Synthesis and Dihydrofolate Reductase Inhibitory Activities of 2,4-Diamino-5-deaza and 2,4-Diamino-5,10-dideaza Lipophilic Antifolates[1]

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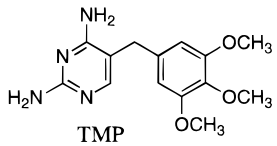
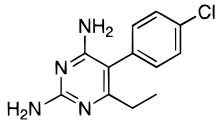
Two series of nonclassical antifolates (2,4-diamino-5-deaza compounds **2**−**5** and 5,10-dideaza compounds **6**−**13**) were synthesized as inhibitors of dihydrofolate reductase (DHFR) from *Pneumocystis carinii* (pc) and *Toxoplasma gondii* (tg) organisms that are responsible for fatal opportunistic infections in AIDS patients. Rat liver (rl) DHFR served as the mammalian reference enzyme to determine selectivity. Syntheses of the target 5-deaza compounds were achieved by initial construction of the pivaloyl-protected 2,4-diamino-6-bromopyrido[2,3-*d*]-pyrimidine **17** *via* a cyclocondensation of 2,4,6-triaminopyrimidine with bromomalonaldehyde. Sequential Heck coupling of **17** with styrene followed by ozonolysis afforded the 6-formyl derivative **19**. Reductive amination of **19** with 3,4,5-trimethoxyaniline afforded the N10-H analog. The N10-Me and N10-Et analogs were synthesized by nucleophilic displacement of the 6-bromomethyl derivative **22** (obtained from the 6-formyl derivative **19** by reduction and bromination) with the appropriate *N*-alkylaniline. The *trans*-5,10-dideaza analogs **6**−**8** were synthesized *via* a Heck coupling of the appropriate methoxystyrene with **17**, and selective reduction of the resulting 9,10-double bond afforded target compounds **9**−**11**. Further reduction to the tetrahydro derivatives afforded analogs **12** and **13**. The 5-deaza N10-Me 3,4,5-trimethoxy analog **3** maintained the best balance of potency and selectivity against both tgDHFR and pcDHFR. Compared to trimethoprim, compound **3** was only slightly less selective but was 300-fold more potent against tgDHFR. The 5,10-dideaza analogs were generally less potent and selective than the 5-deaza compounds.

Introduction

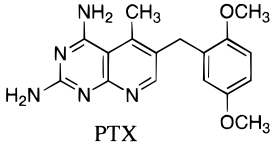
Opportunistic infections caused by *Pneumocystis carinii* and *Toxoplasma gondii* remain the principal cause of death in patients with the acquired immune deficiency syndrome (AIDS).[2−5] In recent years several nonclassical, lipophilic dihydrofolate reductase (DHFR) inhibitors have been used to treat the infections caused by these organisms. Although lipophilic antifolates such as trimethoprim (TMP),[6] pyrimethamine,[7] trimetrexate, (TMQ),[8,9] and piritrexim (PTX)[10] are currently used for the treatment of these opportunistic infections, they suffer from several drawbacks. TMP is a selective but weak inhibitor of DHFR derived from *P. carinii* and *T. gondii;* pyrimethamine is also a weak inhibitor with no selectivity for *P. carinii* (pc) DHFR and modest selectivity for *T. gondii* (tg) DHFR. Both these drugs must be used with sulfonamides to provide synergistic effects.[11] TMQ and PTX are potent inhibitors of *P. carinii* DHFR and *T. gondii* DHFR; however, they have a higher affinity for the mammalian enzyme.[12,13] Thus, both TMQ and PTX must be used in combination with the reduced folate leucovorin (5-formyl-5,6,7,8-tetrahydrofolate) to selectively protect the host.[14,15] In addition to the high cost and lack of selectivity, the severe side effects frequently require cessation of treatment with these antifolate regimens.[2,16,17] Thus there has been a considerable effort to develop more potent and more selective inhibitors of pcDHFR and tgDHFR. A selective agent would obviate the necessity to use either sulfonamides or leucovorin and could result in safer and less expensive therapy.



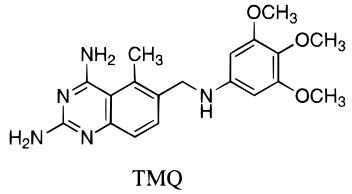
TMP



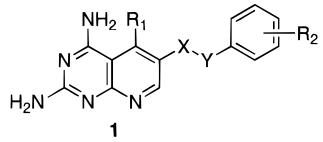
Pyrimethamine



PTX



TMQ



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1a X = CH_2, Y = NCH_3, R_1 = CH_3, R_2 = 3,4,5-$(OCH_3)_3$
1b X = NCH_3, Y = CH_2, R_1 = H, R_2 = 2,5-$(OCH_3)_2$

Gangjee *et al.*[18−23] and others[24−27] have reported several bicyclic lipophilic antifolates as potent and/or selective inhibitors of DHFR isolated from *P. carinii* and *T. gondii*. Investigations of the 2,4-diamino-5-methyl-6-(anilinomethyl)pyrido[2,3-*d*]pyrimidine (5-methyl-5-deazapteridine, **1**) class of lipophilic antifolates have provided agents superior in both selectivity and potency compared to TMQ and PTX against pcDHFR and

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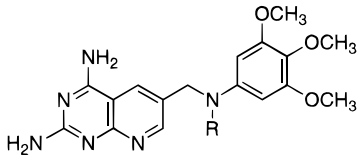
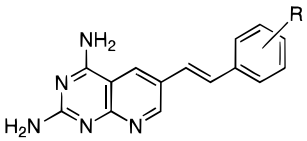
tgDHFR.[18,19,23,24] In particular, the 5-methyl-5-deazapteridine analog with a 3,4,5-trimethoxy substitution on the phenyl ring and a methyl group on the N10 nitrogen, compound **1a**, was reported by Gangjee *et al.*[18] to be an extremely potent inhibitor of tgDHFR (IC_{50} = 0.85 nM) with good selectivity for this enzyme compared to rat liver (rl) DHFR (selectivity ratio = IC_{50}(rlDHFR)/IC_{50}(tgDHFR) = 8.94).

Several studies have documented the importance of the 5-methyl group of 5-deaza folates for potent inhibition of DHFR from mammalian sources and in some instances bacterial sources as well.[28−30] Thus, removal of the 5-methyl group from the 5-deaza folates was expected to potentially increase the selectivity of these agents provided the decrease in potency against pcDHFR and tgDHFR was less than the decrease against mammalian DHFR. The viability of this idea was recently demonstrated by Gangjee *et al.*[23] in the N9 methyl, reversed bridge analogue **1b**. This compound was significantly potent and highly selective for both pcDHFR and tgDHFR and is currently undergoing animal studies. Utilizing the 3,4,5-trimethoxy side chain substitution pattern that provided excellent potency and good selectivity in the 5-methyl-5-deaza series, we synthesized four 5-desmethyl-5-deaza lipophilic antifolates (**2**−**5**) which have varied substituents on the N10 nitrogen. It has been shown that small substituents on the N10 position in the 5-methyl-5-deaza series have provided for remarkably increased potency and/or selectivity for pcDHFR and tgDHFR.[18,19]

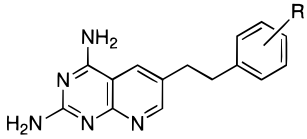


2 R = H
3 R = CH_3
4 R = CH_2CH_3
5 R = CHO

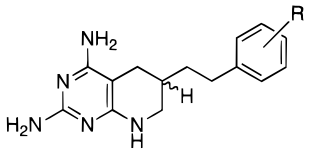
In order to elucidate the importance of the 10-nitrogen atom on DHFR inhibitory potency and selectivity in this class, we also synthesized a series of 5,10-dideaza lipophilic antifolates in which the 10-nitrogen is replaced by a carbon atom. The synthesis of the 3,4-dimethoxyphenyl-substituted 5,10-dideaza analogs **7**, **10**, and **13** was reported by us in a preliminary communication.[31] This report describes the biological activity of analogs **7**, **10**, and **13** and the synthesis and biological activity of additional 5,10-dideaza lipophilic antifolates which varied in the number of methoxy substituents in the 3-, 4-, and 5-positions on the phenyl ring. The methoxy substituent present in several of these analogs was chosen in part on the basis of previous reports from our laboratory with other nonclassical antifolates.[18−23] Three 9,10-dehydro-5,10-dideaza analogs (**6**−**8**) were synthesized as conformationally constrained derivatives of lipophilic antifolates **9**−**11** where the methoxy-substituted phenyl side chain has been locked in an extended (trans) orientation. The reduced 5,6,7,8-tetrahydro-5,10-dideaza analogs **12** and **13** were also of interest as lipophilic DHFR inhibitors related to 2,4-diamino-6-substituted tetrahydroquinazolines which were potent inhibitors of DHFR derived from *P. carinii* and *T. gondii* with selectivity for tgDHFR.[21] It was anticipated that comparison of activity across the series **6**−**13** would illustrate how potency and/or selectivity against pcDHFR and tgDHFR can be affected by the side chain phenyl ring orientation and the number of methoxy groups around the 3-, 4-, and 5-positions of the phenyl ring.



