$ | NO | Cl | 227–229 dec | 75 | 80% aq EtOH | II | $C_{15}H_{11}Cl_3N_6O$ | C, H, N |
| 19 | 3,4-$Cl_2$ | NO | H | 206–208 w/ps[a] | 65 | 20% aq HOAc | II | $C_{15}H_{12}Cl_2N_6 \cdot 1.2C_2H_4O_2 \cdot 1.3H_2O$[f] | C, H, N, Cl, $H_2O$ |
| 20 | 3-$CF_3$, 4-Cl | NO | H | 216–217 | 70 | 80% aq EtOH | II | $C_{16}H_{12}ClF_3N_6O$ | C, H, N |
| 21 | 3,4-$Cl_2$ | NO | $CH_3$ | 234–236 dec | 31 | 2% HOAc/EtOH/$NH_4OH$[b] | II | $C_{16}H_{14}Cl_2N_6O$ | C, H, N |
| 22 | 4-Cl-1-$C_{10}H_6$ | NO | H | 202–205 | 46 | 2% HOAc/EtOH | II | $C_{19}H_{15}ClN_6O \cdot C_2H_4O_2$ | C, H, N |
| 23 | 3,4-$Cl_2$ | CHO | Cl | 205–206[c] | 48 | 50% aq EtOH | III | $C_{16}H_{12}Cl_3N_5O \cdot 1.3H_2O$ | C, H, N, $H_2O$ |
| 24 | 3-$CF_3$, 4-Cl | CHO | H | 188–190 | 83 | 50% aq EtOH/$NH_4OH$ | III | $C_{17}H_{13}ClF_3N_5O \cdot 0.9H_2O$ | C, H, N, $H_2O$ |
| 25 | 3,4-$Cl_2$ | CHO | $CH_3$ | 233–234[d] | 43 | 80% aq EtOH | III | $C_{17}H_{15}Cl_2N_5O \cdot 1.5H_2O$[g] | C, H, N, $H_2O$ |
| 26 | 3,4-$Cl_2$ | $COCH_3$ | H | 224–225[e] | 65 | EtOH–$H_2O$ | IV | $C_{17}H_{15}Cl_2N_5O \cdot 1.5H_2O$ | C, H, N, Cl, $H_2O$ |
| 27 | 6-Cl-2-$C_{10}H_6$ | CHO | H | 209–211 | 69 | 50% aq EtOH/$NH_4OH$ | III | $C_{20}H_{16}ClN_5O \cdot H_2O$ | C, H, N, $H_2O$ |

[a] w/ps = with preliminary sintering. [b] The material was first recrystallized twice from 20% aqueous HOAc and then dissolved in hot EtOH containing 2% HOAc, the solution was filtered, and the filtrate was made alkaline with concentrated $NH_4OH$ to afford the product. [c] Compound initially melts at 137–140 °C (loss of water) and resolidifies. [d] Compound initially melts at 130–133 °C (loss of water) and resolidifies. [e] Compound initially melts at 108–110 °C and resolidifies. [f] $H_2O$: calcd, 5.10; found, 5.53. [g] $H_2O$: calcd, 6.70; found, 6.17.

Scheme I




1–17, Table I) and derivatives (IVb–d, 18–27, Table II) is outlined in Scheme I. The requisite 2,4-diamino-6-quinazolinecarbonitrile[14] (V) was reduced over Raney nickel in the presence of the appropriate benzenamine at an initial pressure of 50 psig to afford the desired 6-[(arylamino)methyl]-2,4-quinazolinediamine (IVa) (procedure I).[14] Treatment of IVa with nitrous acid (procedure II) and with formic acid (procedure III) afforded the corresonding *N*-nitroso (IVb, 18–22) and *N*-formyl (IVc, 23–25 and 27) derivatives (Table II). The *N*-acetyl derivative (IVd, 26) was obtained by treatment of IVa with acetic anhydride in acetic acid (procedure IV).

Acylation and nitrosation on the secondary amine attached to the 6-position of the quinazoline ring of IVa rather than on the primary amino groups at position 2 or 4 was confirmed by NMR spectroscopy. Two amino groups are present in the spectra of the starting material, IVa and the products, IVb–d (ca. 6 and 7 ppm), whereas the secondary amine proton which appears as a triplet (often hidden among aromatic protons) at ca. 6.5 ppm in the spectrum of IVa is absent in the spectra of IVb–d. In addition, the doublet at 4.2 ppm in the spectra of IVa arising from the methylene group at the 6-position appears as a singlet at ca. 5.3 ppm in the substituted products IVb–d. Thus, removal of the proton on the secondary NH eliminates the splitting for the methylene absorption.

**Suppressive Antimalarial Screening in Mice.** The 6-[(arylamino)methyl]-2,4-quinazolinediamines (1–17) and their nitroso and acyl derivative (18–27) were tested initially against a normal drug-sensitive strain of *Plasmodium berghei* in mice by the parenteral route.[15,16] The compounds were dissolved or suspended in sesame or peanut oil and were administered to mice in a single subcutaneous dose 72 h postinfection. The antimalarial activities are summarized in Table III and IV.

Fourteen of the quinazolinediamines (4–9, 11–15, 19, 21, and 26) were also evaluated orally against another normal drug-sensitive strain of *P. berghei* in mice.[17,18] Results of this test, which are expressed both in terms of the $SD_{90}$ and the quinine equivalent *Q* of the compounds, are summarized in Table V.

