2,4-Diamino-5-benzylpyrimidines and Analogues as Antibacterial Agents. 10. 2,4-Diamino-5-(6-quinolylmethyl)- and -[(tetrahydro-6-quinolyl)methyl]pyrimidine Derivatives. Further Specificity Studies[1,2]

Barbara S. Rauckman, Mary Y. Tidwell, Jay V. Johnson, and Barbara Roth*,†

The Wellcome Research Laboratories, 3030 Cornwallis Road, Research Triangle Park, North Carolina 27709.
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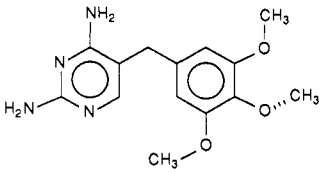
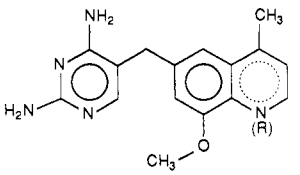
A series of 18 2,4-diamino-5-[(1,2,3,4-tetrahydro-6-quinolyl)methyl]pyrimidines has been prepared by the condensation of 2,4-diamino-5-(hydroxymethyl)pyrimidine with 1,2,3,4-tetrahydroquinolines in acidic medium. Several derivatives were catalytically aromatized; others were synthesized from these by routine aromatic substitution or by condensations of (anilinomethyl)pyrimidines to give quinolinylmethyl analogues. Compounds with 4-methyl-8-methoxy substitution are closely related to trimethoprim (**1a**) in structure and are excellent inhibitors of bacterial dihydrofolate reductase, with activity at least equivalent to that of **1a**. The highest degree of inhibition was achieved with the rigid aromatic series, but greater specificity was accomplished among the tetrahydroquinoline derivatives. This was directly related to N-1 substitution of 4-methyl-8-methoxy derivatives. The spatial relationships around N-1 and protonation at this site may both affect selectivity. Such compounds also had excellent broad-spectrum in vitro antibacterial activity.

The conformational properties of the antibacterial agent trimethoprim (TMP, **1a**), both alone and when complexed with dihydrofolate reductase (EC 1.5.1.3, DHFR), have been well established.[3-5] The 3,5-dimethoxy groups lie in plane bent away from the 4-substituent as shown (**1a**), while the 4-methoxy group of necessity lies out of plane. All three functions contact protein side chains or the nicotinamide moiety of the coenzyme in the *E. coli* DHFR complex.[5] All three functions are involved in the specificity of TMP for bacterial DHFR.[4,6,7] Conversion of the 3,4-substituents to a ring system such as that shown in **1b** might be expected to enhance binding and possibly specificity, due to increased rigidity, with appropriate substitution. Pharmacokinetic and metabolic properties would also be altered.



1a (TMP)



1b

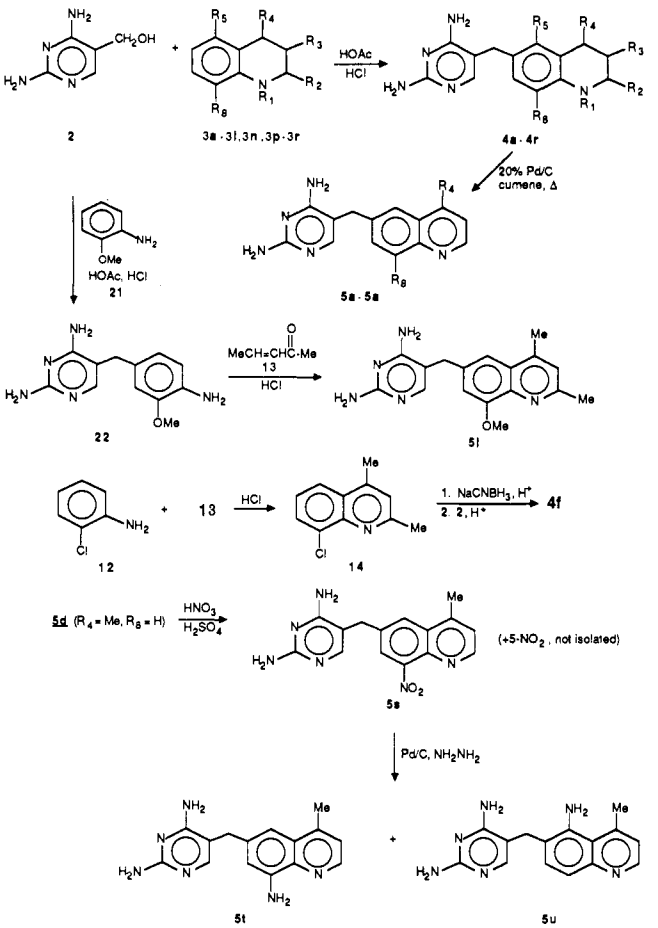
In paper 6 of this series, we described a bicyclic dihydrofuran derivative related in structure to **1b**;[8] additional analogues have been prepared, but the chemistry did not permit the desired substitution patterns.[9] Quinoline analogues, however, are more adaptable to substitution, as well as to study at various stages of reduction.

This paper examines quinolines and tetrahydroquinoline derivatives of type **1b** (where the 4-quinolyl substituent is limited to a methyl function or hydrogen, but which can contain 1,2,3,5- and/or 8-substitution of various types) for their synthesis, inhibition of various DHFRs, and in vitro antibacterial activity.

Chemistry

A route to 2,4-diamino-5-[(1,2,3,4-tetrahydro-6-quinolyl)methyl]pyrimidines was readily available, as shown in Scheme I. We had discovered earlier that compound **2** reacted readily with substituted phenols in acidic medium to produce 5-(*p*-hydroxybenzyl)pyrimidines,[8] and this reaction had been adapted to similar condensations with anilines.[10,11] When we carried out an initial reaction with 1,2,3,4-tetrahydroquinoline, we obtained **4a** (R_1–R_5, R_8 = H) in greater than 50% yield. Compounds **4b–r** of Table I were then prepared by this route. Derivatives **4m**

Scheme I



and **4o** represent acetylated products from hydroxyl-substituted tetrahydroquinoline precursors. Although it was

† Present address: Department of Chemistry, CB #3290, University of North Carolina, Chapel Hill, NC 27599.

(1) Roth, B.; Rauckman, B. S. U.S. Patent 4,587,341, May 6, 1986.
(2) For paper 9 of this series, see: Roth, B.; Baccanari, D. P.; Sigel, C. W.; Hubbell, J. P.; Eaddy, J.; Kao, J. C.; Grace, M. E.; Rauckman, B. S. *J. Med. Chem.* **1988**, *31*, 122.
(3) Bryan, R. F. Personal Communication, 1969. Phillips, T.; Bryan, R. F. *Acta Crystallogr., Sect. A* **1969**, *25*, S200.
(4) Matthews, D. A.; Bolin, J. T.; Burridge, J. M.; Filman, D. J.; Volz, K. W.; Kaufman, B. T.; Beddell, C. R.; Champness, J. N.; Stammers, D. K.; Kraut, J. *J. Biol. Chem.* **1985**, *260*, 381.
(5) Champness, J. N.; Stammers, D. K.; Beddell, C. R. *FEBS Lett.* **1986**, *199*, 61.
(6) Roth, B.; Aig, E. *J. Med. Chem.* **1987**, *30*, 1998.
(7) Baccanari, D. P.; Daluge, S.; King, R. *Biochemistry* **1982**, *21*, 5068.

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Table I. 2,4-Diamino-5-[(1,2,3,4-tetrahydro-6-quinolyl)methyl]pyrimidines Prepared by Condensations of Tetrahydroquinolines with 2,4-Diamino-5-(hydroxymethyl)pyrimidine

	quinoline substituents							recrystn	yield,		
no.	1	2	3	4	5	8	mp, °C	solvent[a]	%	empirical formula	analysis
4a							284–287	A	56	$C_{14}H_{17}N_5 \cdot 2HCl$	C,H,N,Cl
4b						OMe	201–203	B	80	$C_{15}H_{19}N_5O$	C,H,N
4c						OCH_2CH_2OMe	149–151	B		$C_{17}H_{23}N_5O_2$	C,H,N
4d				Me			280–282	A		$C_{15}H_{19}N_5 \cdot 2HCl$	C,H,N,Cl
4e				Me		OMe	221–223	A	93	$C_{16}H_{21}N_5O \cdot 2HCl \cdot H_2O$	C,H,N
4f		Me		Me		Cl	195–197	A		$C_{16}H_{20}ClN_5 \cdot 0.5H_2O$	C,H,N,Cl
4g	Me						190–191	B	68	$C_{15}H_{19}N_5$	C,H,N
4h	Et			Me			250–252	A	83	$C_{17}H_{23}N_5 \cdot 2HCl \cdot H_2O$	C,H,N,Cl
4i	Me			Me		OMe	219–221	B	33	$C_{17}H_{23}N_5O \cdot 2HCl \cdot 0.5H_2O$	C,H,N,Cl
4j	Me			Me		Et	147	A	6	$C_{18}H_{25}N_5$	C,H,N
4k	CH_2CH_2OMe			Me		OMe	187–189	B	16	$C_{19}H_{27}N_5O_2 \cdot 0.3H_2O$	C,H,N
4l	CH_2CH_2OH			Me		OMe	198–201	B	11	$C_{18}H_{25}N_5O_2 \cdot 0.3H_2O$	C,H,N
4m[b]	CH_2CH_2OAc			Me		OMe	181–182	B	16	$C_{20}H_{27}N_5O_3 \cdot 0.3H_2O$	C,H,N
4n			COOEt			OMe	159–161	C, B		$C_{18}H_{23}N_5O_3$	C,H,N
4o[b]			CH_2OAc			OMe	57–60	D, B		$C_{18}H_{23}N_5O_3 \cdot 0.3H_2O$	C,H,N
4p			CH_2OH			OMe	195–196	D, B		$C_{16}H_{21}N_5O_2$	C,H,N
4q	Et		CH_2OH			OMe	97–100	E, B		$C_{18}H_{25}N_5O_2 \cdot 0.25H_2O$	C,H,N
4r			COOEt		OMe	OMe	186–188	B	49	$C_{19}H_{25}N_5O_4$	C,H,N