6 R = 3,4,5-$(OCH_3)_3$
7 R = 3,4-$(OCH_3)_2$
8 R = 4-OCH_3



9 R = 3,4,5-$(OCH_3)_3$
10 R = 3,4-$(OCH_3)_2$
11 R = 4-OCH_3



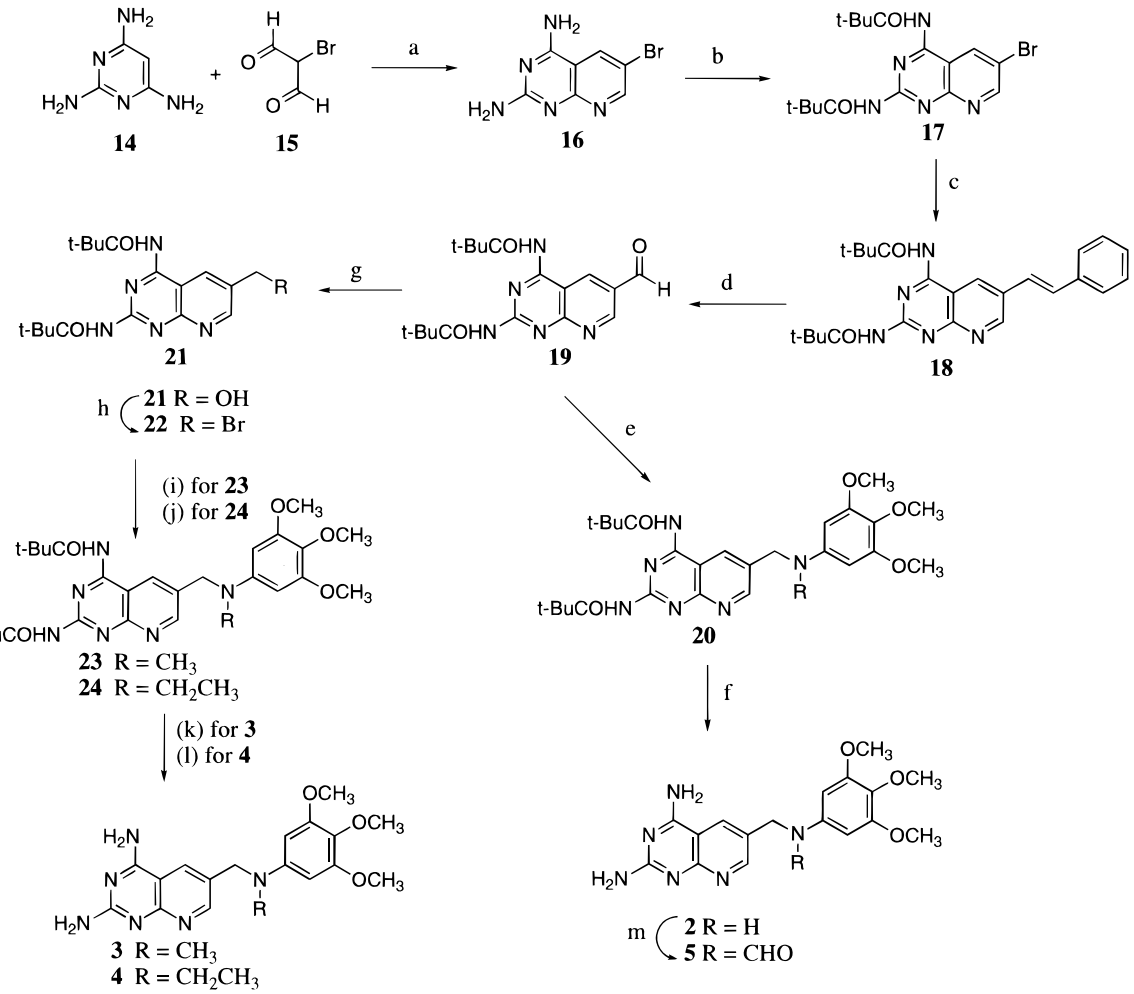
12 R = 3,4,5-$(OCH_3)_3$
13 R = 3,4-$(OCH_3)_2$

Chemistry

The synthesis of all the analogs utilized the common intermediate 2,4-bis(pivaloylamino)-6-bromopyrido[2,3-*d*]pyrimidine (**17**). This critical intermediate **17** was synthesized *via* reaction of 2,4,6-triaminopyrimidine (**14**) and bromomalonaldehyde (**15**) under acidic conditions to afford the cyclized compound **16** followed by protection of the 2- and 4-amino groups with pivaloyl anhydride and pyridine.[31] The synthesis of the 5-deaza analogs **2**−**5** is shown in Scheme 1. A palladium-catalyzed Heck coupling[32,33] of **17** with styrene under the standard conditions afforded the desired product **18** in modest yield (47%). Ozonolysis[34] of the styryl derivative **18** followed by reductive workup with dimethyl sulfide gave the desired 6-formyl derivative **19** in good yield (80%). Reductive amination of **19** with 3,4,5-trimethoxyaniline was best carried out in two stages: formation of the intermediate imine in glacial acetic acid at room temperature followed by reduction of the imine with borane−triethylamine complex. Column chromatographic purification and recrystallization afforded the desired bispivaloylated compound **20** in 48% yield. Deprotection of the pivaloyl groups under the conditions (liquid ammonia, sealed vessel) used for the deprotection of the 5,10-dideaza analogs (see below) did not afford any of the desired product **2**; instead an extremely polar and water soluble material was obtained, which was not identified. Basic hydrolysis of pivaloyl amides have been reported in the literature,[35] but concerns regarding the lability of the 4-amino group under these conditions prompted an investigation of alternate methods of deprotection. Sodium methoxide has been reported to cleave acetamido groups in related pyrido[2,3-*d*]pyrimidines.[36] Utilizing this precedent the di-depivaloylation was carried out with freshly prepared sodium methoxide in anhydrous methanol to afford the desired 5-deaza compound **2** in 52% yield.

A similar reductive amination procedure was also expected to afford the N-alkylated derivatives **3** and **4**. Both *N*-methyl-[37] and *N*-ethyl-3,4,5-trimethoxyaniline[19] were synthesized by direct alkylation with methyl

Scheme 1[a]