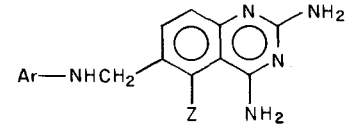
Almost all the compounds tested exhibited curative activity upon parenteral administration. The presence of a halogen in the 4-position of the phenyl ring generally led to good activity. The most potent compound was 13, the 4-chlorophenyl analogue containing a methyl group at C-5, which was strongly curative through 10 mg/kg. As was noted with the $N^6$-[(3,4-dichlorophenyl)methyl]-2,4-quinazolinetriamine series (Ia–c and IIa,b), antimalarial activity appeared to be enhanced by the presence of methyl or chlorine at C-5 (compare, for example, compound 4 with compounds 11 and 1 in Table III). In contrast, potency was not appreciably abetted by the presence of a NO or acyl group on N-6 (compare, for example, Ia in Table III with Ib in Table IV as opposed to compound 4 in Table III with compounds 19, 24, 26 and 27). The presence of a substituent both on N-6 and C-5 seems to lead to variable results, but in any event no distinct advantage is evident from having both positions substituted.

Extremely potent activity was also seen upon oral administration. Although complete correlation between parenteral and oral modes of administration was not seen, the levels of activity were overall reasonably similar. Thus, compound 13, the most active parenterally administered compound, was also the most potent compound when given orally, exhibiting an incredible level of activity 846 times that of quinine. Moreover, compounds 11, 12, 15, and 19, which had reasonable levels of activity upon parenteral dosing, were among the most potent compounds after oral administration.

Of note is that in direct comparison with Ia, wherein the aminomethylene bridge at the 6-position is reversed, 6-[[(3,4-dichlorophenyl)amino]methyl]-2,4-quinazolinediamine (4) displays curative activity at one dose level lower than Ia parenterally (80 vs. 160 mg) (Table III) and is some nine times as dose potent orally as Ia (Table V).

(14) Davoll, J.; Johnson, A. M. *J. Chem. Soc. C* **1970**, 997.
(15) Osdene, T. S.; Russell, P. B.; Rane, L. *J. Med. Chem.* **1967**, *10*, 431.
(16) The parenteral antimalarial screening in mice was carried out by Dr. Leo Rane of the University of Miami, and test results were provided through the courtesy of Drs. T. R. Sweeney and E. A. Steck of the Walter Reed Army Institute of Research.
(17) 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, MI.
(18) For a description of the test method, see ref 5 and 6.

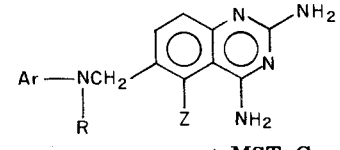
Table III. Parenteral Suppressive Antimalarial Effects of 6-[(Arylamino)methyl]-2,4-quinazolinediamines against Trophozoite-Induced *P. berghei* in Mice




