Nonclassical 2,4-Diamino-6-(aminomethyl)-5,6,7,8-tetrahydroquinazoline Antifolates: Synthesis and Biological Activities[1a,b]

Aleem Gangjee,*,† Nurulain Zaveri,†,‡ Mohit Kothare,† and Sherry F. Queener§

Division of Medicinal Chemistry, Graduate School of Pharmaceutical Sciences, Duquesne University, Pittsburgh, Pennsylvania 15282, and Department of Pharmacology and Toxicology, Indiana University School of Medicine, Indianapolis, Indiana 46202

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Twenty 6-substituted 2,4-diaminotetrahydroquinazolines were designed, synthesized, and biologically evaluated as novel nonclassical inhibitors of dihydrofolate reductase (DHFR) from *Pneumocystis carinii* and *Toxoplasma gondii* and as antitumor agents. The 6-substituents included substituted anilinomethyls, with alkoxy (OCH_3 and OCH_2CH_3) and halogen (Cl and Br) moieties on the phenyl ring; an indolinomethyl; and 1-naphthylaminomethyls. The compounds were synthesized from a protected key intermediate 2,4-bis(acetamido)-5,6,7,8-tetrahydroquinazoline-6-carboxaldehyde (**26**) by reductive amination with the appropriate amine. Compound **26** was obtained *via* a Diels–Alder reaction of 2-(trimethylsiloxy)-1,3-butadiene with acrolein to afford cyclohexanone-4-carboxaldehyde dimethyl acetal (**23**) after deprotection of the silyloxy group and protection of the aldehyde in a single step. Cyclocondensation of **23** with dicyandiamide followed by protection of the 2,4-diamino groups and deprotection of the 6-acetal gave **26**. The compounds were significantly potent ($(7-330) \times 10^{-9}$ M) and selective against *T. gondii* (versus rat liver DHFR). The most selective analogue against *T. gondii* DHFR was 2,4-diamino-6-[[(2′,5′-dimethoxyphenyl)methylamino]methyl]-5,6,7,8-tetrahydroquinazoline (**5**) which showed exceptionally high inhibitory activity against the growth of *T. gondii* cells in culture ($IC_{50} = 5.4 \times 10^{-8}$ M). Selected analogues were evaluated as inhibitors of the growth of tumor cells in culture. The most active analogues inhibited the growth of tumor cells at $GI_{50} = 10^{-8}$ M.

Opportunistic infections with *Pneumocystis carinii* and *Toxoplasma gondii* are among the leading causes of mortality and morbidity in patients with AIDS.[2,3] Current regimens for the treatment of *P. carinii* and *T. gondii* infections include the combination of trimethoprim/sulfamethoxazole and pyrimethamine/sulfadiazine, respectively.[4] Recently, trimetrexate (TMQ; Figure 1) along with leucovorin rescue has been approved for *P. carinii* infections in patients with AIDS.[5] Trimethoprim (TMP; Figure 1) is a nonclassical antifolate which weakly inhibits dihydrofolate reductase (DHFR) from *P. carinii* and needs sulfamethoxazole to potentiate its effects.[6] However, TMP has been shown to be somewhat selective for *P. carinii* (pc) DHFR compared to mammalian DHFR.[6] TMQ, on the other hand, is a highly potent inhibitor of pcDHFR and *T. gondii* (tg) DHFR but lacks selectivity for these organisms compared to mammalian DHFRs[6,7] and has been approved for *P. carinii* infections only with leucovorin rescue. Leucovorin bypasses the DHFR blockade only in mammalian systems since both *P. carinii* and *T. gondii* lack the folate uptake systems required for leucovorin.[7]

We[8–10] have been involved in the design and synthesis of DHFR inhibitors with both high selectivity and potency against pcDHFR and/or tgDHFR to provide single agents against *P. carinii* and/or *T. gondii* infections. Such single entities would not suffer from the disadvantages present in sulfa drug combinations where dose-limiting side effects, attributed to the sulfa drug component, restrict or prevent their use in several patients.[11] Though TMQ is an effective agent, the cost of leucovorin and patient compliance become of serious consideration due to the long-term prophylactic necessity of agents against *P. carinii* and *T. gondii* infections.[12]

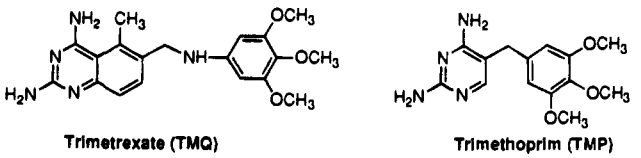

Figure 1.

On the basis of crystal structures of binary and ternary complexes of DHFR, NADPH, and inhibitors, Matthews *et al.*[13] have offered an explanation of the 3000-fold greater inhibition of *Escherichia coli* DHFR with TMP compared to avian DHFR and suggested that the selectivity arises, in part, due to different conformations adopted by the 3,4,5-trimethoxyphenyl side chain of TMP when bound to *E. coli* (ec) DHFR and avian DHFR.

Taira and Benkovic[14] have shown that the hydrophobic interactions which involve the side chain in folate inhibitor binding to DHFR are as important as the salt bridge formed with the enzyme and the N1 and 2-NH_2 moieties of the pyrmidine ring of the inhibitors.

We reasoned that since the side chain and its conformation(s) are important to both selectivity as well as potency, compounds which orient their side chains differently from that in DHFR-bound TMQ[15] could provide selectivity while maintaining potency against pcDHFR and tgDHFR. Partial saturation of the B-ring of 6-substituted 2,4-diaminoquinazolines affords tet-

† Duquesne University.
‡ Present address: SRI International, Menlo Park, CA 94025.
§ Indiana University School of Medicine.
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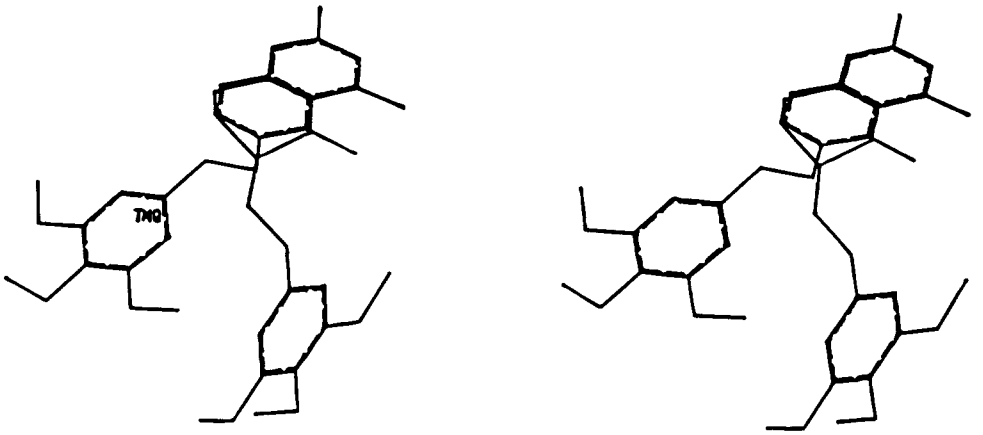


Figure 2. Stereoview of compound 1 C6-axial superimposed on TMQ (bound to DHFR). Hydrogens have been deleted for clarity.