[a] A, 95% EtOH; B, absolute EtOH; C, chromatography; see text; D, chromatography silica gel, CH_2Cl_2/MeOH, 2–5%; E, 2 N NaOH to remove Ac function. [b] Acetylation occurred in part during the condensation; products were separated by chromatography.

Table II. 2,4-Diamino-5-(6-quinolylmethyl)pyrimidines Prepared by Oxidation of 1,2,3,4-Tetrahydro Derivatives

	quinoline substituents			recrystn	yield,		
no.	4	8	mp, °C	solvent[a]	%	empirical formula	analysis
5a[b]			264–266	A	8	$C_{14}H_{13}N_5 \cdot 0.33EtOH$	C,H,N
5b		OMe	285–287	B	35	$C_{15}H_{15}N_5O$	C,H,N
5c		OCH_2CH_2OMe	253–255	B	20	$C_{17}H_{19}N_5O_2$	C,H,N
5d	Me		262–268	B	55	$C_{15}H_{15}N_5$	C,H,N
5e	Me	OMe	287–290	B	17	$C_{16}H_{17}N_5O$	C,H,N

[a] A, absolute EtOH; B, 2-methoxyethanol. [b] The tetrahydro derivative **4a** was dehydrogenated with $PdCl_2$ in dilute HCl, according to the directions of Cooke, G. W.; Gulland, J. M. *J. Chem. Soc.* **1939**, 872.

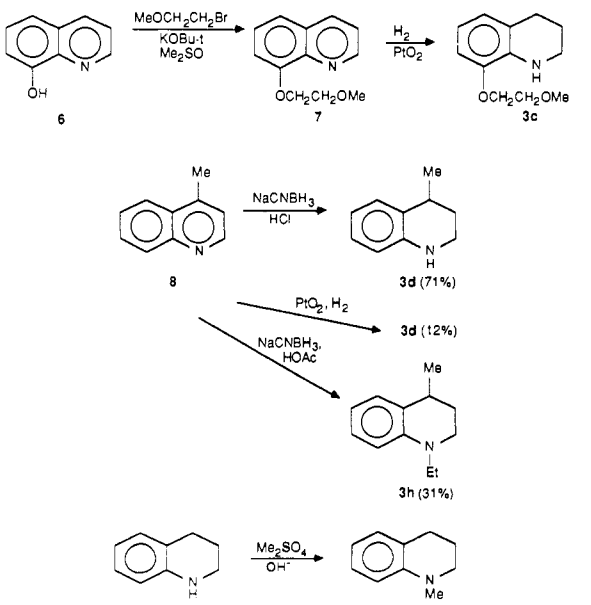
not necessary to use acetic acid as the solvent in this reaction, it was a good solubilizing medium, and yields were usually better than when an alcohol plus *p*-toluenesulfonic acid, for example, were employed.

The tetrahydroquinolines **4** could be oxidized to the aromatic (quinolylmethyl)pyrimidines in the presence of a palladium catalyst at temperatures above 120 °C; **5a–e** (Table II) were obtained in this way. Yields were not particularly good, and the resultant products were not particularly selective in their biological activity, so the remaining compounds were not submitted to this procedure. However, a few such derivatives were prepared by other routes.

Condensation of **2** with aniline **21** gave an (anilinomethyl)pyrimidine (**22**), which reacted with **13** to produce a 5-[(2,4-dimethylquinolyl)methyl]pyrimidine (**5i**). Conversely, **13** could be treated with an aniline (**12**) to give quinoline **14**, which upon reduction and condensation with **2** gave the [(tetrahydroquinolyl)methyl]pyrimidine derivative **4f**.

The (quinolylmethyl)pyrimidine **5d** was nitrated to give a mixture of 5- and 8-nitro derivatives; the latter was purified by chromatography (**5s**). Upon reduction of the reaction mixture without purification, both the 5- and 8-amino derivatives were separated (**5t** and **5u**, Scheme I).

Scheme II



Scheme II shows some simple quinoline interactions. The reduction of **8** should be noted. Catalytic reduction was poor, no doubt because of catalyst poisoning by the amine function. A report by Glennon et al.[12] on the reduction with $NaCNBH_3$ and acetic acid was investigated; in our hands it produced the 1-ethyl derivative as a major product (**3h**). However, when hydrochloric acid was employed instead, **3d** was obtained in 71% yield. This method was applied to the reduction of **14** (Scheme I) and

(8) Stuart, A.; Paterson, T.; Roth, B.; Aig, E. *J. Med. Chem.* **1983**, *26*, 667.
(9) Roth, B.; Tidwell, M. Y.; Ferone, R.; Baccanari, D. P.; Sigel, C. W.; DeAngelis, D.; Elwell, L. *J. Med. Chem.* Accepted for publication.
(10) Swaringen, R. A.; Eaddy, J. F., III; Henderson, R. R. U.S. Patent 4,568,744, 1986.
(11) Roth, B.; Rauckman, B. S.; Ferone, R.; Baccanari, D. P.; Champness, J. N.; Hyde, R. M. *J. Med. Chem.* **1987**, *30*, 348.
(12) Glennon, R. A.; Jaynco, J. M.; Salley, J. J. *J. Med. Chem.* **1982**, *25*, 68.

Table III. Inhibitory Activities of 2,4-Diamino-5-[(1,2,3,4-tetrahydro-6-quinolyl)methyl]pyrimidines against Dihydrofolate Reductases

	quinoline substituents						inhibition vs DHFR, I_{50}, M, × 10^8		
no.	1	2	3	4	5	8	*E. coli*	rat liver	*Neisseria gonorrhoeae*
4a							45	14000	
4b						OMe	4.4	7600	51
4c						$O(CH_2)_2OMe$	5.7	17000	53
4d				Me			13	2200	40
4e				Me		OMe	0.81	3300	
4f		Me		Me		Cl	3.0	4100	24
4g	Me						15.6	8900	95
4h	Et			Me			7.4	3800	69
4i	Me			Me		OMe	0.68	25000	89
4j	Me			Me		Et	0.24	4400	30
4k	$(CH_2)_2OMe$			Me		OMe	2.3	26000	140
4l	$(CH_2)_2OH$			Me		OMe	1.2	14200	61
4m	$(CH_2)_2OAc$			Me		OMe	1.6	19000	63
4n			COOEt			OMe	1.9	4400	
4o			CH_2OAc			OMe	0.74	6100	16
4p			CH_2OH			OMe	2.2	6400	41
4q	Et		CH_2OH			OMe	4.9	44000	260
4r			COOEt		OMe	OMe	22	14200	190
1a (TMP)[a]							0.5	34000	45

[a] Standard.

11 (Scheme III). Scheme III shows various additional synthetic routes to quinoline and tetrahydroquinoline precursors.

The preparation of quinolines such as **9** from anilines and diketene are well described in the literature.[13] In this case the preparation of sizeable quantities of **11** was accomplished by chlorination as usual to **10**, followed by reduction with hydrazine plus catalyst on a large scale, which gave a quantitative yield of **11**. Reduction to the tetrahydro derivatives was accomplished as described above.

Alkylation at N-1 could be accomplished by acylation of the tetrahydro derivative, followed by reduction of the acyl group, as with **3i** and **3k**, or by quaternization of the N-1 aromatic nitrogen followed by ring reduction as for **3l**.