| | | | Δ MST; C or T[a] after single sc dose, mg/kg | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| no. | Ar | Z | 640 | 320 | 160 | 80 | 40 | 20 | 10 | 5 | 2.5 | 1.25 |
| 1 | 3,4-$Cl_2C_6H_3$ | Cl | T5 | T5 | C5 | C5 | C5 | C5 | 11.5 | 4.3 | 4.1 | 2.9 |
| | | | | T5 | C5 | C5 | C5 | C5 | 17.8 | | | |
| | | | | | | | C5 | C5 | | | | |
| 2 | 3-$BrC_6H_4$ | Cl | T5 | C3, T2 | C5 | C5 | 11.3 | 8.5 | 7.3 | 4.7 | 1.5 | 0.5 |
| | | | | C2, T3 | C5 | C5 | 11.5 | 8.3 | 7.5 | | | |
| | | | | | | | 11.7 | 8.5 | | | | |
| 3 | 4-$ClC_6H_4$ | Cl | T5 | T5 | C5 | C5 | C5 | 16.9; C3 | 10.7 | 6.9 | 6.1 | 2.7 |
| | | | | T5 | C5 | C5 | C5 | 16.9; C3 | 10.9 | | | |
| | | | | | | | C5 | 17.4; C3 | | | | |
| 4 | 3,4-$Cl_2C_6H_3$ | H | C5 | C5 | 18.8; C3 | 11.8; C1 | 11.4 | 5.8 | 1.8 | 0.6 | 0.4 | 0.2 |
| | | | | C5 | 19.8; C3 | 12.1; C1 | 11.2 | 5.8 | 1.8 | | | |
| | | | | | | | | 5.8 | | | | |
| 5 | 3,5-$Cl_2C_6H_3$ | H | 13.7 | 12.9 | 6.9 | 4.7 | 0.7 | 0.3 | 0.3 | | | |
| | | | | 12.9 | 6.9 | 4.9 | 0.7 | 0.3 | | | | |
| 6 | 3-$BrC_6H_4$ | H | C5 | 9.2; C3 | 9.2; C3 | 10.1 | 3.1 | 1.5 | 0.4 | | | |
| | | | | 9.8; C3 | 8.8; C3 | 10.2 | 3.6 | 1.8 | | | | |
| 7 | 2-$ClC_6H_4$ | H | | 9.9; C3 | 8.4; C1 | 7.9 | 3.1 | 1.3 | 0.5 | 0.7 | | |
| | | | | | 8.4; C1 | 7.7 | 3.1 | 1.9 | 0.7 | | | |
| 8 | 3-$ClC_6H_4$ | H | 9.9; C4 | 20.6; C2 | 8.7 | 3.3 | 1.7 | 0.7 | 0.3 | | | |
| | | | | 16.4; C3 | 8.9 | 3.3 | 1.7 | 0.5 | | | | |
| 9 | 4-$ClC_6H_4$ | H | C5 | C5 | 9.9; C4 | 7.1 | 6.9 | 5.1 | 5.1 | | | |
| 10 | 3-$CF_3$-4-$ClC_6H_3$ | H | C5 | 29.9; C4 | 27.2; C2 | 18.4; C2 | 10.3 | 4.9 | 4.9 | | | |
| | | | | C5 | 23.9; C3 | 18.7; C2 | 10.5 | 5.1 | 2.7 | | | |
| 11 | 3,4-$Cl_2C_6H_3$ | $CH_3$ | T5 | T5 | C4, T1 | C5 | 29.8; C4 | 15.5; C2 | 11.2 | 8.6 | 7.2 | 4.0 |
| | | | | T5 | C4, T1 | C5 | C5 | 15.9; C2 | | | | |
| | | | | | | | C5 | 15.8; C3 | 11.6; C1 | | | |
| 12 | 3-$BrC_6H_4$ | $CH_3$ | T5 | C2, T3 | C5 | 29.7; C3 | 9.2; C3 | 12.7 | 11.2 | 7.7 | 4.3 | 0.5 |
| | | | | C2, T3 | C5 | 21.8; C4 | 9.3; C3 | 12.6 | | | | |
| | | | | | | | 11.2; C3 | 12.7 | 11.3 | | | |
| 13 | 4-$ClC_6H_4$ | $CH_3$ | | | C5 | C5 | C5 | 21.8; C4 | 19.8; C4 | 8.8 | 0.7 | |
| | | | | | | C5 | C5 | 20.9; C4 | 25.9; C3 | 8.7 | | |
| 14 | 3,4,5-$(OCH_3)_3C_6H_2$ | H | C5 | 7.9; C1 | 4.9 | 4.3 | 0.7 | 0.3 | 0.3 | | | |
| | | | | 7.9; C1 | 4.9 | 4.5 | 0.7 | 0.7 | | | | |
| 15 | 3,4,5-$(OCH_3)_3C_6H_2$ | $CH_3$ | T5 | C2, T3 | C5 | C5 | 14.7; C1 | 11.5 | 7.0 | 6.5 | 4.7 | 1.9 |
| | | | | C2, T3 | C5 | 30.8; C4 | 16.3; C1 | 12.0 | 7.1 | | | |
| | | | | | | | 14.7; C2 | 11.7 | | | | |
| 16 | 6-Cl-2-$C_{10}H_6$ | H | C5 | C5 | C5 | C5 | 20.6; C2 | 8.3 | 3.3 | | | |
| | | | | C5 | C5 | C5 | 20.7; C2 | 8.5 | | | | |
| 17 | 4-Cl-1-$C_{10}H_6$ | H | | C5 | C5 | C5 | C5 | 11.9; C2 | 10.3 | 9.9 | 5.5 | 1.7 |
| | | | | | C5 | C5 | C5 | 12.6; C2 | 10.5 | 9.9 | | |
| | | | | | | | | 12.9; C2 | 10.7 | | | |
| Ia acetate | | | C5 | C5 | 9.9; C3 | 12.9 | 7.1 | 2.5 | 0.7 | | | |
| | | | | | 9.9; C2 | 13.1 | 7.3 | 2.7 | 0.7 | | | |
| cycloguanil hydrochloride | | | T5 | C3, T2 | C5 | 21.6; C2 | 13.4; C1 | 7.9 | 4.9 | | | |
| pyrimethamine | | | C1; T2 | C2; T3 | C5 | C3 | C1 | 7.7 | 6.1 | 5.3 | 4.7 | 3.1 |

[a] Δ 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 6.3 days. T signifies the number of toxic deaths, occurring on days 2–5 after injection, that are attributed to drug action. Compounds are arbitrarily considered to be "active" when they produce at least a 100% increase in the mean survival time of treated mice. 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.

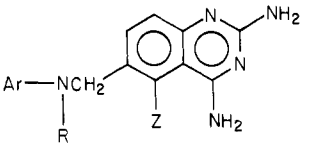
Table IV. Parenteral Suppressive Antimalarial Effects of $N^{\omega}$-Nitroso and $N^{\omega}$-Acyl Derivatives of 6-[(Arylamino)methyl]-2,4-quinazolinediamines against Trophozoite-Induced *P. berghei* in Mice