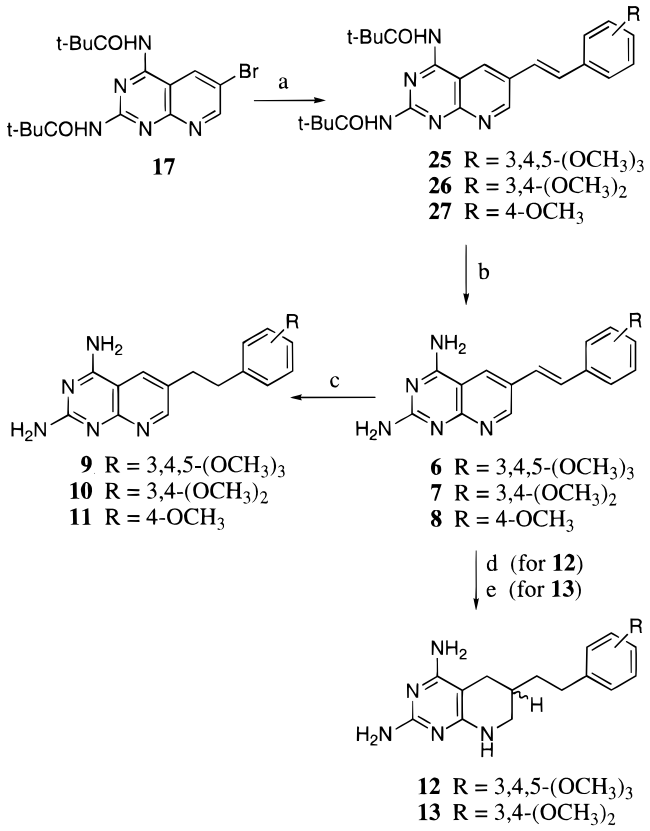
[a] Reagents (a) HCl, EtOH, Δ; (b) $[(CH_3)_3CCO]_2O$, pyridine, reflux; (c) styrene, $Pd(OAc)_2$, (*o*-tol)$_3$P, CuI, CH_3CN, reflux; (d) (i) O_3, CH_2Cl_2/MeOH, −78 °C, (ii) O_2, Me_2S; (e) (i) 3,4,5-trimethoxyaniline, glacial AcOH, rt, (ii) $BH_3{\cdot}Et_3N$; (f) NaOMe, MeOH, rt to 50 °C; (g) $NaBH_4$, MeOH, 0−5 °C; (h) Ph_3P, Br_2, CH_2Cl_2, rt; (i) for **23** (R = CH_3) *N*-methyl-3,4,5-trimethoxyaniline, DMAP, *N*,*N*-DMAc; (j) for **24** (R = CH_2CH_3) *N*-ethyl-3,4,5-trimethoxyaniline, DMAP, *N*,*N*-DMAc; (k) for **3** (R = CH_3) NaOMe, MeOH, rt to 50 °C; (l) for **4** (R = CH_2CH_3) 30% HBr in AcOH, THF, rt to 50 °C; (m) 98% HCOOH, Ac_2O, rt.

iodide. Reductive amination of **19** with either of the two secondary amines under the conditions used for the synthesis of **20** did not afford the desired products **23** and **24** in acceptable yields. We then turned our attention to a nucleophilic displacement to synthesize the N10 alkyl compounds. Reduction of the aldehyde moiety (Scheme 1) present in **19** with sodium borohydride afforded the desired 6-hydroxymethyl derivative **21** in good yield. Bromination of the alcohol **21** with triphenylphosphine and bromine[38] afforded the bromide **22** which was not stable to storage and was used immediately in the next step.

Nucleophilic displacement of the bromide **22** (Scheme 1) with *N*-methyl-3,4,5-trimethoxyaniline afforded the dipivaloylated compound **23** which was deprotected to afford the desired *N*-methyl derivative **3** in 48% yield from bromide **22**. A similar nucleophilic displacement with *N*-ethyl-3,4,5-trimethoxyaniline afforded the protected derivative **24**. Although the di-depivaloylation could be achieved in principle under the reported conditions, we were interested in exploring other methods of cleavage of the 2- and 4-pivaloyl groups without concomitant hydrolysis of the 4-amino group. This was achieved for **24** with 30% hydrogen bromide in acetic acid in anhydrous tetrahydrofuran. Following column chromatographic purification the desired *N*-ethyl derivative **4** was obtained in 42% yield from the bromide **22**. Formylation of the N10 nitrogen of compound **2** with 98% formic acid and a catalytic amount of acetic anhydride[18] afforded the *N*-formyl compound **5** in good yield (86%).

The syntheses of the 5,10-dideaza compounds are shown in Scheme 2 and followed the conditions reported in our previous communication[31] for the synthesis of the 3,4-dimethoxy derivatives. 3,4,5-Trimethoxystyrene was not commercially available and was synthesized in 86% yield by a Wittig reaction of 3,4,5-trimethoxybenzaldehyde with the anion of methyltriphenylphosphonium bromide.[39] A palladium-catalyzed Heck coupling of 3,4,5-trimethoxystyrene with **17** afforded the dipivaloylated derivative **25** in 59% yield. A similar Heck coupling of **17** with 4-methoxystyrene afforded **27** in a lower yield (45%). The trans stereochemistry for the 9,10-double bond of the monomethoxy derivative **27** and compound **25** was evident by the large coupling constant between the two protons (J = 16.0 Hz) in the ^{1}H NMR spectrum of **27** in deuterated dimethyl sulfoxide and the ^{1}H NMR spectrum of compound **25** run in deuterated chloroform. Deprotection of the 2- and 4-pivaloyl groups of **25** and **27** in a Parr acid digestion

Scheme 2[a]



[a] Reagents: (a) 3,4,5-trimethoxystyrene (for **25**), 3,4-dimethoxystyrene (for **26**), or 4-methoxystyrene (for **27**), $Pd(OAc)_2$, CuI, Et_3N, CH_3CN, reflux; (b) liquid NH_3, $MeOH/CH_2Cl_2$, Parr bomb; (c) (i) CF_3COOH, (ii) DMF, 5% Pd−C, 25 psi H_2; (d) 10% CF_3COOH in MeOH, 5% Pd−C, 50 psi H_2; (e) 60% aq AcOH, 5% Pd−C, 50 psi H_2.

bomb afforded the desired diamino compounds **6** and **8** in good yields (78−80%). The trans stereochemistry for the 9,10-double bond in compound **8** was also assigned from the large coupling constant (J = 16.2 Hz) in the ^{1}H NMR spectrum. Literature evidence suggests that in analogous pyrido[2,3-*d*]pyrimidines containing mixtures of cis and trans isomers, the aromatic 7-CH protons occur separately, with the proton of the cis isomer occurring more upfield due to shielding by the side-chain phenyl group.[40−42] For compounds **6**−**8** the chemical shifts of the 7-CH proton were quite similar and were within 0.1 ppm of each other, which further supports the trans geometry.

The free bases of the diamino compounds **6** and **8** were insoluble in conventional organic solvents; thus the reduction of the 9,10-double bond was carried out using the trifluoroacetate salts of **6** and **8** in *N*,*N*-dimethylformamide. Hydrogenation (Scheme 2) with 5% palladium on carbon under pressure afforded the desired 5,10-dideaza compounds **9** and **11** in 51−55% yield. Hydrogenation of **6** with 5% palladium under pressure for 24 h afforded the desired hexahydro analog **12** in 59% yield.

Biological Activity and Discussion

The compounds were evaluated[12,13] as inhibitors of pcDHFR, tgDHFR, and rlDHFR, and the results are reported as IC_{50} values in Table 1. Selectivity ratios were determined using rlDHFR as the mammalian source and are also listed in Table 1. The results

Table 1. Inhibitory Concentrations (IC_{50}, μM) against DHFRs from *P. carinii* (pc), *T. gondii* (tg), and Rat Liver (rl) and Selectivity Ratios[a]

compd	pcDHFR	tgDHFR	rlDHFR	rl/pc	rl/tg
1a[b]	0.013	0.00085	0.0076	0.58	8.9
2	1.5	0.3	1.9	1.3	6.3
3	0.24	0.009	0.28	1.2	31
4	0.19	0.049	0.12	0.63	3.2
5	18.5	1.1	7.4	0.40	6.7
6	>5.0	1.4	12.9		9.2
7	2.6	1.4	2.1	0.81	1.5
8	5.3	1.5	11.8	2.2	7.9
9	5.0	0.2	1.14	0.23	5.7
10	1.4	0.2	0.61	0.44	3.0
11	0.29	0.25	0.26	0.9	1.0
12	61.7	0.47	6.1	0.1	13.0
13	7.7	1.1	2.1	0.27	1.9
TMP	12.0	2.7	133.0	11.1	49
TMQ	0.042	0.010	0.003	0.07	0.3
PTX	0.038	0.011	0.0015	0.04	0.14

[a] IC_{50} values were determined as described in the Experimental Section. [b] Data from ref 18.

indicate that as a series the 5-deaza-5-desmethyl analogs **2**−**5** of **1a** were less potent against all three DHFRs compared to compound **1a**. For compound **3**, the decrease in potency against pcDHFR and tgDHFR was less than the decrease against rlDHFR, and compound **3** had better selectivity ratios for both pcDHFR (1.2) and tgDHFR (31.1) than **1a**. Replacement of the N10 methyl of **3** with a hydrogen (compound **2**) afforded a decrease in potency against all three enzymes compared to **3**, but the selectivity against pcDHFR was maintained and the selectivity against tgDHFR was 5-fold lower than **3**. The N10 ethyl analog **4** was more potent than the N10-unsubstituted analog **2**, but the selectivity for pcDHFR and tgDHFR was less than that for **2** or **3**. The N10 formyl analog **5** was the least potent of the series (compounds **2**−**5**). It was however reasonably selective for tgDHFR.