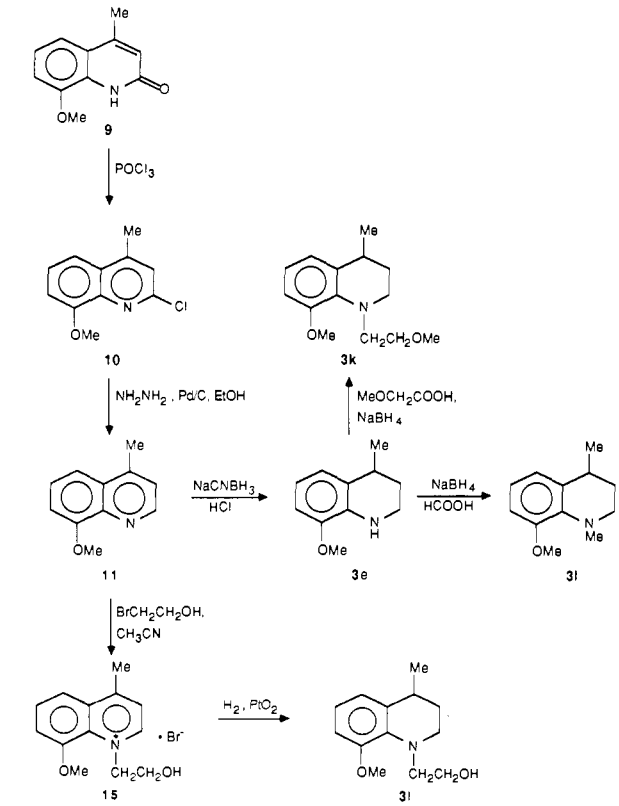
Scheme IV illustrates the preparation of several 3-substituted tetrahydroquinolines and their aromatic counterparts. Compound **16**, obtained from *o*-anisidine and diethyl (ethoxymethylene)malonate in several steps,[14] was condensed with **2** as in Scheme I. Reduction of **16** with $LiAlH_4$ to 3-hydroxymethylene analogues gave partial cleavage and partial reduction of the 1-acetyl group in a 1:2 ratio. Table I provides data on the condensations with **2**. Compound **17**,[15,16] upon chlorination and catalytic reduction, gave a mixture of dechlorinated products, including 1,4-dihydro- and 1,2,3,4-tetrahydro derivatives **19** and **3r**, as well as **20**. The structures were assigned by NMR spectroscopy.

The pK_a values for three of the tetrahydroquinolines (**3**) were determined. These are

no.	substituents	pK_a (20 °C)[17]
3g	1-methyl	4.10
3h	1-ethyl-4-methyl	4.18
3i	1,4-dimethyl-8-methoxy	6.51

(13) (a) Elderfield, R. C. *Heterocyclic Compounds*; John Wiley & Sons: New York, 1952; Vol. 4. (b) Jones, G. *Heterocyclic Compounds*; John Wiley & Sons: New York, 1977; Vol. 32, Part I.
(14) This compound was prepared by Dr. Kenneth Ingold in our laboratories.
(15) Kaslow, C. E.; Young, V. V. *J. Am. Chem. Soc.* **1950**, *72*, 5325.
(16) Erickson, E. H.; Hainline, C. F.; Lenon, L. S.; Matson, C. J.; Rice, T. K.; Swingle, K. F.; Van Winkle, M. *J. Med. Chem.* **1979**, *22*, 816.

Scheme III



Biological Activities and Discussion

Table III lists the inhibition, expressed as I_{50} values, for the [(tetrahydroquinolyl)methyl]pyrimidines against *Escherichia coli*, rat liver, and *Neisseria gonorrhoeae* DHFR, compared to 1a. Table IV shows comparable numbers with *E. coli* and rat liver DHFR for the aromatic (quinolylmethyl)pyrimidines prepared. For a compound to be of interest as a broad spectrum antibacterial agent, we look for I_{50} values against *E. coli* DHFR of 1×10^{-8} M or less and for a wide separation in activity against vertebrate DHFR, as shown for 1a. For the gonococcal enzyme an interesting compound would normally have an I_{50} value 10 times less than that of 1a for this enzyme. Other factors are of course involved, but these are initial guidelines.

Table IV. Inhibitory Activities of 2,4-Diamino-5-(6-quinolylmethyl)pyrimidines against Dihydrofolate Reductases

	quinoline substituents				inhibition vs DHFR, I_{50}, M, × 10^8	
no.	2	4	5	8	*E. coli*	rat liver
5a					9.0	1800
5b				OMe	1.7	1200
5c				$O(CH_2)_2OMe$	4.3	990
5d		Me			1.4	2200
5e		Me		OMe	<0.2	2000
5i	Me	Me		OMe	0.19	4300
5s		Me		NO_2	0.2	570
5t		Me		NH_2	2.49	3200
5u		Me	NH_2		29	1500

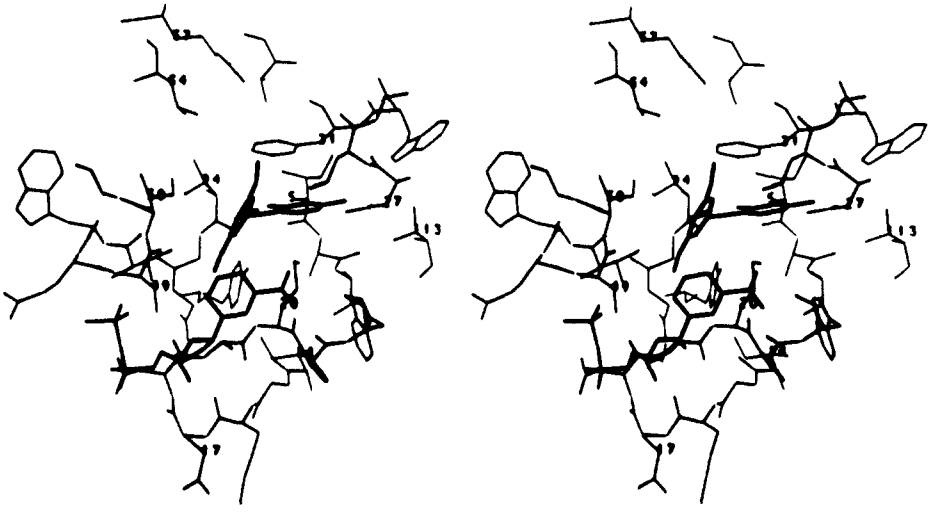
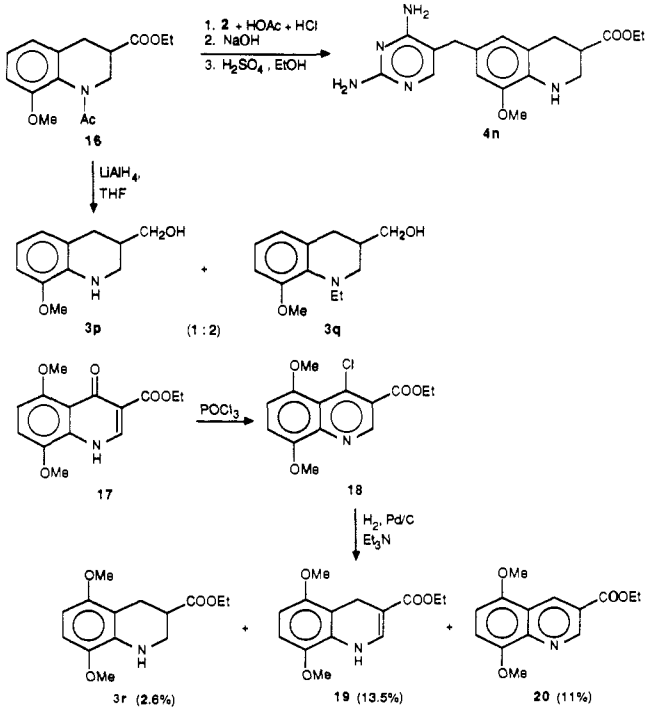


Figure 1. Stereo skeletal representation of part of the active site of *E. coli* DHFR in ternary complex with **1a** and cofactor NADPH. The two ligand molecules are drawn with bold lines. Reproduced from ref 5 (Figure 1) with permission of the authors.

Scheme IV



The compound that most closely resembles **1a** in substituent pattern in Table III is **4i**, as can be seen by comparing structures **1a** and **1b**. The *N*-methyl function will probably be forced out of plane, as with the 4-methoxy group of TMP. Only the 4-methyl group of **4i** differs from the corresponding methyl group of **1a** in locus, probably being out of plane in at least one of its two enantiomeric forms. Not only is **4i** the most selective and second most active compound of the table for *E. coli* DHFR but it is also as inhibitory as **1a**, within experimental error. This suggests that it indeed binds almost identically to TMP with these enzymes. However, due to lack of symmetry, it has the opportunity of selecting two rotamers in the protein.

Figure 1 reproduces a stereo view of **1a** in ternary complex with *E. coli* DHFR and NADPH.[5] Our quinoline analogues may be visualized as having the ring nitrogen atom replacing the oxygen of the 4-methoxy group of **1a**; this atom would lie at the solvent interface. The second ring might be joined at the locus of either the 3- or 5-methoxy group of **1a**, since no interference can be observed with the enzyme. The preference probably depends upon the substituents present. If **4i** has its second ring in the "down" position in the figure, the 4-methyl group will face the nicotinamide ring of the cofactor and interact with Met-20 on the right and Ser-49 on the left. The 8-methoxy group will interact with Leu-28 on the right, Ile-50 and Leu-54 on the left, and Phe-31 behind. A 180° torsional rotation at the juncture of the aromatic ring with the methylene group would cause the substituents to interact in the reverse manner.