| | | | | Δ MST; C or T[a] after single sc dose, mg/kg | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| no. | Ar | R | Z | 640 | 320 | 160 | 80 | 40 | 20 | 10 | 5 | 2.5 | 1.25 |
| 18 | 3,4-$Cl_2C_6H_3$ | NO | Cl | C5 | C5 | 21.9; C4 | 13.4; C1 | 8.1 | 6.1 | 3.5 | | | |
| | | | | | C5 | C5 | 13.4; C1 | 8.1 | 6.3 | | | | |
| 19 | 3,4-$Cl_2C_6H_3$ | NO | H | | C5 | 28.7; C3 | 12.3 | 9.9 | 6.7 | 3.7 | 2.0 | | |
| | | | | | | 22.8; C4 | 12.0 | 9.8 | 6.8 | 4.0 | | | |
| 20 | 3-$CF_3$-4-$ClC_6H_3$ | NO | H | C2, T3 | C4, T1 | C5 | 14.9; C1 | 10.9 | 5.1 | 1.3 | | | |
| | | | | | C5 | C5 | 15.2; C1 | 11.1 | 5.3 | | | | |
| 21 | 3,4-$Cl_2C_6H_3$ | NO | $CH_3$ | | | C5 | C5 | C5 | 21.7; C4 | 12.0; C1 | 9.9 | 4.1 | |
| | | | | | | | C5 | C5 | 24.9; C4 | 11.9; C1 | 10.5 | | |
| 22 | 4-Cl-1-$C_{10}H_6$ | NO | H | C5 | 14.7 | 12.9 | 5.7 | 2.9 | 0.7 | 0.3 | | | |
| | | | | | 14.9 | 13.1 | 5.9 | 2.7 | 0.5 | | | | |
| 23 | 3,4-$Cl_2C_6H_3$ | CHO | Cl | T5 | C3, T2 | C5 | C5 | 22.9; C3 | 21.2; C2 | 9.5 | 7.9 | 4.1 | 3.1 |
| | | | | | C2, T3 | C5 | C5 | 23.9; C3 | 21.9; C2 | 9.7 | | | |
| | | | | | | | | 24.4; C3 | 21.6; C2 | | | | |
| 24 | 3-$CF_3$-4-$ClC_6H_3$ | CHO | H | 9.9; C4 | 12.5 | 7.5 | 6.3 | 1.5 | 0.5 | 0.3 | | | |
| | | | | | 12.3 | 7.7 | 6.1 | 1.7 | 0.3 | | | | |
| 25 | 3,4-$Cl_2C_6H_3$ | CHO | $CH_3$ | T5 | C2, T3 | C5 | C5 | C5 | 9.9; C3 | 7.9 | 5.3 | 3.9 | 0.3 |
| | | | | | C3, T2 | C5 | C5 | 29.9; C4 | 9.9; C3 | 7.7 | | | |
| | | | | | | | | C5 | 9.4; C3 | | | | |
| 26 | 3,4-$Cl_2C_6H_3$ | $COCH_3$ | H | T5 | C1, T4 | 11.7 | 8.3 | 3.7 | 0.9 | | | | |
| | | | | | C1, T4 | 11.9 | 8.3 | 4.1 | 1.3 | 0.9 | | | |
| 27 | 6-Cl-2-$C_{10}H_6$ | CHO | H | 16.9; C3 | 13.9 | 10.9 | 4.1 | 1.5 | 0.5 | 0.3 | | | |
| | | | | | 13.7 | 10.7 | 4.3 | 1.3 | 0.5 | | | | |
| Ic base | | | | C5 | C5 | C5 | C5 | C5 | 20.9; C2 | 7.5 | 2.9 | | |
| | | | | | | | | | | 9.9 | | | |

[a] See footnote *a* of Table III.

Table V. Oral Suppressive Antimalarial Effects of 6-[(Arylamino)methyl]-2,4-quinazolinediamines and Derivatives against Trophozoite-Induced *P. berghei* in Mice[a]



| no. | Ar | R | Z | no. of mice | $SD_{90}$, mg/(kg day)[b] | Q[c] |
|---|---|---|---|---|---|---|
| 4 | $3,4\text{-}Cl_2C_6H_3$ | H | H | 21 | 0.92 | 81 |
| 5 | $3,5\text{-}Cl_2C_6H_3$ | H | H | 14 | 51 | 1.5 |
| 6 | $3\text{-}BrC_6H_4$ | H | H | 28 | 9.0 | 8.3 |
| 7 | $2\text{-}ClC_6H_4$ | H | H | 14 | 8.0 | 9.3 |
| 8 | $3\text{-}ClC_6H_4$ | H | H | 14 | 8.5 | 8.8 |
| 9 | $4\text{-}ClC_6H_4$ | H | H | 14 | 1.9 | 39 |
| 11 | $3,4\text{-}Cl_2C_6H_3$ | H | $CH_3$ | 28 | 0.33 | 226 |
| 12 | $3\text{-}BrC_6H_4$ | H | $CH_3$ | 28 | 0.20 | 372 |
| 13 | $4\text{-}ClC_6H_4$ | H | $CH_3$ | 21 | 0.088 | 846 |
| 14 | $3,4,5\text{-}(OCH_3)_3C_6H_2$ | H | H | 21 | 62 | 1.2 |
| 15 | $3,4,5\text{-}(OCH_3)_3C_6H_2$ | H | $CH_3$ | 35 | 0.44 | 169 |
| 19 | $3,4\text{-}Cl_2C_6H_3$ | NO | H | 28 | 0.25 | 298 |
| 21 | $3,4\text{-}Cl_2C_6H_3$ | NO | $CH_3$ | 21 | 1.15 | 64.8 |
| 26 | $3,4\text{-}Cl_2C_6H_3$ | $COCH_3$ | H | 21 | >15.1 | <4.9 |
| Ia | | | | | 8.5 | 8.8 |