Replacement of the N10 of **2** with a carbon afforded the 5,10-dideaza analog **9** which had decreased potency and selectivity against pcDHFR and retained selectivity against tgDHFR compared to **2**. Sequential removal of the methoxy moieties from **9** (compounds **10** and **11**) surprisingly increased potency against pcDHFR and rlDHFR, but potency remained unchanged against tgDHFR. This led to a decrease in selectivity for tgDHFR and a increase in selectivity for pcDHFR. The trans precursors of **9**−**11** (compounds **6**−**8**) were less potent against all three DHFRs, but the trimethoxy analog **6** showed reasonable selectivity (9.2) for tgDHFR.

Reduction of the B-ring of **9** and **10** afforded the tetrahydropyrido[2,3-*d*]pyrimidines **12** and **13**. Both reduced analogs were less potent than their unreduced precursors. In particular the decrease in potency for **12** compared to **9** was 12-fold for pcDHFR and 5-fold for rlDHFR but only 2-fold for tgDHFR which increases the selectivity of compound **12** to 13.0 for tgDHFR compared to 5.7 for compound **9**. Compound **13** was less potent and less selective than **10** against all three DHFRs.

In summary compound **3** retained significant potency against tgDHFR and was much less potent against rlDHFR which translated to a 3-fold increase in selectivity for tgDHFR compared to **1a** and a 2-fold increase in selectivity for pcDHFR compared to **1a**. Thus the premise that the removal of the 5-methyl moiety would

allow a decrease in DHFR inhibition which was anticipated to be less for pcDHFR and/or tgDHFR than for rlDHFR was realized. Compared to TMP and TMQ (Table 1) compound **3** combines the selectivity of TMP and potency of TMQ for tgDHFR. Compared to TMQ and PTX compound **3** is 18- and 29-fold more selective against pcDHFR, respectively, and 104- and 222-fold more selective against tgDHFR. Compared to TMP compound **3** was only 1.5-fold less selective but 300-fold more potent against tgDHFR.

For pcDHFR all the 5-desmethyl compounds synthesized (**2**−**13**) were significantly more selective than TMQ and PTX; however, except for **2**, **3,** and **8**, the compounds were more potent against rlDHFR than pcDHFR. In addition for tgDHFR, all of the 5-desmethyl analogs were more selective than TMQ and PTX, but only **3**, **6**, and **12** were more selective than **1a**. Similar to the 5-methyl series of analogs, the most potent and selective analog in the 5-desmethyl series of this study, the N10 methyl 3,4,5-trimethoxy derivative **3**, was the most potent and most selective for tgDHFR. Compound **3** is undergoing further biological evaluation, and the results of these studies will be reported in a future communication.

Experimental Section

Melting points were determined on a Mel-Temp or Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra (IR) were recorded with a Perkin Elmer 1430 or 1320 infrared spectrophotometer in Nujol mulls and are reported in reciprocal centimeters (cm^{-1}). The ^1H NMR spectra were recorded on a Varian EM 390 (300 MHz) or Bruker WH-300 (300 MHz) spectrometer. The ^{13}C NMR spectra were recorded on a Varian EM 390 instrument at 75.46 MHz, 90° pulse, 14 μs. The data were accumulated by 16K size with 0.5 s delay time and 70° tip angle. The chemical shift (δ) values are expressed in parts per million (ppm) relative to tetramethylsilane as an internal standard: s = singlet, d = doublet, t = triplet, m = multiplet; Ar-CH = aromatic proton. Thin layer chromatography (TLC) was performed on cellulose or silica gel plates with fluorescent indicator and visualized with UV light at 254 and 350 nm. Flash chromatography was performed on 230−400 mesh silica gel purchased from Aldrich, Milwaukee, WI. Samples for microanalysis were dried *in vacuo* over phosphorus pentoxide with heating over refluxing ethanol or toluene. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, GA. Fractional moles of solvents in the analytical samples frequently found in such antifolates could not be prevented in spite of vigorous drying *in vacuo* and were confirmed, where possible, by their presence in the NMR spectrum.

2,4-Bis(pivaloylamino)-6-bromopyrido[2,3-*d*]pyrimidine (17). 2,4,6-Triaminopyrimidine (**14**) (20.0 g, 160.0 mmol) was dissolved in concentrated HCl (30 mL) and absolute ethanol (20 mL) at 80 °C under nitrogen. To this vigorously stirred solution was added bromomalonaldehyde (**15**) (12.06 g, 80.0 mmol). The solution was brought to reflux for 5 min, when an orange-colored solid fell out of solution. The thick suspension was cooled to 5 °C and diluted with water (30 mL). The mixture was made basic with concentrated NH_4OH to pH 8, with the temperature maintained below 10 °C. The precipitate **16**, was filtered, washed with water until neutral, air-dried, and further dried *in vacuo* over phosphorus pentoxide at 70 °C. To the crude dried precipitate **16** were added pyridine (60 mL) and pivaloyl anhydride (100 mL, 480.0 mmol). The mixture was refluxed under nitrogen for 8 h and the reaction mixture cooled to room temperature. The excess pyridine and pivaloyl anhydride were removed under reduced pressure (oil pump). To the residue was added CH_2Cl_2 (1000 mL), and the suspension was stirred overnight at room temperature. The undissolved material was filtered and the filtrate evaporated to ~70 mL and chromatographed on a silica gel column (4.2 × 58 cm, packed with CH_2Cl_2). The column was eluted with CH_2Cl_2, collecting 10 mL fractions. Fractions showing a single spot on TLC were pooled and evaporated to afford a white residue. This residue was recrystallized twice from acetone to afford 22.8 g (44%) of **17** as small needles: mp 212−214 °C (lit.[31] mp 212−214 °C); TLC R_f 0.67 (CH_2Cl_2/MeOH, 15:1, silica gel); MS (EI) calculated for $C_{17}H_{22}N_5O_2Br$ m/z 409 (M^++ 2), 407 (M^+).

2,4-Bis(pivaloylamino)-6-(2-phenylethenyl)pyrido[2,3-*d*]pyrimidine (18). A mixture of **17** (2.86 g, 7.0 mmol), palladium acetate (0.016 g, 0.07 mmol, 1 mol %), tri-*o*-tolylphosphine (0.043 g, 0.14 mmol), cuprous iodide (0.007 g, 0.035 mmol), and triethylamine (10 mL) in acetonitrile (40 mL) was brought to reflux under nitrogen. Styrene (0.73 g, 7.0 mmol) was added to the refluxing mixture and the reflux continued for 24 h. A second portion of styrene (0.73 g, 7.0 mmol) was added, and reflux was continued for an additional 24 h. The mixture was then cooled and evaporated to dryness under reduced pressure. The gummy residue was dissolved in CH_2Cl_2 and chromatographed on a silica gel column (2.4 × 32 cm, packed with CH_2Cl_2). The column was first eluted with CH_2Cl_2 (500 mL) followed by 1% MeOH in CH_2Cl_2. Fractions showing a single spot were pooled, evaporated to dryness, and dried to afford 1.42 g (47%) of **18** as a bright yellow solid. An analytical sample was recrystallized from a mixture of EtOAc and hexanes: mp 228−230 °C; TLC R_f 0.64 (CH_2Cl_2/MeOH, 15:1, silica gel); ^1H NMR (DMSO-d_6, 300 MHz) δ 1.28−1.30 (2s, 18 H, 2 × $C(CH_3)_3$), 7.30−7.70 (m, 7 H, Ar-CH, and 9-, 10-CH), 8.76 (s, 1 H, 5-CH), 9.30 (s, 1 H, 7-CH), 11.42 (br s, 1 H, 4-NH), 15.45 (br s, 1 H, 2-NH). Anal. Calcd for ($C_{25}H_{29}N_5O_2$·0.5H_2O) C, H, N.