The best inhibitor, 8-ethyl derivative **4j**, is more active than **4i** by 3- to 6-fold against all three enzymes. This result does not match data with the 3,5-diethyl-4-methoxybenzyl and 3,4,5-triethylbenzyl analogues precisely (papers 7 and 8),[6,11] since in those instances the alkyl derivatives were slightly *less* active against *E. coli* enzyme, although they were several times more active against gonococcal and vertebrate DHFR. We related the earlier observations to the degree of hydrophobicity of each

pocket by measuring the solvent-exposed areas with 1a and with the triethyl analogue. This was possible, since X-ray data were available that showed the substituents to be more deeply buried in vertebrate DHFR. Thus desolvation energy was required for binding the more polar methoxy derivatives in the latter enzymes. Since **4i** and **4j** are unsymmetrical, they may possibly adopt different conformations with *E. coli* DHFR to optimize van der Waals interactions. Attempts to crystallize these compounds in ternary complex with *E. coli* DHFR and NADPH were unsuccessful.[18]

That **4i** cannot be compared precisely with 1a is suggested by the fact that its close analogues **4k–m**, which introduce polar substituents at N-1, are less active than **4i**. In the case of trimethoprim, replacement of the 4-methoxy group by similar substituents had virtually no effect on binding, suggesting that atoms beyond the methyl moiety no longer were in contact with the enzyme. Modeling confirmed this conclusion.

The 1-methyl substituent of **4i** is extremely important to its selectivity for bacterial DHFR. This is seen by comparing the *E. coli* and rat liver DHFR data with those of **4e**, where the activity against mammalian DHFR is almost 1 order of magnitude greater than with **4i**. This also occurred, although to a lesser degree, upon demethylation of 1a, and we had suggested that the out-of-plane 4-methoxy group had a deleterious effect on binding to vertebrate DHFR, possibly by preventing a close fit of the aromatic ring and substituents to the enzyme.[19] The very high selectivity of the 4-isopropenyl analogue of 1a reinforced this conclusion.[20] It must also be mentioned, however, that 4-aminobenzyl analogues of 1a were highly active and selective for bacterial DHFR, a fact that might seem to argue against the above conclusions.[11,21] Since quinoline **4e** contains an amino substituent (although secondary, rather than primary) at a similar position, it too might have been expected to be highly selective.

It is important to consider the pK_a values of the tetrahydroquinolines. Of the three compounds tested, only **3i**—a compound with both a 1- and 8-substituent, and furthermore an 8-substituent that might serve as a proton acceptor—has a pK_a sufficiently high for it to be appreciably protonated at physiological pH. The lone pair on the oxygen of the 8-methoxy group no doubt aids in stabilizing the protonation, and the structure of the resultant protonated species will be tetrahedral. Whether the ionization or the spatial configuration around N-1 of the nonprotonated species assumes the greater importance in decreasing vetebrate DHFR binding of 1-substituted tetrahydroquinolines, one cannot say at this point. Possibly an 8-substituent such as methylamino might engender sufficient basicity to help answer the question.

Removal of the 4-methyl substituent (**4b**), and then 8-methoxy (**4a**), decreases the inhibition by approximately 1 order of magnitude as each substituent is lost, which is also the case with 1a and its dimethoxy and monomethoxy counterparts.[7] In many respects then, the current series is closely comparable in enzyme binding properties to the benzyl derivatives. It does not necessarily follow that their in vitro and in vivo activities will be at all similar, however.

With the 3-substituted derivatives **4n–r** we are exploring a new area in space relative to the enzyme. Compound **4o** is particularly intriguing in its high *E. coli* DHFR activity. Possibly the side chain bends in the direction of the 4-position, so that the methyl of the acetyl function fits into the 4-methyl pocket of the enzyme. Addition of a 1-substituent would probably have created better selectivity (see **4q**).

Compound **4r** contains a substituent pattern which is similar in character to that of the 2,3,4-trimethoxy analogue of 1a, a very poor inhibitor.[8] It was very clear in the latter case that the methoxy groups were all bending in the wrong direction for good enzyme contacts.

We had found earlier that replacement of the 3,5-dimethoxy groups of 1a with appropriate alkyl or halo substituents resulted in considerably increased enzyme binding to *N. gonorrhoeae* DHFR.[11] Only two compounds more lipophilic than **4i** were tested here (**4j**, with an 8-ethyl and **4f**, with an 8-chloro substituent), and both were about 3 times more inhibitory to this enzyme than **4i**. No doubt this result could be improved with further effort. The trend is as expected.

The aromatic series of Table IV is marked by some compounds of very high inhibition against bacterial DHFR; however, none have sufficiently low activity against vertebrate DHFR to be early choices for therapeutic utility.

The activity pattern parallels that of the tetrahydro derivatives with regard to 4- and 8-substitution. However, compound **5e** is several times more inhibitory to *E. coli* DHFR than is **1a**; a K_i value was not determined. Compound **5e** is also at least 4 times more active than its tetrahydro counterpart **4e**. Whether the increased activity is completely due to the rigidity attained in the planar aromatic system cannot be stated arbitrarily; the π electrons may assist the van der Waals interaction. The extra ring atoms of the quinolines compared to the benzyl derivatives are located very near the edge of the cleft in a largely polar environment, so a significant contribution is not expected from them per se.

The high degree of inhibition of the 4-methyl-8-nitro compound against both enzymes is worthy of note, as is the comparison with the polar 8-amino analogue, which intuitively would be expected to be less active than it is since it replaces a methoxy group that has important van der Waals contacts with the enzyme. One suspects that some adjustments in binding loci occur to accommodate such different substituents. A 5-amino substituent is very deleterious; it would be expected to influence torsional angles about the methylene group in an adverse manner.

Tables V and VI present in vitro antibacterial activities of these compounds, expressed as a ratio when compared to trimethoprim activity. Serial dilutions of 1–3–10–30...etc. were carried out, and the minimum inhibitory concentrations (MIC) were divided by that of 1a. Numbers greater than 1 then signify activity less than that of 1a. The most active compounds of Table V are **4i** and **4j**, in direct agreement with the enzyme inhibitory data, and they also can be considered to be essentially equivalent to 1a in the MIC screen. The compounds are more active against the Gram-positive organisms *Staphylococcus aureus* and *Streptococcus faecalis* (*faecium*) than is 1a.

The most active compounds of Table VI are **5e** and **5i**, the 4-methyl-8-methoxy and 2,4-dimethyl-8-methoxy derivatives, both of which are fully equipotent to the standard. This might be expected from their high enzyme inhibition, but is often not the case. The high activity against *Proteus* species is to be noted in particular. Fol-

(17) Roth, B.; Strelitz, J. Z. *J. Org. Chem.* **1969**, *34*, 821.
(18) Stammers, D. K. Personal communication.
(19) Roth, B.; Aig, E.; Rauckman, B. S.; Strelitz, J.; Philips, A. P.; Ferone, R.; Bushby, S. R. M.; Sigel, C. W. *J. Med. Chem.* **1981**, *24*, 933.
(20) Kompis, I.; Then, R.; Boehni, E.; Rey-Bellet, G.; Zanetti, G.; Montavon, M. *Eur. J. Med. Chem.* **1980**, *15*, 17.
(21) Kompis, I.; Rey-Bellet, G.; Zanetti, G. Ger. Offen. 2,443,682, 1975; *Chem. Abstr.* **1975**, *83*, 43376*h*.

Table V. Comparative in Vitro Antibacterial Activity (MIC Compound/MIC 1a) of 2,4-Diamino-5-[(1,2,3,4-tetrahydro-6-quinolyl)methyl]pyrimidines (4)[a]

	4a	4b	4c	4d	4e	4f	4g	4h	4i	4j	4k	4l	4m	4n	4o	4p	4q	4r
S. pyogenes CN 10	10	3	3	1	1	3				1	1	3	10	3	3	10	10	b
S. faecalis CN 478	10	3	3	3	1	3	3	3	0.3	0.03	0.3	0.3	1	30	3	3	3	
S. agalactiae CN 1143	10	3	10	3	1	3	10	3	0.3	1	3	1	1	10	10	10	30	
S. aureus CN 491	30	3	10	3	1	3	10	3	1	0.03	3	1	3	30	10	3	10	
B. bronchiseptica CN 385	10	1	30	10	10	100	30	100	3	1	100	10	3	>100	10	30	30	
V. cholerae ATCC 14035	10	1	10	3	1	3	10	10	3	3	100	3	10	30	10	3	100	
P. multocida ATCC 6587	10	3	30	3	3	30	30	30	3	3	30	10	10	30	30	30	100	
M. smegmatis S 3254	3	1	3	3	1	10	10	10	3	3	10	3	3	30	30	10	100	
S. typhimurium S 8587	10	3	100	10	10	100	30	100	10	1	100	10	30	30	30	10	30	
S. typhosa CN 512	10	3	100	10	10	100	30	100	3	10	30	30	30	100	30	10	100	
S. flexneri CN 6007	30	10	100	30	10	300	10	100	10	10	100	10	30	10	30	30	100	
E. coli CN 314	30	10	100	30	3	100	30	100	3	3	30	30	30	30	30	10	100	
S. marcescens CN 2398	10	3	>10	10	3	>10	30	>30	3	3	>10	10	>10	>10	>10	>10	>10	
K. pneumoniae CN 3632	10	3	100	30	3	100	30	100	3	3	30	10	10	100	100	10	30	
E. aerogenes 2200/86	10	3	100	10	3	100	30	100	3	1	30	30	30	10	30	30	10	
C. freundii 2200/77	10	10	100	30	10	100	30	100	3	3	100	3	10	10	30	30	100	
P. vulgaris CN 329	10	3	100	10	10	100	30	100	10	10	>100	10	10	>100	30	100	>100	
P. mirabilis S 2409	10	3	>30	10	3	30	10	30	3	3	-	10	30	>30	30	>30	>30	

[a] Numbers greater than 1 signify lower activity than trimethoprim. Differences of ±1 dilution (1:3) are not considered significant. [b] Inactive at <100 μg/mL.