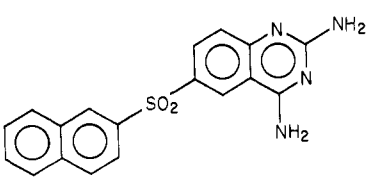
[a] Compounds were administered continuously in the diet of mice for six consecutive days. [b] All doses were calculated as the free base equivalent. $SD_{90}$ represents the daily dose (mg/kg) required for 90% suppression of the parasitemia in treated mice relative to control mice. The $SD_{90}$ was estimated graphically using semilog paper. [c] The quinine equivalent Q is the ratio of the $SD_{90}$ of quinine hydrochloride to the $SD_{90}$ of the test substance under comparable experimental conditions.

**Antimalarial Screening in Monkeys.** Against susceptible strains of *Plasmodium falciparum* in rhesus monkeys, the dose of 6-[[(3,4-dichlorophenyl)amino]-methyl]-2,4-quinazolinediamine (**4**) administered orally that cures 50% of the monkeys ($CD_{50}$) was determined to be 10 mg/kg.[19]

Moreover, against the chloroquine-susceptible, pyrimethamine-resistant Malayan Camp CH/Q strain of *P. falciparum* in the *Aotus trivirgatus* owl monkey[20,21] the $CD_{50}$ of an oral daily dose given for 7 days was 25 mg/kg. In addition, against the chloroquine-resistant Vietnam Oak Knoll strain, the $CD_{50}$ of an oral daily dose given for 7 days was 6.25 mg/kg.

**Antibacterial Studies.** Most of the 6-[(arylamino)-methyl]-2,4-quinazolinediamines and their *N*-nitroso and *N*-acyl derivatives (**1–18, 20–23,** and **26,27**) were also tested in vitro against a spectrum of pathogenic bacteria, including *Streptococcus faecalis* (MGH-2), normal (UC-76) and drug-resistant (S18713) *Staphylococcus aureus*, *Pseudomonas aeruginosa* (28), *Escherichia coli* (Vogel), *Shigella sonnei* (C-10), and *Mycobacterium tuberculosis* $H_{37}Rv$. A modification of the gradient plate procedure of Szybalski[22] and Webb and Washington[23] was employed throughout. Most of the compounds (**2, 4–10, 12–15, 17, 18, 20–23, 26,** and **27**) tested inhibited the growth of *S. faecalis* (MGH-2) and *S. aureus* (UC-76 and S18713) at drug concentrations of <0.25 μg/mL. Although end points were not determined, compounds **2, 12, 13,** and **23** were equipotent with trimethoprim against *S. faecalis* (MGH-2), *S. aureus* (UC-76 and S18713), *E. coli* (Vogel), and *S. sonnei* (C-10) at the levels tested, and two of these (**2** and **13**) were also active against *P. aeruginosa* (28).

**Conclusion.** The 6-[(phenylamino)methyl]-2,4-quinazolinediamines exhibit potent antimalarial activity in the rodent model and in limited testing against both normal and drug-resistant strains of parasite in a primate model. In addition, the potent oral activity of this class in the rodent model may portend improved efficacy in man over the only other related class examined clinically to date. Thus, WR 158122 (VI), which proved to be extremely potent parenterally in the rodent model and orally in the primate model,[24] was only very weakly active in man[25] and inactive as well in the rodent model upon oral administration.[19]

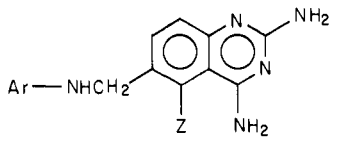


VI

**Antitumor Activity.** Many of the analogues were evaluated against the L1210 leukemia in tissue culture. The data are shown in Tables VI and VII. Clearly, a variety of these analogues exhibit potent activity in this system. Seventeen analogues were also tested as inhibitors of dihydrofolate reductase from L1210 leukemia cells and from human leukemia cells. On the basis of this, two analogues (VII and VIII) were evaluated further against murine tumors in vivo, and both showed a broad spectrum of antitumor effects.[26] Trimetrexate (VIII)[3c] was active against B-16 melanoma, colon carcinoma 26, colon carcinoma 38, and the L1210 tumor and became of interest for further study.

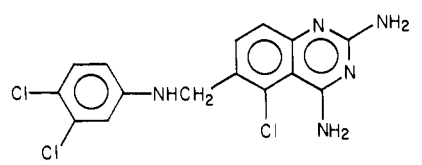
(19) Private communication from Col. David E. Davidson, Walter Reed Army Institute of Research.
(20) *WHO Tech. Rep. Ser.* **1973**, *no. 529*.
(21) Schmidt, L. H. *Trans. R. Soc. Trop. Med. Hyg.* **1973**, *67*, 446.
(22) Szybalski, W. *Microb. Genet. Bull.* **1951**, *5*, 16.
(23) Webb, A. H.; Washington, L. *Bacteriol. Proc.* **1966**, *52*, M88.
(24) Elslager, E. F.; Hutt, M. P.; Jacobs, P.; Johnson, J.; Temporelli, B.; Werbel, L. M.; Worth, D. F.; Rane, L. *J. Med. Chem.* **1979**, *22*, 1247.
(25) Summarized in Schmidt, L. H. *Am. J. Trop. Med. Hyg.* **1979**, *28*, 808.
(26) Bertino, J. R.; Sawicki, W. L.; Moroson, B. A.; Cashmore, A. R.; Elslager, E. F. *Biochem. Pharmacol.* **1979**, *28*, 1983.