2,4-Bis(pivaloylamino)-6-formylpyrido[2,3-*d*]pyrimidine (19). A solution of **18** (1.10 g, 2.55 mmol) was dissolved in a mixture of CH_2Cl_2 (70 mL) and MeOH (10 mL), and this solution was cooled to −78 °C in a dry ice−acetone bath. Ozone was passed through this solution until a blue color persisted. A stream of oxygen was then passed through the solution for 15 min to remove excess ozone. Dimethyl sulfide (1 mL) was added, the reaction mixture stirred for 15 min, and the solution was evaporated to dryness under reduced pressure. The residue so obtained was dissolved in a minimum amount of CH_2Cl_2 and chromatographed on a silica gel column (2.4 × 22 cm, packed with CH_2Cl_2) eluting first with CH_2Cl_2 (500 mL) followed by 1% MeOH in CH_2Cl_2. Fractions showing a single spot (TLC) were pooled and evaporated to dryness to afford 0.73 g (80%) of **19** as a white solid: mp 241−242 °C; TLC R_f 0.58 (CH_2Cl_2/MeOH, 15:1, silica gel); IR (Nujol) 3300, 1720, 1680 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 1.27−1.29 (s, 18 H, 2 × $C(CH_3)_3$), 9.11 (s, 1 H, 5-CH), 9.31 (s, 1 H, 7-CH), 10.18 (s, 1 H, 6-CHO), 11.63 (s, 1 H, NH), 15.43 (s, 1 H, NH). Anal. Calcd for ($C_{18}H_{23}N_5O_3$) C, H, N.

2,4-Bis(pivaloylamino)-6-[(3′,4′,5′-trimethoxyanilino)-methyl]pyrido[2,3-*d*]pyrimidine (20). To a solution of **19** (0.36 g, 1.0 mmol) in glacial acetic acid (10 mL) was added 3,4,5-trimethoxyaniline (0.20 g, 1.10 mmol), and the mixture was stirred at room temperature, under nitrogen, for 18 h. To this solution was added borane−triethylamine complex (51 μL, 0.35 mmol), and the mixture was stirred for an additional 4 h. The mixture was then evaporated to dryness under reduced pressure. The residue was dissolved in CH_2Cl_2 (50 mL) and washed with a saturated solution of $NaHCO_3$ (2 × 40 mL) followed by back-extraction of the aqueous layers with CH_2Cl_2 (50 mL). The combined organic layers were washed with water (50 mL) and brine (50 mL), dried ($MgSO_4$), and filtered. The filtrate was evaporated to a small volume and chromatographed on a silica gel column (2.4 × 18 cm, packed with CH_2Cl_2). The column was eluted with CH_2Cl_2 (250 mL), then with 1% MeOH in CH_2Cl_2 (100 mL), and finally with 2% MeOH in CH_2Cl_2 (100 mL). The fractions showing a single spot (TLC) were pooled and evaporated to dryness. The residue so obtained was recrystallized from a mixture of EtOAc and hexanes to afford 0.25 g (48%) of **20** as an orange solid: mp 214−216 °C; TLC R_f 0.45 (CH_2Cl_2/MeOH, 15:1, silica gel), ^1H NMR (DMSO-d_6, 300 MHz) δ 1.22 (s, 9 H, $C(CH_3)_3$), 1.27 (s, 9 H, $C(CH_3)_3$), 3.50 (s, 3 H, 4′-OCH_3), 3.66 (s, 6 H, 3′-, 5′-OCH_3), 4.44 (d, 2 H, 9-CH_2, J = 6.0 Hz), 5.95 (s, 2 H, 2′-, 6′-CH), 6.23

(br t, 1 H, 10-NH), 8.70 (s, 1 H, 5-CH), 8.94 (s, 1 H, 7-CH), 11.35 (br s, 1 H, NH). Anal. Calcd for ($C_{27}H_{36}N_6O_5 \cdot H_2O$) C, H, N.

2,4-Diamino-6-[(3′,4′,5′-trimethoxyanilino)methyl]-pyrido[2,3-*d*]pyrimidine (2). To a solution of sodium hydride (0.05 g, 2.10 mmol) in anhydrous methanol (15 mL) was added **20** (0.37 g, 0.70 mmol), and the mixture was stirred under nitrogen at room temperature for 24 h. Another portion of sodium hydride (0.05 g, 2.1 mmol) in anhydrous methanol (5 mL) was added to the reaction mixture, and it was stirred at 50 °C for 12 h. Silica gel (1 g) was added to this mixture and the suspension evaporated under reduced pressure to dryness. The solid plug obtained was loaded on a silica gel column (2.4 × 20 cm) and the column flushed with chloroform (300 mL). Stepwise elution with 100 mL portions of 1−14% MeOH in $CHCl_3$ afforded fractions which showed a spot corresponding to that of the desired product at R_f 0.34 ($CHCl_3$/MeOH, 3:1, silica gel) along with a minor trailing impurity. These fractions were pooled and evaporated to dryness under reduced pressure. The residue so obtained was dissolved in a minimum amount of glacial acetic acid, filtered, and evaporated to dryness. This oily residue was redissolved in MeOH and the solution stored at 0 °C for 72 h to deposit a solid which was filtered, washed with ether, and dried to afford 0.13 g (52%) of **2** as a light brown solid: mp 249−252 °C dec; TLC (a) R_f 0.34 ($CHCl_3$/MeOH, 3:1, silica gel), (b) R_f 0.17 ($CHCl_3$/MeOH/NH_4OH, 14:2:1, silica gel); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.51 (s, 3 H, 4′-OCH_3), 3.67 (s, 6 H, 3′-, 5′-OCH_3), 4.20 (d, 2 H, 9-CH_2, J = 3.8 Hz), 5.90−5.93 (overlapping peaks, 3 H, 10-NH, 2′-, 6′-CH), 6.28 (br s, 2 H, 4-NH_2), 7.47 (br s, 2 H, 2-NH_2), 8.38 (s, 1 H, 5-CH), 8.64 (s, 1 H, 7-CH). Anal. Calcd for ($C_{17}H_{20}N_6O_3 \cdot 0.5CH_3COOH \cdot 0.75H_2O$) C, H, N.

2,4-Bis(pivaloylamino)-6-(hydroxymethyl)pyrido[2,3-*d*]pyrimidine (21). To a cooled (ice bath) solution of **19** (0.375 g, 1 mmol) in MeOH (8 mL) was added a solution of sodium borohydride (0.038 g, 1 mmol) in MeOH (2 mL), and the mixture stirred for 30 min under nitrogen. TLC (EtOAc, silica gel) indicated the disappearance of starting material (R_f 0.40) and formation of a product spot (R_f 0.08). The reaction mixture was diluted with water (50 mL) and the pH adjusted to 4 with dropwise addition of 0.5 N HCl. This mixture was extracted with CH_2Cl_2 (2 × 75 mL), the combined organic layers were dried ($MgSO_4$) and filtered, and the filtrate was evaporated under reduced pressure to dryness. The residue so obtained was chromatographed on a silica gel column (2.4 × 16 cm) eluting with a mixture of EtOAc/$CHCl_3$ (2:1). Fractions which showed a single spot (TLC) were pooled and evaporated to afford 0.27 g (75%) of **21** as a white solid: mp 166−168 °C; TLC R_f 0.19 (EtOAc/MeOH, 19:1, silica gel); IR (Nujol) 3480, 3400, 3200, 1670 cm^{-1}, ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.26−1.28 (s, 18 H, 2 × $C(CH_3)_3$), 4.66 (d, 2 H, 6-CH_2OH, J = 5.7 Hz), 5.50 (t, 1 H, 6-CH_2O*H*, J = 5.7 Hz), 8.67 (d, 1 H, 5-CH, J = 2.4 Hz), 8.86 (d, 1 H, 7-CH, J = 2.4 Hz), 11.36 (s, 1 H, NH); MS (FAB) calcd for $C_{18}H_{25}N_5O_3$ m/z 360 (MH^+); high-resolution FABMS calcd MH^+ 360.4388, found 360.4398.

2,4-Bis(pivaloylamino)-6-(bromomethyl)pyrido[2,3-*d*]-pyrimidine (22). To a solution of triphenylphosphine (0.32 g, 1.22 mmol) in CH_2Cl_2 was added liquid bromine until the solution just turned yellow in color. Alcohol **21** (0.22 g, 0.61 mmol) was then added as a solid and the mixture stirred for 1 h at room temperature until TLC (EtOAc, silica gel) indicated disappearance of starting material (R_f 0.08) and formation of product (R_f 0.27). The solution was diluted with CH_2Cl_2 (70 mL) and washed with water (2 × 50 mL), and the combined organic layers were dried ($MgSO_4$) and filtered. The filtrate was evaporated to a small volume and flash chromatographed on a silica gel column (2.4 × 10 cm) eluting with a mixture of EtOAc/$CHCl_3$ (2:1). Fractions showing a single spot (TLC) were pooled and evaporated to dryness under reduced pressure to afford 0.20 g (78%) of **22** as a pale yellow solid: mp >150 °C dec; TLC R_f 0.27 (EtOAc, silica gel); MS (FAB) calcd for $C_{18}H_{24}N_5O_2$ Br m/z 424 (MH^++ 2), 422 (MH^+). This compound was immediately used in the next step.