Table VI. Comparative in Vitro Antibacterial Activity (MIC Compound/MIC 1a) of 2,4-Diamino-5-(6-quinolylmethyl)pyrimidines (5)

	5a	5b	5c	5d	5e	5i	5s	5t	5u
S. pyogenes CN 10	3	3	3	3	1	0.1	1	-	30
S. faecalis CN 478	3	3	3	1	1	1	3	3	10
S. agalactiae CN 1143	3	3	10	1	1	1	1	10	100
S. aureus CN 491	30	3	10	1	0.3	0.3	1	3	30
B. bronchiseptica CN 385	10	30	30	1	3	3	3	30	>100
V. cholerae ATCC 14035	3	1	30	1	0.3	0.3	1	3	100
P. multocida ATCC 6587	10	3	30	1	1	1	3	10	300
M. smegmatis S 3254	0.3	1	3	1	0.3	1	1	10	100
S. typhimurium S 8587	10	3	100	3	3	3	10	30	100
S. typhosa CN 512	10	3	100	1	1	1	3	10	100
S. flexneri CN 6007	10	3	100	3	1	3	10	30	100
E. coli CN 314	3	3	100	3	1	3	10	10	100
S. marcescens CN 2398	3	1	>10	1	1	1	30	30	>10
K. pneumoniae CN 3632	3	3	100	1	1	1	10	10	100
E. aerogenes 2200/86	3	3	100	3	1	3	10	10	300
C. freundii 2200/77	10	10	300	3	3	3	10	10	100
P. vulgaris CN 329	10	3	>100	1	1	3	10	3	>100
P. mirabilis S 2409	3	3	>30	1	1	0.3	10	1	30

lowing very closely in activity are **5d**, the 4-methyl derivative, and **5b**, its 8-methoxy congener. Even the unsubstituted compound 5a is very active. These results suggest that simplicity of aromatic substitution and avoidance of bulky side chains (for example, **5c**) aid in penetration through bacterial cell walls. We have often observed this in the past, in attempting to adjust log *P* values of side chains to aid passage into cells; this usually has little useful effect unless shapes and bulk are considered as well.[22]

In conclusion, we have identified several quinoline or tetrahydroquinoline derivatives with in vitro antibacterial activities equivalent to that of the standard 1a. This activity matches the *E. coli* DHFR inhibitory data rather closely in most instances, with the exception that some of the enzyme data would suggest that antibacterial data should show slightly enhanced activity over that of 1a. The specificity for bacterial DHFR is considerably increased in the tetrahydroquinoline series compared to its aromatic analogues. Several of the compounds are currently undergoing in vivo examination for efficacy, toxicity, and pharmacokinetic properties.

Experimental Section

Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Where analyses are indicated by symbols of the elements only, analytical results obtained for these elements were within ±0.4% of the theoretical values. Nuclear magnetic resonance (NMR) spectra were recorded on Varian XL-100 and T60 spectrophotometers; chemical shifts are reported in parts per million (δ) from internal tetramethylsilane. Ultraviolet spectra were recorded on a Cary 118 spectrophotometer. Thin-layer chromatography was carried out on silica gel with CH_2Cl_2/MeOH, $CHCl_3$/MeOH, $CHCl_3$/EtOH/NH_3, or EtOAc/MeOH as solvent mixtures. Column chromatographic separations were carried out on silica gel, normally with CH_2Cl_2/MeOH mixtures, or as otherwise stated. Yields quoted refer to products that were chromatographically homogeneous except as described. The biological assays were carried out according to methods previously detailed.[23,24]

General Method for Preparing 2,4-Diamino-5-[(1,2,3,4-tetrahydro-6-quinolyl)methyl]pyrimidines (4) from 1,2,3,4-Tetrahydroquinolines (3) and 2,4-Diamino-5-(hydroxymethyl)pyrimidine (2). A mixture of equivalent amounts of 2,4-diamino-5-(hydroxymethyl)pyrimidine (**2**)[8] and a 1,2,3,4-tetrahydroquinoline derivative (**3**) in glacial acetic acid containing 2 equiv of concentrated hydrochloric acid or other strong acid is heated under reflux for about 1–6 h, while the course of the reaction is followed by TLC. Normally a clear solution is formed. This may be clarified and taken to dryness; however, sometimes the product crystallizes. The residue is taken up in water and

(22) Painter, G. R.; Grunwald, R.; Roth, B. *Mol. Pharmacol.* **1988**, *33*, 551.
(23) Roth, B.; Strelitz, J. Z.; Rauckman, B. S. *J. Med. Chem.* **1980**, *23*, 379.
(24) Bushby, S. R. M.; Hitchings, G. H. *Br. J. Pharmacol. Chemother.* **1968**, *33*, 72.

the solution made basic with ammonia, which results in the precipitation of the product, occasionally as a gummy solid. The product may be crystallized, usually from EtOH, and is purified by column chromatography on silica gel usually by eluting with CH_2Cl_2/MeOH. Final crystallization from EtOH/HCl converts the product to a crystalline hydrochloride. Products prepared in this way are described in Table I, and an example is provided below.

2,4-Diamino-5-[(1,2,3,4-tetrahydro-8-methoxy-6-quinolyl)methyl]pyrimidine (4b). 8-Methoxy-1,2,3,4-tetrahydroquinoline (**3b**)[25] (2.88 g, 0.021 mol) was mixed with 2.80 g (0.02 mol) of 2,4-diamino-5-(hydroxymethyl)pyrimidine (**2**), 35 mL of glacial AcOH, and 3.45 mL of concentrated hydrochloric acid and heated under reflux for 3.5 h. The product crystallized from the reaction mixture as an off-white solid, which was washed with water and treated with ammonia, followed by recrystallization from absolute EtOH (5.0 g, 80%). A slight impurity was removed by chromatography on a silica gel column, with 19:1 CH_2Cl_2/MeOH as the eluent. The eluate was taken to dryness, and the residue crystallized from absolute EtOH; mp 201–203 °C. Anal. ($C_{15}H_{19}N_5O$) C, H, N.

8-(2-Methoxyethoxy)quinoline (7). To 8-hydroxyquinoline (**6**) (9.47 g, 0.065 mol) in Me_2SO (50 mL) was added 7.69 g (0.0685 mol) of KO-*t*-Bu, which produced a bright yellow solution. This was followed by the addition of 2-methoxyethyl bromide (8.96 g, 0.065 mol). The mixture was stirred at room temperature for 2 h and turned a dark red. The solvent was removed under vacuum, and the residue was dissolved in water. The aqueous solution was extracted several times with EtOAc, the EtOAc solution was then washed well with water and dried, and the solvent was removed; the residual oil weighed 7.45 g. This was purified on a silica gel column, eluted with heptane/ethyl acetate, with increasing proportions of the latter. This produced **7** as a light blue oil (6.18 g, 47%): NMR ($CDCl_3$) δ 3.51 (s, 3, OMe), 4.01 (tr, 2, CH_2), 4.48 (tr, 2, CH_2), 7.20 (m, 1, pyridine β-H), 7.45 (m, 3, Ar), 8.15 (dd, 1, pyridine γ-H), 8.98 (dd, 1, pyridine α-H). Anal. ($C_{12}H_{13}NO_2$) C, H, N.

1,2,3,4-Tetrahydro-8-(methoxyethoxy)quinoline (3c). Compound **7** (6.48 g, 31.9 mmol) was dissolved in MeOH (50 mL) and reduced on a Parr hydrogenation apparatus with PtO_2 catalyst. The catalyst was removed, and the solution was taken to dryness. The residual dark oil was purified on a short silica gel column with 4:1 heptane/EtOAc for elution. The isolated oil **3c** (4.87 g, 74%) had the following NMR spectrum: ($CDCl_3$) δ 1.93 (quintet, 2, CH_2, β-H), 2.76 (tr, 2, CH_2), 3.32 (tr, 2, CH_2), 3.43 (s, 3, OMe), 3.72 (tr, 2, OCH_2), 4.11 (tr, 2, CH_2O), 4.31 (br, 1, NH), 6.57 (s, + sh, 3, Ar-3H). Anal. ($C_{12}H_{17}NO_2$) C, H, N.