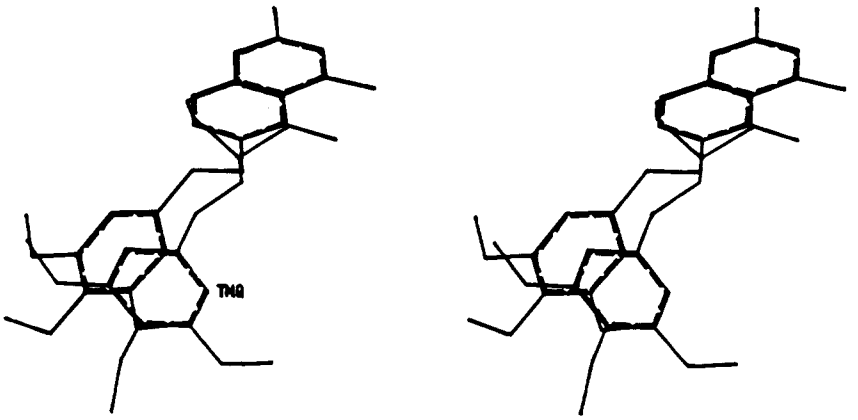


Figure 3. Stereoview of compound 1 C6-equatorial superimposed on TMQ (bound to DHFR). Hydrogens have been deleted for clarity.

rahydroquinazoline analogues. Molecular modeling using SYBYL[16] and its SEARCH and MINIMIZE options was employed to generate energy-minimum conformations of these tetrahydroquinazolines, starting from structures which overlapped the DHFR-bound conformation of TMQ.[15] The 6-substituted tetrahydroquinazoline ring affords a chiral center at C6 which orients the side chain in an axial (6*R*) or equatorial (6*S*) position. Thus, both 6-substituted axial and equatorial tetrahydroquinazolines were subjected to the conformational SEARCH option, in an attempt to determine the orientations of the 6-substituents in the energy-minimized conformation and to compare them to that of DHFR-bound TMQ. The energy-minimum conformation of the C6 axial isomer of **1** was 6.3 kcal/mol and is shown in Figure 2 superimposed on TMQ with the pyrimidine rings overlapped. The energy-minimum conformation of **1** orients its side chain, C9–N10–triOCH$_3$Ph, quite differently from the DHFR-bound conformation of TMQ. In addition, side-chain conformations of **1** which differ from the minimum energy conformation by 1 kcal/mol, also do not superimpose onto the C9–N10–triOCH$_3$Ph side chain of TMQ.

A similar SEARCH study of the equatorial isomer of **1** is shown in Figure 3. The energy-minimum conformation of this isomer was 5.3 kcal/mol, and again conformers which differed by 1 kcal/mol from 5.3 kcal/mol (i.e., up to 6.3 kcal/mol) orient their side chains differently than that of DHFR-bound TMQ. It was interesting to note that if the side chains of either the equatorial or axial isomer of **1** were forced to overlap that of bound TMQ the energy for each isomer was 6–8 kcal/mol greater than that of the energy-minimum conformation, indicating that it was highly unlikely that **1** would adopt the same side-chain conformation as TMQ when bound to DHFR.

On the basis of these molecular modeling studies which indicated that the side-chain conformation of the tetrahydroquinazoline analogues were different from that of TMQ, we decided to explore these analogues with various substituents in the side-chain phenyl ring as in compounds **1**–**20** (Table 1) as potential inhibitors of DHFR from *P. carinii*, *T. gondii*, and rat liver and to develop a structure–activity/selectivity relationship for this series. Compound **18**, where the N10–C1′ bond is conformationally restricted within an indoline ring, and the *N*-naphthyl analogues **19** and **20** were also synthesized and evaluated for their DHFR inhibitory activity. In addition, selected analogues **1**, **11**, **12**, **15**, **18**, and **19** were evaluated *in vitro* as inhibitors of growth of various tumor cells in culture.

To our knowledge, a relatively small number of 2,4-diaminotetrahydroquinazolines have been reported as potential antifolates. This probably stems from the difficulty in the synthesis of the tetrahydroquinazoline ring system with 6-substitutions. The first reported synthesis of a classical 2,4-diaminotetrahydroquinazoline analogue of aminopterin was by DeGraw *et al.*[17] We[18] recently reported the synthesis of the tetrahydroquinazoline N10–CH$_3$ aminopterin analogue. Elslager *et al.*[19] reported the synthesis and antimalarial and antibacterial activities of a variety of nonclassical 6-substituted 2,4-diaminotetrahydroquinazoline antifolates; however, no DHFR inhibitory activities were

Scheme 1

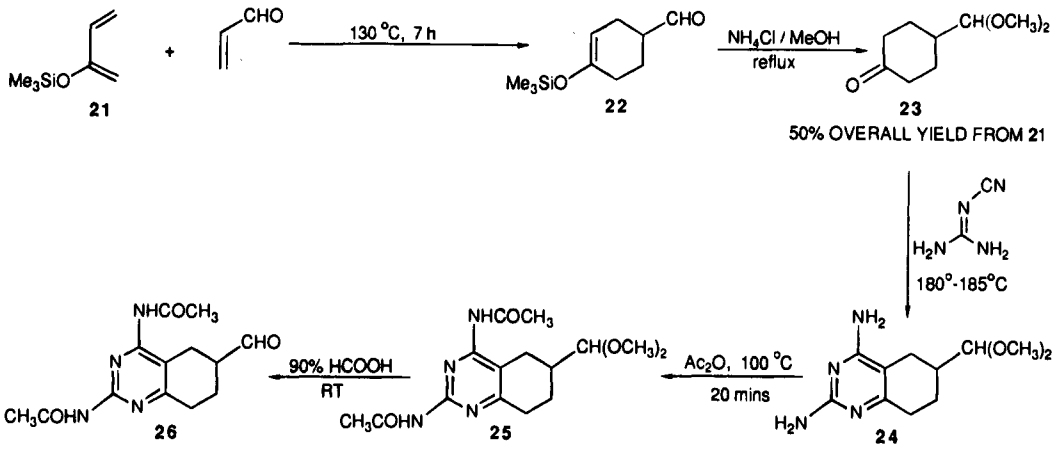
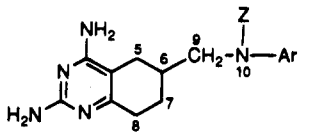
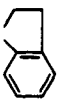