***N*-Methyl-3,4,5-trimethoxyaniline.** To a solution of 3,4,5-trimethoxyaniline (1.83 g, 10.0 mmol) in anhydrous *N*,*N*-DMAc (10 mL) were added *N*,*N*-diisopropylethylamine (2.09 mL, 12.0 mmol) and methyl iodide (0.75 mL, 12.0 mmol), and the mixture was stirred at room temperature, under nitrogen, for 5 days. The solvent was removed under reduced pressure (pump) and the residue dissolved in CH_2Cl_2 (100 mL). The CH_2Cl_2 layer was washed with water (50 mL), a saturated solution of $NaHCO_3$ (50 mL), and brine (50 mL). The organic layers were dried ($MgSO_4$), filtered, concentrated under reduced pressure, and subjected to column chromatography on silica gel (2.4 × 24 cm, packed with toluene/EtOAc, 14:1). Elution with the same solvent afforded fractions showing a single spot (TLC) which were pooled and evaporated to dryness under reduced pressure to afford 0.75 g (38%) of the desired compound as a tan semisolid: TLC R_f 0.30 (toluene/EtOAc, 4:1, silica gel); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.82 (s, 3 H, N-CH_3), 3.60 (s, 1 H, NH), 3.80 (s, 3 H, 4′-OCH_3), 3.86 (s, 6 H, 3′-, 5′-OCH_3), 5.88 (s, 2 H, 2′-, 6′-CH).

***N*-Ethyl-3,4,5-trimethoxyaniline.** This compound was prepared in a manner similar to that described above for the preparation of *N*-methyl-3,4,5-trimethoxyaniline in 39% yield from 3,4,5-trimethoxyaniline and ethyl iodide, dark brown oil: TLC R_f 0.33 (toluene/EtOAc, 4:1, silica gel); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.23 (t, 3 H, CH_2CH_3), 3.15 (q, 2 H, CH_2CH_3), 3.76 (s, 3 H, 2′-OCH_3), 3.83 (s, 6 H, 3′-, 5′-OCH_3), 5.86 (s, 2 H, 2′-, 6′-CH).

2,4-Diamino-6-[(3′,4′,5′-trimethoxy-*N*-methylanilino)-methyl]pyrido[2,3-*d*]pyrimidine (3). To a solution of **22** (0.21 g, 0.50 mmol) and *N*-methyl-3,4,5-trimethoxyaniline (0.20 g, 1.0 mmol) in anhydrous *N*,*N*-DMAc (5 mL) was added 4-(dimethylamino)pyridine (0.12 g, 1.0 mmol), and the mixture was stirred under nitrogen at room temperature for 4 days. TLC (CH_2Cl_2/MeOH, 15:1, silica gel) at this time indicated the formation of the product (**23**) spot at R_f 0.47. The solvent was then removed under reduced pressure (pump) and the residue dissolved in CH_2Cl_2 (50 mL). This solution was washed with water (50 mL) and a saturated solution of $NaHCO_3$ (50 mL), and the organic layers were dried ($MgSO_4$) and filtered. The filtrate was evaporated under reduced pressure to afford crude **23** as a dark brown residue which was dissolved in anhydrous MeOH (20 mL). Sodium hydride (dry 95%, 60 mg, 2.5 mmol) was carefully added to this solution and the mixture stirred at room temperature for 24 h and then at 50 °C for 12 h. Silica gel (1.0 g) was then added and the suspension evaporated to dryness under reduced pressure. This plug was loaded on a dry silica gel column (2.4 × 18 cm) and flushed with $CHCl_3$ (500 mL). Stepwise elution with 100 mL portions of 1−14% MeOH in $CHCl_3$ afforded fractions showing a single spot on TLC, which were pooled and evaporated under reduced pressure to dryness to afford 0.09 g (48%) of **3** as a yellow solid: mp 248−250 °C dec; TLC (a) R_f 0.50 ($CHCl_3$/MeOH, 3:1, silica gel), (b) R_f 0.28 ($CHCl_3$/MeOH/NH_4OH, 14:2:1, silica gel); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.97 (s, 3 H, N-CH_3), 3.53 (s, 3 H, 4′-OCH_3), 3.71 (s, 6 H, 3′-, 5′-OCH_3), 4.50 (s, 2 H, 9-CH_2), 6.04 (s, 2 H, 2-NH_2), 8.30 (s, 1 H, 5-CH), 8.58 (s, 1 H, 7-CH). Anal. Calcd for ($C_{18}H_{22}N_6O_3 \cdot 0.75H_2O$) C, H, N.

2,4-Diamino-6-[(3′,4′,5′-trimethoxy-*N*-ethylanilino)-methyl]pyrido[2,3-*d*]pyrimidine (4). To a solution of **22** (0.21 g, 0.5 mmol) and *N*-ethyl-3,4,5-trimethoxyaniline (0.21 g, 1.0 mmol) in anhydrous *N*,*N*-DMAc (5 mL) was added 4-(dimethylamino)pyridine (0.12 g, 1.0 mmol), and the mixture was stirred under nitrogen at room temperature for 4 days. The TLC (CH_2Cl_2/MeOH, 15:1, silica gel) at this time indicated the formation of the product (**24**) spot at R_f 0.48. The solvent was then removed under reduced pressure (pump) and the residue dissolved in CH_2Cl_2 (50 mL). This solution was washed with water (50 mL) and a saturated solution of $NaHCO_3$ (50 mL), and the organic layers were dried ($MgSO_4$) and filtered. The filtrate was evaporated to dryness under reduced pressure. The crude product **24** was obtained as a dark residue which was dissolved in anhydrous THF (30 mL); 30% HBr in acetic acid (2 mL) was added to this solution and the mixture stirred at room temperature under nitrogen for 24 h and then at 50 °C for 3 h. The reaction mixture was evaporated to dryness and the oily residue coevaporated twice with 50 mL portions of absolute MeOH. The residue was dissolved in MeOH, silica gel (1.2 g) was added, and the suspension was evaporated to afford a plug which was loaded

on a dry silica gel column (2.4 × 18 cm) and flushed with $CHCl_3$ (500 mL). The column was then eluted stepwise with 100 mL portions of 1−14% MeOH in $CHCl_3$. Fractions showing a single spot on TLC were pooled and evaporated to dryness under reduced pressure. The residue obtained was stirred in anhydrous ether (30 mL) for 4 h and filtered to afford 0.08 g (42%) of **4** as a light brown solid: mp 220−223 °C dec; TLC (a) R_f 0.54 ($CHCl_3$/MeOH, 3:1, silica gel), (b) R_f 0.33 ($CHCl_3$/MeOH/NH_4OH, 14:2:1, silica gel); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.11 (t, 3 H, N-CH_2CH_3), 3.48−3.52 (overlapping q and s, 5 H, N-CH_2CH_3, 4′-OCH_3), 3.67 (s, 6 H, 3′-, 5′-OCH_3), 4.45 (s, 2 H, 9-CH_2), 5.98 (s, 2 H, 2′-, 6′-CH), 6.43 (br s, 2 H, 4-NH_2), 7.64 (br s, 2 H, 2-NH_2), 8.31 (s, 1 H, 5-CH), 8.57 (s, 1 H, 7-CH). Anal. Calcd for ($C_{19}H_{24}N_6O_3$·0.25HBr·0.75H_2O) C, H, N.