1,2,3,4-Tetrahydro-4-methylquinoline (3d). Method A. By Catalytic Reduction. A solution of lepidine (**8**) (7.16 g) in MeOH (50 mL) was reduced in a Parr hydrogenation apparatus with a total of 1.25 g of PtO_2 catalyst, added in three portions at intervals. The reduction was very slow. After 36 h, the catalyst was removed, followed by the solvent. The residue proved to be a mixture that still contained considerable lepidine. This was separated on a silica gel column with 10:1 hexane/EtOAc for elution. A 0.91-g fraction of **3d** (12%) was isolated: NMR ($CDCl_3$) δ 1.26 (d, 3, CH*Me*), 1.5–2.2 (m, 2, CH_2), 2.89 (septet, 1, C*H*Me), 3.26 (tr, 2, NCH_2), 3.78 (br s, 1, NH), 6.37–7.2 (m, 4, ArH_4); MS 147 (M^+). Anal. ($C_{10}H_{13}N$) C, H, N.

Method B. By Reduction with $NaCNBH_3$ and HCl. The reaction was repeated in Et_2O with 2 equiv of $NaCNBH_3$ and 2 equiv of concentrated hydrochloric acid by using the general procedure for compound **3e** below. This produced 71% of **3d**. When glacial acetic acid was used as the solvent, an N-ethylated derivative was obtained (see **20** below).

2-Chloro-8-methoxy-4-methylquinoline (10). 8-Methoxy-4-methyl-2-quinolone (**9**)[26] (3.93 g) was treated with 6 mL of $POCl_3$ at 120 °C for 2 h. The reaction mixture was poured on ice (100 g), the pH adjusted to 9 with 15 mL of concentrated NH_4OH, and the product extracted with 2 × 100 mL of EtOAc. Evaporation of the EtOAc extracts and chromatography of the residue on a silica gel column with 3:1 heptane/EtOAc as the eluent gave 4.2 g (97%) of **10**, mp 106–108 °C. Anal. ($C_{11}H_{10}ClNO$) C, H, N.

8-Methoxy-4-methylquinoline (11). Method A. Compound **10** (1.85 g) was dissolved in 50 mL of absolute EtOH and dechlorinated on a Parr apparatus with 5% Pd/C. The catalyst was removed and the solvent evaporated, followed by neutralization of the residue with 50 mL of 0.5 M $NaHCO_3$. This was extracted with 2 × 50 mL of CH_2Cl_2, and the combined extracts were dried and evaporated: yield, 1.35 g (88%) of 11, mp 68–72 °C; NMR ($CDCl_3$) δ 2.52 (s, 3, Me), 4.03 (s, 3, OMe), 6.9–7.05 (m, 1, Ar), 7.18 (d, 1, pyr-β-H, J = 4.5 Hz), 7.45 (m, 2, ArH_2), 8.73 (d, 1, pyr-α-H, J = 4.5 Hz). Anal. ($C_{11}H_{11}NO$) C, H, N.

Method B.[27] Compound **10** (203 g, 0.976 mol) and 285 mL of $NH_2NH_2{\cdot}H_2O$ (4.88 mol) in 2.7 L of absolute EtOH were heated to gentle reflux under N_2.[27] To the mixture was added 11.5 g of 5% Pd/C in five portions over 2.5 h. Heating was continued until the evolution of N_2 had ceased. After cooling, the catalyst was removed by filtration and the volume of the filtrate was reduced to 500 mL in vacuo. Then 1.5 L of H_2O was added, followed by extraction with 2 L of CH_2Cl_2. The organic layer was dried over $MgSO_4$, and the solvent was removed, which gave 166 g (98%) of 11.

1,2,3,4-Tetrahydro-8-methoxy-4-methylquinoline (3e). Compound 11 (1.25 g) was reduced in 40 mL of absolute EtOH with 4 equiv of $NaCNBH_3$ plus 4 equiv of concentrated hydrochloric acid.[28] The reaction was stirred at room temperature for 1 h, heated at 60 °C for 2 h, and then allowed to stir overnight at room temperature. The reaction mixture was made basic with NH_4OH, diluted with 50 mL of H_2O, and extracted three times with 75-mL portions of CH_2Cl_2, followed by drying of the extracts and evaporation of the solvent. The residual orange oil, 1.26 g, was purified on a silica gel column eluted with 2% EtOAc/heptane, which produced a light yellow oil, 0.95 g (74%) of **3e**: NMR ($CDCl_3$) δ 1.25 (d, 3, Me, J = 7 Hz), 1.6–2.3 (m, 2, C^3H_2), 2.6–3.2 (m, 1, C^4-H), 3.27 (tr, 2, C^2H_2, J = 5.5 Hz), 3.74 (s, 3, OMe), 4.07 (br, 1, NH), 6.53 (m, 3, ArH_3). Anal. ($C_{11}H_{15}NO$) C, H, N.

8-Chloro-2,4-dimethylquinoline (14). To 4.0 g (0.03 mol) of *o*-chloroaniline (**12**) in 50 mL of concentrated hydrochloric acid at 100 °C was added dropwise 3.4 g (0.04 mol) of 3-penten-2-one (**13**). The mixture was refluxed for 12 h and then neutralized with 5 N NaOH and extracted with CH_2Cl_2. The organic extract was dried and concentrated to an oil. This was purified on a silica gel column to give 2.54 g (42%) of 14, mp 66–68 °C. Anal. ($C_{11}H_{10}ClN$) C, H, Cl, N. This was reduced to **1,2,3,4-tetrahydro-8-chloro-2,4-dimethylquinoline (3f)** with $NaCNBH_3$ as described for **3e**, purified on a short silica gel column, and used directly in the condensation to produce **4f** without further identification.

1,2,3,4-Tetrahydro-1-methylquinoline (3g). 1,2,3,4-Tetrahydroquinoline (6.66 g, 50 mmol) was added to 40 mL of water, 40 mL of EtOAc, and 5.04 g (60 mmol) of $NaHCO_3$, followed by the dropwise addition of 5.68 g (60 mmol) of Me_2SO_4. The mixture was stirred at room temperature for 2.5 h, and the organic layer was separated. The aqueous layer was extracted with EtOAc, and the combined organic layers were dried and evaporated, giving 4.56 g (62%) of **3g**: NMR ($CDCl_3$) δ 1.93 (quintet, 2, CH_2), 2.74 (tr, 2, CH_2), 2.81 (s, 3, NMe), 3.17 (tr, 2, CH_2), 6.55 (m, 2, Ar), 6.97 (m, 2, Ar).

1,2,3,4-Tetrahydro-1-ethyl-4-methylquinoline (3h). Lepidine (**8**) (1.43 g, 10 mmol) and 50 mL of glacial AcOH were mixed and cooled to 10 °C, followed by the gradual addition of 2.64 g (42 mmol) of $NaCNBH_3$. After being stirred at room temperature for 2 h, the mixture was heated to 55 °C for 1.5 h and then allowed to stand at room temperature overnight. The solution was diluted with water and neutralized, followed by extraction of the product into CH_2Cl_2 and evaporation. Purification was accomplished by column chromatography, eluting with hexane, yield, 0.55 g (31%) of **3h**: MS 175 (M^+), 160 (M^+ – Me); NMR ($CDCl_3$) δ 1.22 (tr, 3, NCH_2Me, J = 7 Hz), 1.30 (d, 3, CHMe, J = 7 Hz), 1.5–2.3 (m, 2, CH_2), 2.89 (sextet, 1, CHMe), 3.29 (tr, 2, NCH_2), 3.30 (quartet,

(25) Neumeyer, J. L.; Cannon, J. G. *J. Pharm. Sci.* **1962**, *51*, 804.
(26) Forbes, R. M.; Rinehart, K. L., Jr. *J. Am. Chem. Soc.* **1973**, *95*, 5003.
(27) Pollak, A.; Stanovnik, B.; Tisler, M. *J. Org. Chem.* **1966**, *31*, 4297.
(28) Modification of the procedure of ref 12, which used HOAc in place of HCl.

2, NCH_2Me), 6.59 (m, tr, 2, Ar), 7.10 (m, tr, 2, Ar). A 5% yield of **3d** was also separated.

1,2,3,4-Tetrahydro-1,4-dimethyl-8-methoxyquinoline (3i). Compound **3e** (0.71 g, 4 mmol) was methylated by dissolving in 15 mL of THF under N_2, chilling to 0 °C, and adding 1.14 g (30 mmol) of $NaBH_4$, followed by slow addition of 12 mL of HCOOH. The reaction was allowed to warm to room temperature and stirred overnight. The solvent was removed, the residue was slurried in water and made basic with NH_4OH, and the product was extracted into CH_2Cl_2 and chromatographed on a silica gel column. Elution with hexane/EtOAc 19:1 gave a light brown oil. Anal. ($C_{12}H_{17}NO$) C, H, N.