Table 1. N^{10}-Substituted 2,4-Diamino-6-(aminomethyl)-5,6,7,8-tetrahydroquinazolines



Compound	Ar	Z
1	3', 4', 5' - $(OMe)_3$ C_6H_2	H
2	3', 4', 5' - $(OMe)_3$ C_6H_2	CH_3
3	3', 4', 5' - $(OMe)_3$ C_6H_2	$CH_2C \equiv CH$
4	2', 5' - $(OMe)_2$ C_6H_3	H
5	2', 5' - $(OMe)_2$ C_6H_3	CH_3
6	2', 5' - $(OMe)_2$ C_6H_3	C_2H_5
7	2', 5' - $(OEt)_2$ C_6H_3	H
8	2', 5' - $(OEt)_2$ C_6H_3	CH_3
9	3', 4' - Cl_2 C_6H_3	H
10	3', 4' - Cl_2 C_6H_3	CH_3
11	2', 5' - Cl_2 C_6H_3	H
12	2', 6' - Cl_2 C_6H_3	H
13	4' - Cl C_6H_4	H
14	4' - Cl C_6H_4	CH_3
15	3'-Br C_6H_4	H
16	$-CH_2$-3', 4', 5'-$(OMe)_3C_6H_2$	H
17	$-CH_2$-3', 4', 5'-$(OMe)_3C_6H_2$	CH_3
18	Ar, Z = 	
19		H
20		CH_3

reported. In addition, classical 6-substituted 2-amino-4-oxo-tetrahydroquinazolines have also been explored as antifolates and were reported by Koehler *et al.*,[20] Nair *et al.*,[21] and Rosowsky *et al.*[22] These 2-amino-4-oxo analogues were targeted at folate metabolizing enzymes other than DHFR. In this paper, we describe 20 new tetrahydroquinazoline analogues and, for the first time, the inhibition of DHFRs by nonclassical 6-substituted 2,4-diaminotetrahydroquinazoline antifolates.

Chemistry

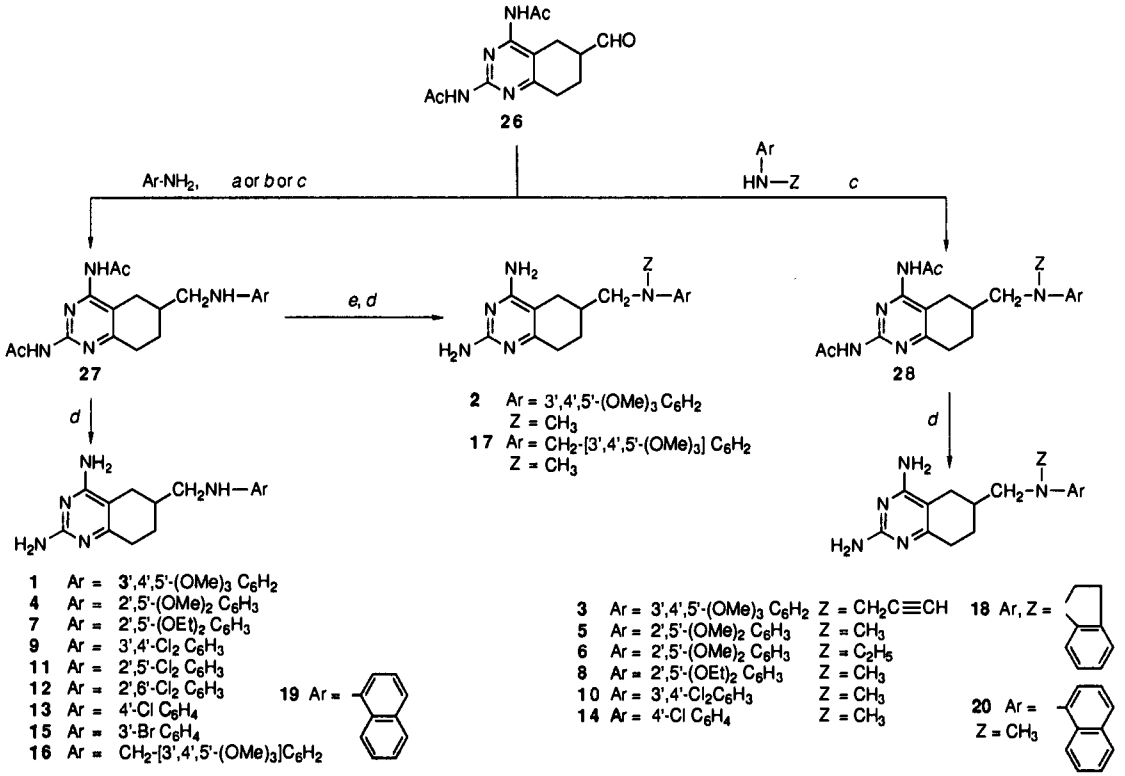
The target compounds **1**–**20** listed in Table 1 were synthesized from a common intermediate, 2,4-bis(acetamido)-5,6,7,8-tetrahydroquinazoline-6-carboxaldehyde (**26**), by reductive amination with the appropriate amine. This intermediate **26** was previously synthesized by DeGraw and co-workers,[17] from cyclohexanone-4-carboxaldehyde dimethyl acetal (**23**), which in turn was synthesized in four steps starting from 1,3-butadiene, in a 20% yield.[23]