Table VI. Effects of 6-[(Arylamino)methyl]-2,4-quinazolinediamines against L1210 Leukemia in Tissue Culture[a]

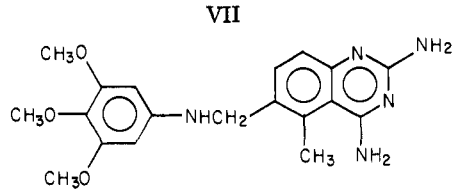


| no. | Ar | Z | $ID_{50}$[b] |
|---|---|---|---|
| 1 | 3,4-$Cl_2C_6H_3$ | Cl | |
| 2 | 3-$BrC_6H_4$ | Cl | 2.1, 2.2 × $10^{-9}$ |
| 3 | 4-$ClC_6H_4$ | Cl | |
| 4 | 3,4-$Cl_2C_6H_3$ | H | 1.8, 2.3, 6.7 × $10^{-8}$ |
| 5 | 3,5-$Cl_2C_6H_3$ | H | 1.2, 0.74 × $10^{-7}$ |
| 6 | 3-$BrC_6H_4$ | H | 7.1, 8.6 × $10^{-8}$ |
| 7 | 2-$ClC_6H_4$ | H | 6.8, 9.3 × $10^{-8}$ |
| 8 | 3-$ClC_6H_4$ | H | 4.6, 7.0 × $10^{-8}$ |
| 9 | 4-$ClC_6H_4$ | H | 2.7, 3.5 × $10^{-8}$ |
| 10 | 3-$CF_3$-4-$ClC_6H_3$ | H | |
| 11 | 3,4-$Cl_2C_6H_3$ | $CH_3$ | 8.4, 4.3 × $10^{-9}$ |
| 12 | 3-$BrC_6H_4$ | $CH_3$ | 3.7, 4.4 × $10^{-9}$ |
| 13 | 4-$ClC_6H_4$ | $CH_3$ | 1.9 × $10^{-9}$ |
| 14 | 3,4,5-$(OCH_3)_3C_6H_2$ | H | 5.7, 8.7 × $10^{-8}$ |
| 15 | 3,4,5-$(OCH_3)_3C_6H_2$ | $CH_3$ | 1.1, 2 × $10^{-8}$ |
| 16 | 6-Cl-2-naphthyl | H | 1.4, 2.6 × $10^{-7}$ |
| 17 | 4-Cl-1-naphthyl | H | 2.2, 1.3 × $10^{-8}$ |

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



VII



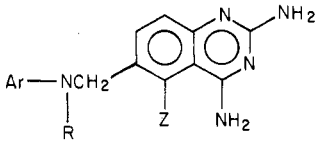
VIII

Trimetrexate now has been evaluated at the National Cancer Institute in 10 experimental murine tumor systems utilizing various routes of tumor implantation and drug administration. In addition, it has been tested against a spectrum of human cancer cells (xenografts) implanted and grown in immunosuppressed nude mice. These data may be summarized as follows.[27]

The drug showed moderate activity in mice bearing the transplanted L1210 tumor and exceptional activity against the P388 leukemia and a leukemic strain of L1210 made resistant to dichloromethotrexate. Increase in life spans far exceeding 100% were obtained. In mice bearing B16 melanoma, moderate activity was observed with increase in life spans ranging from 50 to 65%. Significant activity was also observed against colon 26, colon 38, and the $CD8F_1$ mammary tumors. Of particular interest were the high numbers of cures observed with the $CD8F_1$ mammary and colon 38 tumors. Borderline to no discernible activity was noted against the Lewis lung and M5076 ovarian murine tumors and against the implanted human xenografts.

(27) A summary of these data provided through the courtesy of Drs. K. Paull, V. Narayanan, M. Wolpert, and J. Plowman of the National Cancer Institute, Silver Spring, MD.

Table VII. Effects of $N^{\omega}$-Nitroso and $N^{\omega}$-Acyl Derivatives of 6-[(Arylamino)methyl]-2,4-quinazolinediamines against L1210 Leukemia in Tissue Culture[a]



| no. | Ar | R | Z | $ID_{50}$[a] |
|---|---|---|---|---|
| 18 | 3,4-$Cl_2C_6H_3$ | NO | Cl | |
| 19 | 3,4-$Cl_2C_6H_3$ | NO | H | 4.0, 7.0 × $10^{-8}$ |
| 20 | 3-$CF_3$-4-$ClC_6H_3$ | NO | H | |
| 21 | 3,4-$Cl_2C_6H_3$ | NO | $CH_3$ | 0.7, 1.0 × $10^{-7}$ |
| 22 | 4-Cl-1-naphthyl | NO | H | 1.3, 1.7 × $10^{-7}$ |
| 23 | 3,4-$Cl_2C_6H_3$ | CHO | Cl | |
| 24 | 3-$CF_3$-4-$ClC_6H_3$ | CHO | H | |
| 25 | 3,4-$Cl_2C_6H_3$ | CHO | $CH_3$ | 2.1, 2.6 × $10^{-8}$ |
| 26 | 3,4-$Cl_2C_6H_3$ | $COCH_3$ | H | 1.9, 3.0 × $10^{-7}$ |
| 27 | 6-Cl-2-naphthyl | CHO | H | 1.5, 2.5 × $10^{-7}$ |

[a] See footnotes *a* and *b* of Table VI.