1,2,3,4-Tetrahydro-1,4-dimethyl-8-ethylquinoline (3j). This compound was prepared in six steps from 2-ethylaniline by using the same route as for **3i**. The final product was obtained as a light brown oil which was purified by column chromatography: yield, 21%; NMR ($CDCl_3$, 60 MHz) δ 1.2 (t, 3, Me), 1.2–2.2 (m, 2, CH_2), 1.25 (d, 3, Me), 2.6–3.2 (m, 3, CH and NCH_2), 2.65 (s, 3, NMe), 3.0 (m, 2, $ArCH_2$), 6.8–7.2 (m, 3, ArH_3).

1,2,3,4-Tetrahydro-1-(2-methoxyethyl)-8-methoxy-4-methylquinoline (3k). To a stirred mixture of 0.79 g (4.5 mol) of **3e** and $NaBH_4$ (1.8 g, 45 mmol) in 15 mL of dry THF at 0 °C under N_2 was added a solution of methoxyacetic acid (10 g, 111 mmol) in THF (1:1) dropwise over 45 min. The mixture was allowed to stir at room temperature overnight and then heated to 50 °C. The reaction was followed by TLC (hexane/EtOAc 8:1). Daily additions of 1 equiv each of $NaBH_4$ and methoxyacetic acid were made to the reaction mixture until no starting material remained (7 days). After cooling of the reaction mixture to room temperature, water (25 mL) and concentrated NH_4OH (10 mL) were added carefully. The resultant basic solution was extracted with CH_2Cl_2, and the organic layer was dried over $MgSO_4$ and evaporated to dryness. The crude product was purified on a silica gel column eluted with 10–20% EtOAc/hexane to give 0.85 g (81%) of **3k** as a light yellow oil: NMR ($CDCl_3$) δ 1.25 (d, 3, 4-Me), 1.4–2.1 (m, 2, 3-CH_2), 2.5–3.4 (m, 5, $N(CH_2)_2$ + ArH), 3.35 (s, 3, OMe), 3.4–3.8 (m, 2, CH_2O), 3.8 (s, 3, ArOMe), 6.5–7.2 (m, 3, ArH_3).

1,2,3,4-Tetrahydro-1-(2-hydroxyethyl)-8-methoxy-4-methylquinoline (3l). 8-Methoxy-4-methylquinoline (**11**) (2.47 g, 14.3 mmol), 2-bromoethanol (10 mL), and acetonitrile (10 mL) were stirred and heated at reflux for 18 h. After cooling of the reaction mixture, two volumes of Et_2O were added to the mixture, and the resultant precipitate was filtered off and recrystallized from *i*-PrOH/EtOH 4:1. The quinolinium bromide intermediate (**15**) thus obtained was then hydrogenated in absolute EtOH with PtO_2 (0.25 g/g) at 50 psi. After removal of the catalyst and concentration of the filtrate in vacuo, the crude product was purified on a silica gel column which was eluted with 15–35% of EtOAc/hexane to give 1.5 g (47%) of **3l**: mp 45–48 °C; NMR ($CDCl_3$) δ 1.2 (d, 3, Me), 1.3–2.1 (m, 2, CH_2), 2.5–3.1 (m, 1, CH), 2.8–3.3 (m, 4, $N(CH_2)_2$), 3.6–3.8 (m, 2, CH_2O), 3.8 (s, 3, ArOMe), 6.5–7.0 (m, 3, ArH_3). Anal. ($C_{13}H_{19}NO_2$) C, H, N.

1,2,3,4-Tetrahydro-1-acetyl-3-carbethoxy-8-methoxyquinoline (16).[14] 3-Carbethoxy-8-methoxyquinoline[29] (5.5 g, 23.8 mmol) was dissolved in 130 mL of Ac_2O plus 200 mL of AcOH and reduced catalytically on a Parr shaker with 2.2 g of PtO_2. After removal of the catalyst, the solvent was evaporated and the residual oil slurried in water containing an excess of K_2CO_3. The oil was extracted into $CHCl_3$, the $CHCl_3$ fraction was dried over Na_2SO_4, and the solvent then was removed. The resultant oil was purified by chromatography on silica gel, which was eluted with hexane/EtOAc 1.5:1. The product (**16**) was further purified by vacuum distillation: bp 160 °C (0.15 mm); 4.29 g (65.1%); IR 1650 (Ac), 1718 (COOEt) cm^{-1}. Anal. ($C_{15}H_{19}NO_4$) C, H, N.

2,4-Diamino-5-[(1,2,3,4-tetrahydro-3-carbethoxy-8-methoxy-6-quinolyl)methyl]pyrimidine (4n). A 0.5-g sample (0.0018 mol) of **16** was treated with **2** in the manner described for **4b**. The product was treated with 1 N NaOH to remove the 1-acetyl function, followed by reesterification of the resultant acid with absolute EtOH and H_2SO_4. The product was purified by flash chromatography on silica gel, eluting with CH_2Cl_2/MeOH 12:1 to produce **4n**: mp 159–161 °C; UV (free base) (pH 12) λ_{max} 232 nm (ϵ 18 400), 269.5 (7240), 288.5 (10 000), (cation) (0.01 N HCl) 272.5 (7500). Anal. ($C_{18}H_{23}N_5O_3$) C, H, N.

3-(Hydroxymethyl)-8-methoxy-1,2,3,4-tetrahydroquinoline (3p) and 1-Ethyl-3-(hydroxymethyl)-8-methoxy-1,2,3,4-tetrahydroquinoline (3q). Compound **16** (1.04 g, 3.75 mmol) dissolved in 10 mL of freshly distilled THF was slowly added to a solution of 0.25 g (6 mmol) of $LiAlH_4$ in 15 mL of THF. After being stirred for 1 h, the mixture was warmed gently for 1 h, followed by the addition of EtOAc and then water. The EtOAc layer was dried over $MgSO_4$ and evaporated. The NMR spectrum of the residue suggested a 1:2 mixture of **3p** and **3q**. These were separated by repeated column chromatography on silica gel, eluting with CH_2Cl_2/MeOH, 0, 1, 2, 5%, which produced **3p**, mp 86–90 °C. Anal. ($C_{11}H_{15}NO_2$) C, H, N. Later fractions also contained **3q**, mp 65–66 °C. Anal. ($C_{13}H_{19}NO_2$) C, H, N. The NMR spectra of the two products were as follows. Compound **3p**: ($CDCl_3$) δ 2.05 (s, 1, OH), 2.28 (m, 1, C^3H), 2.66 (tr, 2, C^2H_2), 3.0–3.4 (m, C^4H_2 + NH), 3.58 (d, 2, CH_2OH), 3.76 (s, 3, OMe), 6.53 (s, 3, Ar). Compound **3q**: ($CDCl_3$) δ 1.19 (tr, 3, CH_2Me), 1.58 (br, 2, OH, H_2O), 2.16 (br, 1, C^3H), 2.4–2.9 (m, 2, C^4H_2), 3.02 (q, 2, CH_2Me), 3.1–3.4 (br m, 2, NCH_2), 3.64 (br q, 2, CH_2OH), 3.83 (s, 3, OMe), 6.6–6.8 (m, 3, Ar).

Ethyl 1,2,3,4-Tetrahydro-5,8-dimethoxy-3-quinolinecarboxylate (3r). Ethyl 1,4-dihydro-5,8-dimethoxy-4-oxo-3-quinolinecarboxylate (**17**)[15,16] was chlorinated in $POCl_3$ as described in ref 16, and the crude product (**18**) was then reduced catalytically as in that reference, with a Parr hydrogenation apparatus. The reduction mixture included the chloroquinoline **18** (20.34 g, 0.069 mol) in 150 mL of absolute EtOH, plus 1 g of 5% Pd/C and 22.5 mL of Et_3N. In contrast to the previously reported results with a related compound,[16] three products were formed, which were separated on a silica gel column by elution with hexane, followed by hexane/EtOAc 4:1 and finally hexane/EtOAc 1:1. This produced 0.46 g (2.6%) of the tetrahydro derivative **3r**: NMR ($CDCl_3$) δ 1.23 (tr, 3, CH_2Me), 2.94 (br m, 2, CH_2), 3.2–3.6 (m, 3, CH_2, CH), 3.76 (s, 6, $(OMe)_2$), 4.21 (quartet, 2, CH_2Me), 4.2 (br, 1, NH), 6.12 (d, 1, Ar), 6.57 (d, 1, Ar). Also obtained was 3.31 g of the 1,4-dihydroquinoline **19** (13.5%): NMR ($CDCl_3$) δ 1.28 (tr, 3, CH_2Me), 3.61 (s, 2, CH_2), 3.73 (s, 6 $(OMe)_2$), 4.19 (quartet, 2, CH_2Me), 6.2–6.7 (br, 1, NH), 6.29 (d, 1, Ar), 6.60 (d, 1, Ar), 7.32 (d, 1, pyr-H). There was also produced 2.04 g (11%) of the ethyl 5,8-dimethoxy-3-quinolinecarboxylate (**20**).[15]

General Method for the Oxidation of 2,4-Diamino-5-[(1,2,3,4-tetrahydro-6-quinolyl)methyl]pyrimidines to 2,4-Diamino-5-(6-quinolylmethyl)pyrimidines. Reactions were carried out in cumene by heating the compounds at 150 °C with 20% Pd/C over a 21–24-h period and following the course of the reactions with TLC. Yields were variable, and usually rather low. Products prepared in this way are described in Table **II**, and an example is provided below.