We[18] recently reported an alternate synthesis of **23**, also in four steps, *via* a different route, starting from cyclohexane-1,4-dione monoethylene ketal, in an overall yield of 25%. This synthetic route, however, was not convenient for large-scale preparation of **23**, required for the synthesis of the desired compounds. A search of the literature revealed the synthesis of 1-(trimethylsiloxy)-cyclohexene-4-carboxaldehyde (**22**),[24] which was a suitable precursor to **23**. Diels–Alder reaction of the commercially available 2-(trimethylsiloxy)-1,3-butadiene (**21**) with acrolein was carried out as shown in Scheme 1 and afforded **22** in 64% yield. Simultaneous deprotection of the trimethylsilylenol ether and protection of the aldehyde of **22** was achieved in one step, by refluxing **22** in MeOH with catalytic amounts of NH_4Cl, to yield **23**. The synthesis of **23** was thus achieved in two steps in an overall yield of 50%, which is a significant improvement over the previous routes.[18,23] Cyclocondensation of **23** with dicyandiamide afforded 2,4-diamino-5,6,7,8-tetrahydroquinazoline-6-carboxaldehyde dimethyl acetal (**24**), which was converted to the protected aldehyde **26**, as illustrated in Scheme 1 and described earlier.[18]

Reductive amination of this key intermediate aldehyde **26** with various amines afforded the target compounds **1**–**20** (Scheme 2). The amination was initially carried out with $NaCNBH_3$/MeOH in the presence of titanium isopropoxide,[25] a mild Lewis acid catalyst. Although these reaction conditions worked well for the synthesis of compounds **1**, **4**, **9**, **13**, and **16**, they were unsuccessful for the synthesis of compounds **7**, **10**, **11**, and **18**.

We reasoned that the failure of the reaction at least in the case of **7** could be attributed to the bulk of Ti(i-PrO)$_4$ which prevented the catalysis. Compound **7** was subsequently synthesized using the less bulky Ti(OEt)$_4$ as the catalyst. Compounds **3**, **5**, **6**, **8**, **10**–**12**, **14**, **15**, and **18**–**20** were synthesized by a Borch reductive alkylation,[26] using **26**, 5 N HCl/MeOH and $NaCNBH_3$, and the appropriate amine (Scheme 2), which afforded the precursors **27** and **28**. The secondary amines required for synthesis of compounds **3**, **5**, **6**, **8**, **14**, and

Scheme 2 [a]



[a] (a) Ti(i-PrO)$_4$/NaCNBH$_3$ (for 1, **4**, **9**, **13**, **16**), (b) Ti(OEt)$_4$/NaCNBH$_3$ (for **7**), (c) 5 N HCl/MeOH/NaCNBH$_3$ (for **3**, **5**, **6**, **8**, **10**, 11, **12**, **14**, **15**, **18**, **19**, **20**), (d) Na/EtOH, (e) 37% HCHO, NaCNBH$_3$, glacial AcOH.

20 were obtained by alkylation of the precursor, commercially available amines, *via* the procedure of McNamara *et al.*[27] The methylated analogues **2** and **17** were synthesized by reductive methylation of the bis(acetamido) intermediate **27**, using formaldehyde and NaCNBH$_3$,[29,30] followed by deprotection. Methylation of the unprotected precursors afforded inseparable mixtures. Reductive aminations of the bis(acetamido) aldehyde **26** in methanol, caused considerable monodeacetylation, and the intermediate bis(acetamido) products **27** and **28** were isolated as a mixture along with the monodeacetylated product. These were not separated but directly deprotected to afford the final compounds. However, in instances where the bisacetylated intermediates **27** were of interest, to prepare the N^{10}-methylated analogues **2** and **17**, the reductive aminations were carried out in CH$_3$CN, which decreased the deacetylation. Deprotection of the bisacetylated products was initially attempted with liquid NH$_3$[28] which afforded the monodeacetylated compound as evidenced by ^{1}H NMR. Longer reaction times (up to 5 days) were also unsuccessful. However, complete deprotection was readily achieved with Na/EtOH at reflux within 10–30 min.

Two previous studies,[21,22] in which the ^{1}H NMR spectra of classical 2-amino-4-oxo-tetrahydroquinazolines were reported, merely mentioned multiplets from δ 1.20–2.90 without any further details of the chemical shift positions of the alicyclic protons of the tetrahydroquinazolines. This probably stems from the overlap of these protons with those of the glutamate. The ^{1}H NMR spectra of the nonclassical antifolates **1**–**20** contained a striking similarity in the region of δ 1.24–2.49, where the 5-, 6-, 7-, and 8-protons of the tetrahydroquinazoline moiety occur as a set of three multiplets. The alicyclic B ring has limited conformational flexibility, and the 6-carbon in the 6-substituted tetrahydroquinazolines is chiral; thus, the 5- and 7-protons are diastereotopic and are expected to be nonequivalent. The ^{1}H NMR spectra of compounds **1**–**20** contain a multiplet at δ 1.24–1.49, integrating for one proton, a second multiplet at δ 1.76–2.06, integrating for three protons, and a third multiplet at δ 2.29–2.49, also integrating for three protons. Since the H7 protons are expected to be the most upfield, the multiplet at δ 1.24–1.49 was assigned to one of the diastereotopic H7 protons. The other H7, expected to be at least 0.5 ppm downfield, occurs as a part of the three-proton multiplet at δ 1.76–2.06. As an example for compound **1**, one of the diastereotopic H7 protons occurs at δ 1.42 as a multiplet. In the 2D COSY spectrum of compound **1**, the 9CH$_2$ protons of the 6-side chain are directly coupled to the adjacent H6 methine proton. The 9CH$_2$ protons of **1** occur as a multiplet at δ 2.99 and show a strong cross peak in the 2D COSY spectrum with the multiplet at δ 1.80–1.90 (which integrates for three protons), indicating that the H6 proton was also a part of the multiplet at δ 1.80–1.90 (along with one H7 proton). The remaining (third) proton of this multiplet was assigned to one of the diastereotopic 5CH$_2$ protons. The other H5 proton was part of the multiplet at δ 2.40–2.49. The remaining two protons of this multiplet at δ 2.40–2.49 were assigned to the 8CH$_2$ protons which are not diastereotopic and occur together as a broad multiplet. These proton assignments were confirmed by the cross peaks in the COSY spectrum of compound **1**.