The effectiveness of methotrexate is often limited by drug resistance. The most common causes of resistance are defects in the membrane transport of the drug and overproduction of the target enzyme, dihydrofolate reductase. Therefore, trimetrexate has been evaluated against a variety of methotrexate-resistant human tumor cell lines with promising results.

Against six sublines of human T cells, B cells, and osteosarcomas that were 8-fold to 13,000-fold resistant to methotrexate, trimetrexate was fully active against the two sublines with defective methotrexate transport.[28] The four sublines with elevated dihydrofolate reductase all showed considerable cross-resistance to trimetrexate.

The relative activity of trimetrexate and methotrexate against a variety of human tumors in a human tumor cloning system has recently been compared.[29] Overall, 8 of 54 (15%) of these tumors were sensitive to 0.1 μg/mL of trimetrexate but resistant to methotrexate (0.3 μg/mL), while only 4 of 54 (7%) were sensitive to methotrexate but refractory to trimetrexate. Collateral sensitivity was observed in 3 of 54 (6%). The greater cytotoxic activity of trimetrexate and its effectiveness against methotrexate-resistant tumors is noteworthy.

A report on the pharmacology of trimetrexate in normal dogs was published recently.[30] Intravenous or oral doses of 2 mg/kg were well tolerated. Higher doses were reported to produce mainly gastrointestinal toxicity without significant hematological or liver abnormalities.

**Conclusion.** The preclinical characterisitics of this agent lend encouragement to its clinical evaluation. Formulation studies have been completed, and the drug has entered preclinical toxicology studies.

## Experimental Section

Melting points were determined on a Thomas-Hoover apparatus (capillary method) and are corrected. Satisfactory infrared spectra

(28) Diddens, H.; Niedhammer, D.; Jackson, R. C., accepted for publication in *Cancer Res.*

(29) Latham, B.; Von Hoff, D.; Elslager, E. F.; Rodriguez, V. "Abstracts of Papers", 74th Meeting of the American Association for Cancer Research, San Diego, CA, May 25–28, 1983; Waverly Press: Baltimore, MD, 1983.

(30) Weir, E. C.; Cashmore, A. R.; Dreyer, R. N.; Graham, M. L.; Hsiao, N.; Moroson, B. A.; Sawicki, W. L.; Bertino, J. R. *Cancer Res.* **1982**, *42*, 1696.

were obtained for all compounds. In some instances, additional proof of structure was provided by NMR spectroscopy on a Bruker WH-90 instrument in $Me_2SO$-$d_6$ and $Me_2SO$-$d_6$ plus $D_2O$. 2,4-Diamino-6-quinazolinecarbonitrile and the corresponding 5-chloro- and 5-methyl-6-quinazolinecarbonitriles were prepared according to a published procedure.[14]

**6-[[(Substituted-phenyl)amino]methyl]-2,4-quinazolinediamines (IVa; 1–17, Table I). Procedure I.** A mixture of 5.6 g (0.03 mol) of 2,4-diamino-6-quinazolinecarbonitrile, 5.8 g (0.03 mol) of 3,4-dichlorobenzenamine, and 1 g of Raney nickel in 135 mL of 67% aqueous HOAc at an initial pressure of 50 psig of hydrogen was shaken at 28 °C for 22 h. The reaction mixture was filtered, and the filter cake was washed with HOAc. The filtrate and wash were combined and evaporated to dryness under vacuum. The residue was triturated with hot $H_2O$, recrystallized from 20% aqueous HOAc, dried, and equilibrated in air to afford 7.3 g (57%) of 6-[[(3,4-dichlorophenyl)amino]methyl]-2,4-quinazolinediamine acetate dihydrate (1), mp 204–208 °C.

Compounds 2–17 were prepared analogously.

**6-[[(Substituted-phenyl)nitrosoamino]methyl]-2,4-quinazolinediamines (IVb; 18–22, Table II). Procedure II.** A solution of 0.43 g (0.0062 mol) of $NaNO_2$ in 4 mL of $H_2O$ was added in portions over a 3-h period to a chilled solution of 1.5 g (0.003 mol) of 6-[[[4-chloro-3-(trifluoromethyl)phenyl]-amino]methyl]-2,4-quinazolinediamine (10) in 50 mL of DMF and 30 mL of 60% aqueous HOAc. The mixture was stirred at 0–5 °C for an additional 2 h and then poured into iced dilute $NH_4OH$. The resulting precipitate was collected, washed with $H_2O$, and recrystallized from 80% EtOH (charcoal) to afford 0.9 g (70%) of 6-[[[4-chloro-3-(trifluoromethyl)phenyl]nitrosoamino]-methyl]-2,4-quinazolinediamine (20), mp 216–217 °C.

Compounds 18, 19, 21, and 22 were prepared similarly.