2,4-Diamino-6-[(3′,4′,5′-trimethoxy-*N*-formylanilino)-methyl]pyrido[2,3-*d*]pyrimidine (5). To a solution of **2** (0.06 g, 0.16 mmol) in 98% formic acid (3 mL) was added 2 drops of acetic anhydride, and the solution was stirred for 48 h at room temperature when TLC ($CHCl_3$/MeOH/NH_4OH, 14:2:1, silica gel) indicated disappearance of starting material **2** (R_f 0.17) and formation of product (R_f 0.25). The solvent was then evaporated under reduced pressure and the residue dissolved in MeOH (20 mL). Silica gel (0.5 g) was added to this solution and the suspension evaporated to dryness. This plug was loaded on a dry silica gel column (1 × 10 cm) and flushed with $CHCl_3$ (100 mL). The column was then eluted stepwise with 75 mL portions of 2−12% MeOH in $CHCl_3$. Fractions showing a single spot (TLC) were pooled and evaporated to dryness. The residue was stirred in anhydrous ether (20 mL) and filtered to afford 0.05 g (86%) of **5** as an off-white solid: mp 239−242 °C; TLC R_f 0.25 ($CHCl_3$/MeOH/NH_4OH, 14:2:1, silica gel); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.60 (s, 3 H, 4′-OCH_3), 3.75 (s, 6 H, 3′-, 5′-OCH_3), 5.04 (s, 2 H, 9-CH_2), 6.43 (br s, 2 H, 4-NH_2), 6.73 (s, 2 H, 2′-, 6′-CH), 7.62 (br s, 2 H, 2-NH_2), 8.19 (s, 1 H, 5-CH), 8.52 (s, 1 H, 7-CH), 8.59 (s, 1 H, N-CHO). Anal. Calcd for ($C_{18}H_{20}N_6O_4$·0.75H_2O) C, H, N.

3,4,5-Trimethoxystyrene. A mixture of methyltriphenylphosphonium bromide (11.43 g, 32 mmol) in anhydrous THF (120 mL) was cooled to 0 °C (ice−salt bath). To this suspension, under nitrogen, was added a 1.6 M solution of nBuLi in hexanes (20.64 mL, 32 mmol) dropwise over a period of 20 min. The suspension was stirred at 0 °C for 30 min, warmed to room temperature, and stirred for an additional 1 h. A solution of trimethoxybenzaldehyde (5.89 g, 30 mmol) in anhydrous THF (25 mL) was added over a period of 10 min and the reaction mixture stirred at room temperature for 5 h. The reaction mixture was diluted with water (300 mL) and the suspension filtered. The filtrate was washed with water (3 × 100 mL) followed by back-extraction of the aqueous layers with ether (100 mL). The combined organic layers were washed with brine (150 mL), dried ($MgSO_4$), and filtered. After evaporation of the filtrate the resulting oil was flash chromatographed on a silica gel column (2.4 × 38 cm) eluting with hexanes/EtOAc (4:1) to afford 5.02 g (86%) of trimethoxystyrene as a viscous oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.82 (s, 3 H, 4′-OCH_3), 3.86 (s, 6 H, 3′-, 5′-OCH_3), 5.20 (d, 1 H, J = 11.0 Hz, *H*CH=CH), 5.60 (d, 1 H, J = 18.0 Hz, HC*H*=CH), 6.60 (dd, 1 H, J = 11.0, 18.0 Hz, CH_2=C*H*), 6.65 (s, 2 H, 2′-, 6′-CH); MS (EI) calcd for $C_{11}H_{14}O_3$ m/z 194 (M^+).

2,4-Bis(pivaloylamino)-6-[2-(3′,4′,5′-trimethoxyphenyl)-ethenyl]pyrido[2,3-*d*]pyrimidine (25). A mixture of **17** (2.65 g, 6.5 mmol), palladium acetate (0.016 g, 0.07 mmol, 1 mol %), tri-*o*-tolylphosphine (0.043 g, 0.14 mmol), cuprous iodide (0.007 g, 0.035 mmol), and triethylamine (10 mL) in acetonitrile (40 mL) was brought to reflux under nitrogen. 3,4,5-Trimethoxystyrene (2.33 g, 12.0 mmol) was added to the solution and the reaction mixture refluxed for 24 h. A second portion of triethylamine (5 mL) was then added and reflux continued for an additional 24 h. The reaction mixture was cooled and evaporated to dryness under reduced pressure. The residue was suspended in CH_2Cl_2, and loaded onto a silica gel column (2.4 × 34 cm, packed with CH_2Cl_2), and flushed with CH_2Cl_2 (500 mL). The column was then eluted with 1% MeOH in CH_2Cl_2. The fractions showing a single spot (TLC) corresponding to the product were pooled and evaporated under reduced pressure to afford 2.0 g (59%) of **25** as an orange solid. An analytical sample was recrystallized from a mixture of ethyl acetate and hexanes: mp 207−208 °C; TLC R_f 0.58 (CH_2Cl_2/MeOH, 15:1, silica gel); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.28−1.30 (2s, 18 H, 2 × C(CH_3)$_3$), 3.69 (s, 3 H, 4′-OCH_3), 3.86 (s, 6 H, 3′-, 5′-OCH_3), 7.01 (s, 2 H, 2′-, 6′-CH), 7.43 (s, 2 H, 9-, 10-CH), 8.65 (s, 1 H, 5-CH), 9.27 (s, 1 H, 7-CH), 11.60 (br s, NH), 15.45 (br s, NH). Anal. Calcd for ($C_{28}H_{35}N_5O_5$·H_2O) C, H, N.

2,4-Bis(pivaloylamino)-6-[2-(4′-methoxyphenyl)ethenyl]-pyrido[2,3-*d*]pyrimidine (27). To a mixture of **17** (3.06 g, 7.50 mmol), palladium acetate (0.084 g, 0.375 mmol, 5 mol %), tri-*o*-tolylphosphine (0.228 g, 0.75 mmol), and cuprous iodide (0.036 g, 0.19 mmol) in acetonitrile (50 mL) was added triethylamine (15 mL), and the reaction mixture was brought to reflux under nitrogen. To this mixture was added 4-methoxystyrene (1.0 g, 7.5 mmol), and the reflux was continued for a period of 36 h. A second portion of 4-methoxystyrene (1.0 g, 7.5 mmol) and triethylamine (5 mL) was added to the hot mixture and reflux continued for an additional 36 h. The reaction mixture was cooled and evaporated to dryness under reduced pressure. The dark gummy residue was dissolved in a mixture of CH_2Cl_2/MeOH (4:1), filtered through Celite, and washed with the same solvent. The combined filtrates were evaporated to dryness, and the residue was dissolved in a minimum amount of CH_2Cl_2/MeOH (96:4) and subjected to column chromatography on silica gel (2.4 × 40 cm, packed with CH_2Cl_2). The column was eluted with CH_2Cl_2 (500 mL) and then with 1% MeOH in CH_2Cl_2. The fractions showing a single spot (TLC) corresponding to that of the product were pooled and evaporated under reduced pressure to a small volume. The solution was stored at 0 °C for 24 h to deposit a solid which was filtered, washed with cold CH_2Cl_2 (20 mL), and dried to afford 1.55 g (45%) of **27** as an orange-yellow solid: mp 240−242 °C; TLC R_f 0.61 (CH_2Cl_2/MeOH, 19:1, silica gel); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.28−1.30 (2s, 18 H, 2 × C(CH_3)$_3$), 3.80 (s, 3 H, 4′-OCH_3), 6.98 (d, 2 H, 2′-, 6′-CH, J = 8.6 Hz), 7.32 (d, 1 H, 9- or 10-CH, J = 16.7 Hz), 7.44 (d, 1 H, 9- or 10-CH, J = 16.7 Hz), 7.63 (d, 2 H, 3′-, 5′-CH, J = 8.6 Hz), 8.72 (s, 1 H, 5-CH), 9.25 (s, 1 H, 7-CH), 10.29 (br s, 1 H, NH). Anal. Calcd for ($C_{26}H_{31}N_5O_3$·1.5H_2O) C, H, N.

2,4-Diamino-6-[2-(3′,4′,5′-trimethoxyphenyl)ethenyl]-pyrido[2,3-*d*]pyrimidine (6). To a solution of **25** (0.55 g, 1.06 mmol) in CH_2Cl_2/MeOH (3:1, 20 mL) was added liquid ammonia (40 mL), and the mixture was stirred in a Parr acid digestion bomb for a period of 72 h. The liquid ammonia was allowed to evaporate and the suspension filtered. The residue was extracted with boiling MeOH (100 mL) and then with boiling acetone (100 mL). The resulting solid was dissolved in 25% aqueous acetic acid and the solution filtered through glass wool. The filtrate was evaporated under reduced pressure to dryness and the residue stirred in the dark in a mixture of EtOAc/MeOH (2:1, 150 mL) and filtered. The residue was washed with EtOAc followed by acetone and dried to afford 0.30 g (80%) of **6** as a yellow solid: mp >300 °C; TLC (a) R_f 0.21 ($CHCl_3$/MeOH/NH_4OH, 14:2:1, silica gel), (b) R_f 0.75 (50% aqueous acetic acid, cellulose); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.67 (s, 3 H, 4′-OCH_3), 3.83 (s, 6 H, 3′-, 5′-OCH_3), 6.88 (s, 2 H, 2′-, 6′-CH), 7.26−7.36 (overlapping s, 4 H, 9-, 10-CH, and 4-NH_2), 8.40 (br s, 2 H, 2-NH_2), 8.83 (s, 1 H, 5-CH), 8.89 (s, 1 H, 7-CH). Anal. Calcd for ($C_{18}H_{19}N_5O_3$·2H_2O) C, H, N.