Biological Activities and Discussions

Compounds **1**–**20** as their 6*R*–6*S* racemic mixtures were evaluated as inhibitors of pcDHFR, tgDHFR, and

Table 2. Inhibitory Concentrations against Purified DHFR from *P. carinii*, *T. gondii*, and Rat Liver and Selectivity Ratios[32,33]

	IC_{50} (nM)			selectivity ratio	
compound	*P. carinii*	*T. gondii*	rat liver	rl/pc	rl/tg
1	4600	54	290	0.06	5.40
2	95	7	38	0.40	5.43
3	119	12	74	0.62	6.20
4	1670	181	560	0.34	3.10
5	300	15	260	0.90	17.33
6	114	17	71	0.62	4.20
7	1570	140	1470	0.94	10.50
8	319	17	116	0.40	6.82
9	6800	110	150	0.02	1.40
10	246	21	34	0.14	1.62
11	410	97	240	0.59	2.50
12	502	9.9	109	0.22	11.01
13	940	78	128	0.14	1.64
14	171	22	67	0.39	3.05
15	330	30	227	0.70	7.60
16	18500	ND	12700	0.69	ND
17	3100	330	1630	0.53	4.94
18	210	27	160	0.76	5.93
19	517	36	139	0.30	3.90
20	100	23	47	0.50	2.04
TMQ	42	10	3	0.07	0.30
TMP	12000	2700	133000	11.10	49.26

rat liver (rl) DHFR,[32,33] and the IC_{50} (in nM) along with the selectivities against pcDHFR and tgDHFR each versus rlDHFR are reported in Table 2. Compound **1**, which contains the 3,4,5-triOCH_3Ph side chain similar to TMQ, was a poor inhibitor of pcDHFR; however, its potency was better against rlDHFR and more so against tgDHFR. Thus, compound **1** was 5 times less potent than TMQ but 18 times more selective against tgDHFR. N^{10}-Methylation (compound **2**) and N^{10}-propargylation (compound **3**) significantly increased activity against all three DHFRs with similar selectivity, indicating that N^{10}-substitution was conducive to potency. Similar effects for 3,4,5-triOCH_3Ph have been reported by us[8] in the pyrido[2,3-*d*]pyrimidine series. The 2,5-diOCH_3-Ph side chain in compound **4** provided an increase in activity against pcDHFR but was detrimental to tgDHFR and rlDHFR compared to **1**. N^{10}-Methylation of **4** to afford **5** increased potency against all three DHFRs. This increased activity was particularly pronounced against tgDHFR which increased more than 10-fold compared to **4**, allowing for a significant increase in the selectivity ratio to 17.33. Compound **5** had about the same potency against tgDHFR as TMQ but was 58-fold more selective. The N^{10}-ethyl analogue **6** had a similar increase in potency against all three DHFRs but did not show the high selectivity against tgDHFR as did **5**. Thus, in the 2,5-diOCH_3Ph as in the 3,4,5-triOCH_3Ph, N^{10}-methylation was conducive to both potency and selectivity. The trend for increase in activity on N^{10}-methylation against all three DHFRs was also seen in the 2,5-diOC_2H_5Ph analogues **7** and **8**.

The electron-withdrawing Cl_2Ph-disubstituted analogues **9**–**12** had potencies and selectivities similar to those of the $-OCH_3$ and $-OC_2H_5$ electron-donating moieties with some exceptions. The 2,5-diCl_2Ph analogue **11** was somewhat more potent than the corresponding 2,5-diOCH_3Ph. The 2,6-diCl_2Ph analogue **12** was significantly more active and selective against tgDHFR than the other analogues, with the exception of **2** (potency) and **5** (selectivity). The *o*-dichloro substituents are clearly important for tgDHFR inhibition and selectivity and could be attributed to the electron-withdrawing effect and/or the conformational restriction of the N10–C1′ bond.

Among the monohalo analogues **13**–**15**, compound **15**, the 3-BrPh analogue, had good potency and selectivity against tgDHFR. N^{10}-Methylation of the 4-Cl analogue **13**, as before, increased potency against all three DHFRs with an increase in selectivity against both pcDHFR and tgDHFR.

In an attempt to study the effect of increasing the bridge length between the 2,4-diaminotetrahydroquinazoline and the substituted phenyl ring, we synthesized a three-atom-bridged analogue **16** and its N10–CH_3 analogue **17**. Increasing the bridge length was significantly detrimental to activity against pcDHFR and rlDHFR compared to the two-atom-bridged analogue **1**. N^{10}-Methylation increased inhibitory activity compared to **16**, but **17** was more than an order of magnitude less active than the corresponding two-atom-bridged analogue **2**. This decrease in activity of **16** and **17** could be attributed to the increase in the bridge length and/or the aliphatic, basic amino moiety in the three-atom-bridged analogues which would be expected to be protonated under the enzyme assay conditions, and the resulting ionization could be incompatible with high DHFR binding.

Conformational restriction of the N10–C1′ bond was achieved in the indoline analogue **18** which provided high inhibitory activity against tgDHFR along with reasonable selectivity. The N^{10}-naphthyl analogues **19** and **20** were potent inhibitors of tgDHFR, and N^{10}-methylation, as observed earlier, increased activity against all three DHFRs, with **20** being one of the two most potent pcDHFR inhibitors in the series.

On the basis of this study, the 6-substituted 2,4-diaminotetrahydroquinazoline system was found to be conducive to tgDHFR inhibition and selectivity. However, these analogues were not selective for pcDHFR, but with the exception of **16**, all the analogues were more potent than TMP against pcDHFR. In addition, N^{10}-methylation or alkylation consistently afforded an increase in potency irrespective of the nature of the side chain. These latter results are different from that observed in the 2,4-diamino-5-methyl-pyrido[2,3-*d*]pyrimidine series[8,10] where the triOCH_3Ph system and the diOCH_3Ph system gave different results on N^{10}-methylation. Thus, extrapolations from one heterocyclic system such as the 5-methyl-pyrido[2,3-*d*]pyrimidines to a different system such as tetrahydroquinazolines are not valid.

This further underscores the previous observations[8–10] that each heterocyclic ring system along with its side chain needs to be synthesized and biologically evaluated separately to develop a structure–activity/selectivity relationship against pcDHFR and tgDHFR.

The most promising analogue **5** with its high selectivity and potency was further evaluated as an inhibitor of the growth of *T. gondii* cells in culture.[8] Compound **5** had an $IC_{50} = 5.4 \times 10^{-8}$ M, indicating excellent *T. gondii* cell penetration. Compound **5** is currently a candidate for animal studies in acute infection mice models of *T. gondii*.