***N*-(Substituted-phenyl)-*N*-[(2,4-diamino-6-quinazolinyl)methyl]formamides (IVc; 23–25 and 27, Table II). Procedure III.** A suspension of 3.5 g (0.009 mol) of 6-[[(3,4-dichlorophenyl)amino]methyl]-5-methyl-2,4-quinazolinediamine acetate (11) in 30 mL of 90% $HCO_2H$ was heated under reflux for 2 h, cooled, and concentrated to dryness under vacuum. A solution of the residue in 10% aqueous EtOH was made basic with $NH_4OH$. The resulting solid was collected, recrystallized from 80% aqueous EtOH, dried, and equilibrated in air to afford 1.4 g (43%) of *N*-[(2,4-diamino-5-methyl-6-quinazolinyl)-methyl]-*N*-(3,4-dichlorophenyl)formamide (25), which foams at 130–133 °C, resolidifies, and melts at 233–234 °C.

The double melting point of this material suggested the possibility of structural alteration upon heating. However, IR and NMR spectra of a sample that had been heated at 160 °C for 0.5 h indicated that the material had lost water but had not changed structurally.

***N*-[(2,4-Diamino-6-quinazolinyl)methyl]-*N*-(3,4-dichlorophenyl)acetamide (IVd; 26, Table II). Procedure IV.** A mixture of 3.3 g (0.01 mol) of 6-[[(3,4-dichlorophenyl)-amino]methyl]-2,4-quinazolinediamine (4) and 1.1 g (0.01 mol) of $Ac_2O$ in 80 mL of HOAc was stirred on the steam bath for 5 h, allowed to cool overnight, and concentrated to dryness under vacuum. A solution of the residue in hot water was made basic with $NH_4OH$. The resulting precipitate was collected, washed with $H_2O$, dried, and recrystallized from EtOH–$H_2O$ to afford 2.6 g (65%) of 26, which foams at 108–110 °C, resolidifies, and melts at 224–225 °C.

**Acknowledgment.** The authors are indebted to Drs. M. W. Fisher and C. L. Heifetz of Warner-Lambert Co. for the antibacterial studies and Dr. Joan Shillis and Co-workers for the L1210 tissue culture studies. We also thank William Pearlman for conducting the hydrogenations, C. E. Childs and associates for the microanalyses, and Dr. J. M. Vandenbelt and co-workers for the determination of spectral data.

**Registry No.** 1·$C_2H_4O_2$, 52128-44-6; 2·$C_2H_4O_2$, 87183-25-3; 3·$xC_2H_4O_2$, 52128-40-2; 4·$C_2H_4O_2$, 52128-16-2; 5·$C_2H_4O_2$, 52128-08-2; 6·$C_2H_4O_2$, 52128-18-4; 7·$C_2H_4O_2$, 87174-61-6; 8·$C_2H_4O_2$, 52128-04-8; 9·$C_2H_4O_2$, 52128-06-0; 10·$C_2H_4O_2$, 52128-20-8; 11·$C_2H_4O_2$, 52128-34-4; 12·$C_2H_4O_2$, 52128-32-2; 13·$C_2H_4O_2$, 52128-30-0; 14·$C_2H_4O_2$, 52128-10-6; 15·$C_2H_4O_2$, 52128-36-6; 16·$C_2H_4O_2$, 52128-12-8; 17·$^3/_2C_2H_4O_2$, 52128-14-0; 18, 52128-45-7; 19·$C_2H_4O_2$, 52128-22-0; 20, 52128-23-1; 21, 52128-38-8; 22·$C_2H_4O_2$, 52128-25-3; 23, 52128-46-8; 24, 52128-27-5; 25, 52128-37-7; 26, 52128-26-4; 27, 52128-28-6; V (Z = H), 18917-68-5; V (Z = Cl), 18917-75-4; V (Z = Me), 18917-72-1.

# *Notes*

## An Extension of the *f*-Fragment Method for the Calculation of Hydrophobic Constants (Log *P*) of Conformationally Defined Systems[1]

Michael A. Pleiss and Gary L. Grunewald*

*Department of Medicinal Chemistry, School of Pharmacy, The University of Kansas, Lawrence, Kansas 66045.*
*Received March 14, 1983*

An extension of the popular fragment methods for the calculation of octanol–water partition coefficient (log *P*) values of conformationally defined compounds is presented. Correction factors for both trans-antiperiplanar and gauche conformational isomers have been developed for both the Rekker and Leo fragment methods and successfully applied to a large, diverse group of conformationally defined phenethylamines. This approach is easy to use and only requires one additional correction factor per isomer. This method thus allows, for the first time, conformation to be taken into account for the fragment calculation of log *P* values.

The partition coefficient in the octanol–water system (log *P*) has been widely employed in quantitative structure–activity relationship (QSAR) studies as a measure of hydrophobicity. Since the experimental determination of log *P* values can be impractical and time consuming, accurate and straightforward methods for theoretical determination of this important property are desired. The initial work toward this aim was that of Hansch and Fujita.[2] It resulted in the hydrophobic substituent param-

(1) Portions of this paper were presented at the 184th National Meeting of the American Chemical Society, Kansas City, MO, Sept 12–17, 1982; see "Abstracts of Papers"; American Chemical Society: Washington, DC, 1982; Abstr MEDI 048.

0022-2623/83/1826-1760$01.50/0 