2,4-Diamino-6-[2-(4′-methoxyphenyl)ethenyl]pyrido-[2,3-*d*]pyrimidine (8). This compound was prepared in a manner similar to that described above for the synthesis of the trimethoxy derivative **6**. Thus ammonolysis of **27** (0.46 g, 1.0 mmol) afforded 0.23 g (78%) of the desired depivaloylated compound **8** as a bright yellow solid: mp >300 °C; TLC (a) R_f 0.20 ($CHCl_3$/MeOH/NH_4OH, 14:2:1, silica gel), (b) R_f 0.52 (50% aqueous acetic acid, cellulose); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.79 (s, 3 H, 4′-OCH_3), 6.99 (d, 2 H, 2′-, 6′-CH, J = 8.0 Hz), 7.11−7.33 (2d overlapped with br s, 4 H, 9-, 10-CH, 4-NH_2, J = 16.2 Hz), 7.54 (d, 2 H, 3′-, 5′-CH, J = 8.0 Hz), 8.37 (br s, 2 H, 2-NH_2), 8.85 (s, 2 H, 5-, 7-CH; separates on addition of D_2O to give 2s at 8.82 and 8.86 ppm). Anal. Calcd for ($C_{12}H_{15}N_5O$·1.5H_2O) C, H, N.

2,4-Diamino-6-[2-(3′,4′,5′-trimethoxyphenyl)ethyl]-pyrido[2,3-*d*]pyrimidine (9). In order to increase the solubility of **6** in DMF it was converted to the trifluoroacetate salt. Compound **6** (0.18 g, 0.51 mmol) was dissolved in CF_3COOH (20 mL), and the solution was evaporated to dryness (<30 °C) with an oil pump. The residue was dissolved in DMF (20 mL), and 5% Pd−C (0.20 g) was added to the solution. The suspension was hydrogenated at 25 psi for 15 min in a Parr apparatus. TLC (cellulose, 10% aqueous acetic acid, v/v) of the reaction mixture showed two spots, the desired product at R_f 0.58 and unreacted starting material **6** at R_f 0.05. The reaction mixture was filtered through Celite and the Celite washed with DMF (20 mL). The filtrate was evaporated under reduced pressure (<50 °C) to dryness. The residue was dissolved in boiling MeOH containing drops of glacial AcOH. To this solution was added silica gel (0.50 g), and the solvent was removed under reduced pressure. This solid dispersion was loaded on a dry silica gel column (35 g, 2.4 × 20 cm) which was flushed with $CHCl_3$ (500 mL) and then eluted stepwise with 100 mL portions of 1−20% MeOH in $CHCl_3$, collecting 10 mL fractions. Fractions showing a single spot on TLC corresponding to the product were pooled and evaporated to dryness. The residue was stirred overnight in anhydrous ether in the dark and filtered. The filtered solid was dried *in vacuo* at 70 °C over phosphorus pentoxide to afford 0.09 g (52%) of **9** as a cream solid: mp 286−289 °C; TLC (a) R_f 0.22 ($CHCl_3$/MeOH/NH_4OH, 14:2:1, silica gel), (b) R_f 0.58 (10% aqueous acetic acid, cellulose); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.86−2.94 (AB system, 4 H, 9-, 10-CH_2, J = 7.5 Hz), 3.59 (s, 3 H, 4′-OCH_3), 3.71 (s, 6 H, 3′-, 5′-OCH_3), 6.52 (s, 2 H, 2′-, 6′-CH), 7.11 (br s, 2 H, 4-NH_2), 8.20 (br s, 2 H, 2-NH_2), 8.41 (d, 1 H, 5-CH, J = 2.0 Hz), 8.56 (d, 1 H, 7-CH, J = 2.0 Hz). Anal. Calcd for ($C_{18}H_{21}N_5O_3$·0.75CF_3COOH·H_2O) C, H, N.

2,4-Diamino-6-[2-(4′-methoxyphenyl)ethyl]pyrido[2,3-*d*]pyrimidine (11). This compound was prepared in a manner similar to that reported above for the synthesis of **9**. Thus conversion of compound **8** (0.15 g, 0.5 mmol) to its trifluoroacetate salt and subsequent hydrogenation and chromatographic purification afforded 0.08 g (55%) of **11** as a light brown solid: mp >300 °C; TLC (a) R_f 0.20 ($CHCl_3$/MeOH/NH_4OH, 14:2:1, silica gel), (b) R_f 0.32 (10% aqueous acetic acid, cellulose); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.87 (s, 4 H, 9-, 10-CH_2), 3.71 (s, 3 H, 4′-OCH_3), 6.23 (br s, 2 H, 4-NH_2), 6.83 (d, 2 H, 2′-, 6′-CH, J = 8.5 Hz), 7.13 (d, 2 H, 3′-, 5′-CH, J = 8.5 Hz), 7.43 (br s, 2 H, 2-NH_2), 8.26 (d, 1 H, 5-CH, J = 2.1 Hz), 8.44 (d, 1 H, 7-CH, J = 2.1 Hz). Anal. Calcd for ($C_{16}H_{17}N_5O$·1.5CF_3COOH·H_2O) C, H, N.

(±)-2,4-Diamino-6-[2-(3′,4′,5′-trimethoxyphenyl)ethyl]-5,6,7,8-tetrahydro-8*H*-pyrido[2,3-*d*]pyrimidine (12). To a solution of **6** (0.16 g, 0.45 mmol) in 10% trifluoroacetic acid in MeOH (25 mL) was added 5% Pd−C (0.32 g), and the suspension was hydrogenated at 50 psi for 24 h in a Parr apparatus. The catalyst was filtered through Celite and washed with 10% trifluoroacetic acid in MeOH (30 mL). The filtrate was evaporated to dryness under reduced pressure, the residue was dissolved in MeOH (50 mL), and silica gel (0.8 g) was added to this solution. The suspension was evaporated to dryness, and the plug was loaded on a dry silica gel column (2.4 × 18 cm) and flushed with $CHCl_3$ (500 mL). The column was then eluted stepwise with 100 mL portions of 1−15% MeOH in $CHCl_3$. Fractions showing a single spot (TLC) were pooled and evaporated to afford a residue which was re-evaporated twice with ether (30 mL). The solid obtained was triturated in anhydrous ether and filtered to afford 0.10 g (59%) of **12** as a white solid: mp >150 °C dec; TLC (a) R_f 0.40 ($CHCl_3$/MeOH/NH_4OH, 14:2:1, silica gel), (b) R_f 0.47 (10% aqueous acetic acid, cellulose); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.53−1.66 (m, 3 H, 6-CH, 9-CH_2), 1.85−1.93 (dd, 1 H, 5-CH, J = 15.3, 9.0 Hz), 2.42−2.49 (dd, 1 H partially obscured by DMSO peak, 5-CH, J = 15.3, 3.4 Hz), 2.58−2.63 (br q, 2 H, 10-CH_2), 2.80−2.87 (dd, 1 H, 7-CH, J = 11.0, 9.0 Hz), 3.22−3.26 (d, 1 H, 7-CH, J = 11.0 Hz), 3.61 (s, 3 H, 4′-OCH_3), 3.75 (s, 6 H, 3′-, 5′-OCH_3), 5.91 (s, 2 H, 4-NH_2), 6.09 (s, 2 H, 2-NH_2), 6.52 (s, 2 H, 2′-, 6′-CH), 6.63 (s, 1 H, 8-NH). Anal. Calcd for ($C_{18}H_{25}N_5O_3$·0.25CF_3COOH·0.75H_2O) C, H, N.

DHFR Inhibitory Concentrations. The enyme assays were carried out at 37 °C in the presence of 90 μM dihydrofolic acid as the substrate and 119 μM NADPH as the cofactor; assays for rlDHFR and tgDHFR also contained 150 mM KCl.[12,13]

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