Compounds **1**, **11**, **12**, **15**, **18**, and **19** were selected for evaluation by the National Cancer Institute in their preclinical *in vitro* tumor screening program.[34] As

shown in Table 3 given as supporting information, compound **18**, the indoline-containing side-chain analogue, was active at $GI_{50} = 10^{-8}$ M against the growth of eight of the tumor cell lines tested. This activity was better than the inhibition of isolated rlDHFR and could indicate more than one mechanism of action. Compounds **12** and **19** were active against non-small cell lung cancer NCI-H460 at $GI_{50} = 5 \times 10^{-8}$ M and the leukemia K-562 at $GI_{50} = 4 \times 10^{-8}$ M, respectively.

Experimental Section

All evaporations were carried out *in vacuo* with a rotary evaporator or by short-path distillation. Analytical samples were dried *in vacuo* (0.2 mmHg) in an Abderhalden drying apparatus over P_2O_5 and refluxing ethanol or toluene. Thin-layer chromatography (TLC) was performed on Eastman Kodak silica gel chromatogram plates with a fluorescent indicator. Spots were visualized by UV light (254 and 350 nm). Proportions of solvents used are by volume. All analytical samples were homogeneous on TLC in at least three different solvent systems. Melting points were determined by the capillary method on a Fisher-Johns melting point apparatus and are uncorrected. Purifications by gravity column and flash chromatography were carried out using Merck silica gel 60 (230–400 mesh). Infrared (IR) spectra were determined neat or in pressed KBr disks on a Perkin-Elmer 1430 ratio recording infrared spectrophotometer and are reported in reciprocal centimeters. The ^{1}H NMR spectra were recorded on Varian EM-360 (60 MHz) or Bruker WH-300 (300 MHz) spectrometers. The chemical shift (δ) values are expressed in ppm (parts per million) relative to tetramethylsilane as the internal standard; s = singlet, d = doublet, t = triplet, m = multiplet, br s = broad singlet, br d = broad doublet, dd = doublet of doublet, exch = protons exchangeable by addition of D_2O. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, GA, or Galbraith Laboratories, Knoxville, TN. Elemental compositions are within ±0.4% of the calculated values. Fractional moles of water and/or organic solvents frequently found in some analytical samples of antifolates could not be prevented, despite 24–48 h of drying *in vacuo*, and were confirmed by their presence in the ^{1}H NMR spectrum. 2-(Trimethylsiloxy)-1,3-butadiene was purchased from Huls America. All other solvents and chemicals were purchased from Aldrich Chemical Co. and Fisher Scientific and were used as received. Ether refers to diethyl ether.

(±)-1-(Trimethylsiloxy)cyclohexene-4-carboxaldehyde (22). A mixture of 2-(trimethylsiloxy)-1,3-butadiene (20 g, 24.7 mL, 141 mmol), acrolein (4.07 g, 4.82 mL, 72.7 mmol), and hydroquinone (0.15 g) was heated in a stainless steel bomb at 140 °C (bath temperature) for 7 h. The resulting green liquid obtained on cooling was purified by short-path vacuum distillation to yield 17.8 g of a colorless liquid (64%); bp 57 °C/0.01 mmHg (lit.[24] bp 48–49 °C/0.02 mmHg); TLC 20% ether in petroleum ether/silica gel, R_f 0.48; IR (neat) 2703 (aldehyde CH str), 1728 (C=O), 1670 (C=C), 1250, 1185, 880, 840 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 0.16 (s, 9 H, $Si(CH_3)_3$), 1.90–2.40 (br m, 7 H, CH_2, CH), 4.85 (br s, 1 H, vinyl CH), 9.69 (s, 1 H, CHO).

(±)-Cyclohexanone-4-carboxaldehyde Dimethyl Acetal (23). To a solution of **22** (4.89 g, 25 mmol) in MeOH (6 mL) was added NH_4Cl (0.07 g). After the vigorous exothermic reaction subsided, the solution was refluxed for 2.5 h. The cooled reaction mixture was evaporated to dryness, and ether (100 mL) was added and the suspension filtered to remove NH_4Cl. The filtrate was washed successively with 5% $NaHCO_3$, H_2O, and saturated NaCl and dried ($MgSO_4$). Evaporation of the solvent afforded 3.65 g (85%) of a light green liquid which was used without further purification: TLC EtOAc/petroleum ether (1:1)/silica gel, R_f 0.48; bp 98–100 °C/3 mmHg (lit.[23] bp 92–96 °C/5 mmHg); IR (neat) 1715 (C=O), 1130, 1105, 1075, 1050 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.60–2.55 (m, 9 H, $(CH_2)_4$, CH), 3.38 (s, 6 H, OCH_3), 4.12 (d, 1 H, $CH(OCH_3)_2$).

Reductive Amination of 26. (6*R*,6*S*)-2,4-Diamino-6-[(3′,4′,5′-trimethoxyanilino)methyl]-5,6,7,8-tetrahydroquinazoline (1). A mixture of **26**[18] (0.55 g, 2 mmol), trimethoxyaniline (0.37 g, 2 mmol), and titanium isopropoxide (0.74 mL, 2.5 mmol) was stirred at room temperature under nitrogen and a drying tube for 3 h. The mixture was then diluted with absolute MeOH (5 mL), and $NaCNBH_3$ (0.12 g, 2 mmol) was added. This mixture was stirred at room temperature for 24 h. Water (5 mL) and MeOH (10 mL) were added to quench the reaction, and the resulting inorganic precipitate was filtered and washed thoroughly with MeOH. The combined filtrate was evaporated to dryness to yield the crude bis(acetamido) product **27**. This was directly used for deprotection of the amino groups. To a refluxing solution of crude **27** in absolute EtOH (90 mL) was added a solution of Na (0.24 g) in 25 mL of absolute EtOH. Within 20 min the deprotection was complete (TLC). The solution was evaporated to dryness, the residue dissolved in water, and the pH adjusted to 8 with AcOH. The aqueous solution was extracted with $CHCl_3$, and the $CHCl_3$ extract was dried over $MgSO_4$ and evaporated to dryness, to afford crude 1, which was purified by flash chromatography, using $CHCl_3$–MeOH (2:1) as eluent. The overall yield of **1** from these two steps was 0.16 g (22%). An analytical sample was recrystallized from CH_3CN: mp 165–170 °C; TLC (a) $CHCl_3$/MeOH (2:1)/silica gel, R_f 0.51, (b) EtOAc/$CHCl_3$/MeOH (2:2:1)/silica gel, R_f 0.20, (c) EtOAc/MeOH/NH_4OH (2:1:2 drops)/silica gel, R_f 0.61; IR (KBr) 3320, 3160 (NH), 1640, 1600, 1500, 1440, 1225, 1120 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.42 (m, 1 H, quinazoline H), 1.94 (m, 3 H, quinazoline CH_2), 2.46 (m, 3 H, quinazoline CH_2), 2.99 (br d, 2 H, 9-CH_2), 3.53 (s, 3 H, 4′-OCH_3), 3.69 (s, 6 H, 3′,5′-OCH_3), 5.34 (broad hump, 1 H, NH), 5.88 (s, 2 H, 2′,6′-CH), 5.92 (s, 2 H, NH_2, exch), 6.35 (s, 2 H, NH_2, exch). Anal. ($C_{18}H_{25}N_5O_3 \cdot 1.1H_2O$) C, H, N.