2,4-Diamino-5-[(4-methyl-6-quinolyl)methyl]pyrimidine (5d). Compound **4d** was oxidized with 20% Pd/C in 50 mL of cumene, by heating at 150 °C for 21 h. After the catalyst was removed and the solvent evaporated, the residue was purified on a silica gel column which was eluted with CH_2Cl_2/MeOH 19:1. The product was then recrystallized from 2-methoxyethanol, yielding 1.44 g (55%) of **5d**: mp 265–268 °C; NMR (Me_2SO-d_6) δ 2.64 (s, 3, Me), 3.83 (s, 2, CH_2), 5.70 (br s, 2, NH_2), 6.16 (br s, 2, NH_2), 7.33 (d, 1, pyridine β-H, J = 4.5 Hz), 7.56 (dd, 1, ArH^7, J = 2, 8 Hz), 7.59 (s, 1, pyrimidine 6-H), 7.92 (d, 1, ArH^8, J = 8.8 Hz), 7.98 (d, 1, ArH^5, J = 1.6 Hz), 8.68 (d, 1, pyridine αH, J = 4.4 Hz). Anal. ($C_{15}H_{15}N_5$) C, H, N.

2,4-Diamino-5-[(4-methyl-8-nitro-6-quinolyl)methyl]pyrimidine (5s). Compound **5d** (0.53 g, 2 mmol) was dissolved in 7 mL of concentrated H_2SO_4 and chilled to 0 °C. Then 0.3 mL (6.4 mmol) of fuming nitric acid (d = 1.5) in 0.5 mL of concentrated H_2SO_4 was added dropwise to the solution. The reaction was stirred at 0–5 °C for 30 min and then at 25 °C for 1 h. It was then poured onto 50 mL of ice and neutralized to pH 9 with concentrated NH_4OH. The precipitate was filtered and dried and then purified on a silica gel column which was eluted with CH_2Cl_2/MeOH 12:1, giving 0.33 g (53%) of **5s**: mp 256–258 °C (2-methoxyethanol/water 2:1); NMR (Me_2SO-d_6) δ 2.72 (s, 3, Me), 3.90 (s, 2, CH_2), 5.77 (br s, 2, NH_2), 6.24 (br s, 2, NH_2), 7.55 (d, 1, pyridine β-H, J = 4.1 Hz), 7.71 (s, 1, pyrimidine-H^6), 8.05 (d, 1, ArH^5, J = 1.8 Hz), 8.28 (d, 1, ArH^7, J = 1.6 Hz), 8.81 (d, 1,

(29) Gopalchari, R. *J. Sci. Ind. Res.* **1962**, *21B*, 183; *Chem. Abstr.* **1962**, *57*, 12432c.

pyridine α-H, J = 4.4 Hz). Anal. ($C_{15}H_{14}N_6O_2 \cdot 0.5H_2O$) C, H, N.

2,4-Diamino-5-[(8-amino-4-methyl-6-quinolyl)methyl]pyrimidine Dihydrochloride (5t). The above nitro derivative (**5s**) (0.78 g, 2.5 mmol) was dissolved in 35 mL of 2-methoxyethanol, and then 0.06 g of 5% Pd/C and 0.3 mL of 95% NH_2NH_2 were added. The reaction was heated under reflux for 1 h, and the catalyst was then removed, followed by evaporation of the solvent and purification of the product on a silica gel column which was eluted with 7% MeOH in CH_2Cl_2; yield, 0.48 g (69%) of the free base, which was crystallized from EtOH/HCl to give the dihydrochloride, mp 303–305 °C. Anal. ($C_{15}H_{16}N_6 \cdot 2HCl \cdot 0.5H_2O$) C, H, N, Cl.

2,4-Diamino-5-[(5-amino-4-methyl-6-quinolyl)methyl]pyrimidine Dihydrochloride (5u). When compound **5d** was nitrated and only partially purified by a silica gel column without recrystallization and then reduced as described above for **5t**, a second aminoquinoline was detected and isolated from a column. On a 2.5-mmol scale, there was obtained 0.235 g (32%) of **5u**: mp 290 °C dec (EtOH/HCl); NMR of the free base (Me_2SO-d_6) δ 2.96 (s, 3, Me), 3.60 (s, 2, CH_2), 5.08, 5.70, 6.14 (3 broad bands, 6, $(NH_2)_3$), 6.99 (d, 1, Ar, J = 8 Hz), 7.16 (d, 1, Ar, J = 8 Hz), 7.24 (s, 1, pyridine-H^6), 7.27 (d, 1, pyridine-H, J = 4 Hz), 8.51 (d, 1, pyridine-H, J = 4 Hz). Anal. ($C_{15}H_{16}N_6 \cdot 2HCl$) C, H, N, Cl.

2,4-Diamino-5-(4-amino-3-methoxybenzyl)pyrimidine (22). A solution of 6.30 g (0.045 mol) of **2**, 6.15 g (0.05 mol) of *o*-anisidine (**21**), and 3.75 mL of concentrated hydrochloric acid in 55 mL of glacial AcOH was heated under reflux for 6 h and then stirred at room temperature overnight. The solvent was removed and the residue taken up in water, and the mixture was basified with NH_4OH and extracted with CH_2Cl_2/MeOH 3:1. The organic layers were combined and dried, followed by concentration to a purple glass, which was purified on a silica gel column to give 7.81 g of 4-N-acetylated product. This was dissolved in 400 mL of 2 N NaOH and the solution was heated to reflux for 6 h, cooled, and neutralized. The mixture was extracted with CH_2Cl_2, which was dried and concentrated, giving 4.0 g of **22**, mp 210–212 °C. Anal. ($C_{12}H_{15}N_5O$) C, H, N.

2,4-Diamino-5-[(2,4-dimethyl-8-methoxy-6-quinolyl)-methyl]pyrimidine. (5i). To a solution of 1.5 g (0.006 mol) of **22** in 30 mL of EtOH, 0.5 mL of concentrated hydrochloric acid, and 2.43 g (0.0089 mol) of ferric chloride hydrate was added 0.5 g (0.006 mol) of 3-penten-2-one. Following the dropwise addition, the solution was refluxed for 6 h. The solvent was removed under vacuum and the residue was dissolved in water and the solution was neutralized with NH_4OH. The resultant precipitate was purified on a silica gel column followed by recrystallization from EtOH, which gave 0.11 g (5.9%) of **5i**, mp 289–290 °C. Anal. ($C_{17}H_{19}N_5O$) C, H, N.

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Registry No. **1a**, 738-70-5; **2**, 42310-45-2; **3b**, 53899-17-5; **3c**, 89445-73-8; **3d**, 19343-78-3; **3e**, 89445-81-8; **3f**, 89445-95-4; **3g**, 491-34-9; **3h**, 57928-07-1; **3i**, 89446-04-8; **3j**, 119908-21-3; **3k**, 119908-22-4; **3l**, 119908-23-5; **3p**, 119908-25-7; **3q**, 119908-26-8; **3r**, 89446-08-2; **4a**, 89445-70-5; **4c**, 89445-71-6; **4d**, 89445-74-9; **4e**, 89445-75-0; **4f**, 89445-83-0; **4g**, 89445-96-5; **4h**, 89445-97-6; **4i**, 89445-99-8; **4j**, 89446-06-0; **4k**, 119908-27-9; **4l**, 119908-28-0; **4m**, 119908-29-1; **4n**, 119908-30-4; **4o**, 119908-31-5; **4p**, 119908-32-6; **4q**, 119908-33-7; **4r**, 119908-34-8; **5a**, 89446-09-3; **5b**, 119908-36-0; **5c**, 89445-84-1; **5d**, 89445-85-2; **5e**, 89445-87-4; **5i**, 89445-86-3; **5s**, 89445-94-3; **5t**, 89445-88-5; **5t** free base, 89446-01-5; **5u**, 89446-00-4; **5u** free base, 89446-03-7; **6**, 89446-02-6; **7**, 148-24-3; **8**, 89445-72-7; **9**, 491-35-0; **10**, 30198-01-7; **11**, 89445-80-7; **12**, 61703-95-5; **13**, 95-51-2; **14**, 625-33-2; **16**, 67358-87-6; **17**, 119908-24-6; **18**, 89446-07-1; **19**, 77156-82-2; **20**, 119908-35-9; **21**, 71083-24-4; **22**, 90-04-0; DHFR, 85544-45-2; 1,2,3,4-tetrahydroquinoline, 9002-03-3; 2-methoxyethyl bromide, 635-46-1; 2-bromoethanol, 6482-24-2; 3-carbethoxy-8-methoxyquinoline, 540-51-2, 71083-22-2.