(6*R*,6*S*)-2,4-Diamino-6-[(3′,4′-dichloroanilino)methyl]-5,6,7,8-tetrahydroquinazoline (9). This was prepared by a procedure similar to that for 1, using **26** (0.3 g, 1.1 mmol) and 3,4-dichloroaniline (0.18 g, 1.1 mmol). The overall yield from **26** was 0.85 g (23%). An analytical sample was recrystallized from CH_3CN: mp 185–188 °C; TLC (a) $CHCl_3$/MeOH(2:1)/silica gel, R_f 0.38, (b) $CHCl_3$/MeOH/NH_4OH (2:1:2 drops)/silica gel, R_f 0.57; IR (KBr) 3300, 3160 (N–H), 1590, 1560, 1430, 1130, 780 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.38 (m, 1 H, quinazoline H), 1.93 (m, 3 H, quinazoline CH_2), 2.41 (m, 3 H, quinazoline CH_2), 2.99 (m, 2 H, 9-CH_2), 5.56 (s, 2 H, NH_2, exch), 5.99 (s, 2 H, NH_2, exch), 6.18 (t, J = 5.13 Hz, 1 H, NH), 6.57 (dd, J = 2.59 and 8.82 Hz, 1 H, 6′-H), 6.74 (d, J = 2.59 Hz, 1 H, 2′-H), 7.24 (d, J = 8.82 Hz, 1 H, 5′-H). Anal. ($C_{15}H_{17}N_5Cl_2 \cdot 0.5CH_3COOH \cdot 0.8CH_3CN$) C, H, N, Cl.

General Procedure for the Synthesis of 4, 7, 13, and 16. A mixture of bis(acetamido) aldehyde **26** (2 mmol), amine (2 mmol), and titanium isopropoxide[31] (2.5 mmol) in EtOH (10 mL) was stirred at room temperature under nitrogen for 3 h. $NaCNBH_3$ (2 mmol) was then added, and the mixture was allowed to stir for 24 h. Water (5 mL) was added to quench the reaction. The inorganic precipitate was washed with EtOH, and the combined EtOH filtrate was evaporated to dryness to yield the appropriate crude bis(acetamido) aminated product **27** which was then directly deprotected using Na/EtOH by the procedure described for 1 and **9**.

(6*R*,6*S*)-2,4-Diamino-6-[(2′,5′-dimethoxyanilino)methyl]-5,6,7,8-tetrahydroquinazoline (4). The compound was synthesized from **26** (0.55 g, 2 mmol) and 2.5-dimethoxyaniline (0.31 g, 2 mmol). The crude product was purified by column chromatography using $CHCl_3$/MeOH (3:1) as eluent which afforded 0.12 g (18%) of **4** from **26**. An analytical sample was recrystallized from MeOH: mp 135–137 °C; TLC (a) EtOAc/$CHCl_3$/MeOH (1:1:1)/silica gel, R_f 0.36, (b) $CHCl_3$/MeOH (1:1)/silica gel, R_f 0.34; IR (KBr) 3300, 3120, 1650, 1625, 1610, 1580, 1520, 1440, 1210 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.38 (m, 1 H, quinazoline H), 1.91 (m, 3 H, quinazoline CH_2), 2.49 (m, 3 H, quinazoline CH_2), 3.05 (br s, 2 H, 9-CH_2), 3.64 (s, 3 H, OCH_3), 3.72 (s, 3 H, OCH_3), 4.85 (br s, 1 H, NH, exch), 5.94 (s, 2 H, NH_2, exch), 6.06 (m, 1 H, ArH), 6.11 (br s, 1 H, ArH), 6.43 (s, 2 H, NH_2, exch), 6.68 (d, 1 H, ArH). Anal. ($C_{17}H_{23}N_5O_2 \cdot 0.6HCl \cdot 0.6CH_3OH$) C, H, N, Cl.

(6*R*,6*S*)-2,4-Diamino-6-[(2′,5′-diethoxyanilino)methyl]-5,6,7,8-tetrahydroquinazoline (7). The reductive amination

of **26** (0.55 g, 2 mmol) with 2,5-diethoxyaniline (0.36 g, 2 mmol) was carried out with $Ti(OEt)_4$ (0.52 mL, 2.5 mmol) as Lewis acid. After deprotection, the compound was purified by column chromatography using $CHCl_3$/MeOH (3:1) as eluent. The resulting solid was dissolved in minimum MeOH and reprecipitated with ether to yield an off-white solid (0.13 g, 18%); mp 151–152 °C; TLC (a) EtOAc/$CHCl_3$/MeOH (1:1:1)/silica gel, R_f 0.5, (b) $CHCl_3$/MeOH/NH_4OH (3:1:2 drops)/silica gel, R_f 0.56; IR (KBr) 3280, 3120, 1640, 1605, 1510, 1430, 1200, 1040 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.28 (m, 7 H, quinazoline H, OCH_2CH_3), 1.91 (m, 3 H, quinazoline CH_2), 2.41 (m, 3 H, quinazoline CH_2), 3.04 (br d, 2 H, 9-CH_2), 3.89 (m, 4 H, OCH_2-CH_3), 4.84 (t, 1 H, NH, exch), 5.75 (s, 2 H, NH_2, exch), 6.02 (br d, J = 8.40 Hz, 1 H, 4'-H), 6.08 (s, 1 H, 6'-H), 6.24 (s, 2 H, NH_2, exch), 6.65 (d, J = 8.40 Hz, 1 H, 3'-H). Anal. ($C_{19}H_{27}N_5O_2 \cdot 0.7H_2O$) C, H, N.

(6*R*,6*S*)-2,4-Diamino-6-[(4'-chloroanilino)methyl]-5,6,7,8-tetrahydroquinazoline (13). Compound **26** (0.55 g, 2 mmol) was condensed with *p*-chloroaniline (0.25 g, 2 mmol) by the procedure described above. Purification of the crude product was carried out by column chromatography using $CHCl_3$/MeOH (3:1) as eluent and afforded 0.112 g (18%) of **13** from **26**: mp 202–204 °C; TLC (a) EtOAc/$CHCl_3$/MeOH (1:1:1)/silica gel, R_f 0.27, (b) $CHCl_3$/MeOH/NH_4OH (3:1:2 drops)/silica gel, R_f 0.39; IR (KBr) 3460, 3280, 3120, 1640, 1620, 1560, 1490, 1425, 805 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.37 (m, 1 H, quinazoline H), 1.90 (m, 3 H, quinazoline CH_2), 2.41 (m, 3 H, quinazoline CH_2), 2.97 (br d, 2 H, 9-CH_2), 5.61 (s, 2 H, NH_2, exch), 5.87 (s, 1 H, NH, exch), 6.07 (s, 2 H, NH_2, exch), 6.58 (ABq, 2 H, 2',6'-H), 7.07 (ABq, 2 H, 3',5'-H). Anal. ($C_{15}H_{18}N_5Cl$) C, H, N, Cl.

(6*R*,6*S*)-2,4-Diamino-6-[[(3',4',5'-trimethoxybenzyl)amino]methyl]-5,6,7,8-tetrahydroquinazoline (16). The compound was prepared by condensing **26** (0.5 g, 1.81 mmol) with (3,4,5-trimethoxybenzyl)amine (0.34 g, 1.81 mmol) by the procedure described above. The crude product was purified by column chromatography using $CHCl_3$/MeOH (1:1) as eluent, with a few drops of NH_4OH to afford **16** (0.17 g) as an off-white solid. The overall yield from **26** was 25%: mp 104–106 °C; TLC $CHCl_3$/MeOH/NH_4OH (1:1:2 drops)/silica gel, R_f 0.25; IR (KBr) 3440, 3320, 3140, 1630, 1580, 1500, 1120 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.32 (m, 1 H, quinazoline H), 1.83–1.93 (m, 3 H, quinazoline CH_2), 2.41 (m, 3 H, quinazoline CH_2), 2.55 (d, 2 H, 9-CH_2), 3.63 (s, 3 H, 4'-OCH_3), 3.71 (s, 2 H, $-CH_2Ar$), 3.76 (s, 6 H, 3',5'-OCH_3), 5.76 (s, 2 H, NH_2, exch), 6.19 (s, 2 H, NH_2, exch), 6.68 (s, 2 H, aromatic H). Anal. ($C_{19}H_{27}N_5O_3 \cdot 0.5H_2O$) C, H, N.

General Procedure for the Synthesis of Compounds 3, 5, 6, 8, 10–12, 14, 15, and 18–20. To a solution of the amine (12 mmol) in anhydrous MeOH (10 mL) at room temperature was added 1 g of molecular sieves (4 Å) and 5 N HCl/MeOH (4 mmol). To this was added **26** (2 mmol) and $NaCNBH_3$ (2 mmol). The solution was stirred under nitrogen for 72 h. The suspension was filtered to remove the molecular sieves and the residue washed with MeOH. The combined filtrates were evaporated to dryness to afford the crude bis(acetamido) product **28**, which was deprotected as before with Na/EtOH.

(6*R*,6*S*)-2,4-Diamino-6-[[(3',4',5'-trimethoxyphenyl)propargylamino]methyl]-5,6,7,8-tetrahydroquinazoline (3). This compound was synthesized by the procedure described above, using **26** (0.55 g, 2 mmol) and *N*-propargyl-3,4,5-trimethoxyaniline (2.56 g, 12 mmol). Purification of the crude product was carried out by column chromatography using $CHCl_3$/EtOAc/MeOH (2:2:1) as eluent to afford 0.08 g (12%) of **3** from **26**; mp 202–205 °C; TLC $CHCl_3$/EtOAc/MeOH (2:2:1)/silica gel, R_f 0.50; IR (KBr) 3450, 3330, 3160, 2930, 1570, 1500, 1440, 1240, 1120, 980, 940, 770 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.40 (m, 1 H, quinazoline H), 1.85–2.06 (m, 3 H, quinazoline CH_2), 2.32–2.39 (m, 3 H, quinazoline CH_2), 3.14 (s, 1 H, $NCH_2C{\equiv}CH$), 3.23 (d, 2 H, 9-CH_2), 3.54 (s, 3 H, 4'-OCH_3), 3.71 (s, 6 H, 3',5'-OCH_3), 4.10 (s, 2 H, $NCH_2C{\equiv}CH$), 5.53 (s, 2 H, NH_2, exch), 6.02 (s, 2 H, NH_2 exch), 6.04 (s, 2 H, 2',6'-H). Anal. ($C_{21}H_{27}N_5O_3 \cdot 0.5H_2O$) C, H, N.

(6*R*,6*S*)-2,4-Diamino-6-[[(2',5'-dimethoxyphenyl)methylamino]methyl]-5,6,7,8-tetrahydroquinazoline (5). This compound was synthesized by the procedure described above, using **26** (0.55 g, 2 mmol) and *N*-methyl-2,5-dimethoxyaniline (2.00 g, 12 mmol). Purification of the crude product was carried out by column chromatography using $CHCl_3$/MeOH (5:1) as eluent to afford 0.06 g (9%) of **5** from **26**; mp 150 °C; TLC (a) $CHCl_3$/MeOH/NH_4OH (5:1:1 drop)/silica gel, R_f 0.54, (b) $CHCl_3$/EtOAc/MeOH/NH_4OH (2:2:1:1 drop)/silica gel, R_f 0.40; IR (KBr) 3460, 3300, 3150, 2930, 1570, 1500, 1440, 1220, 1090, 960, 760 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.28 (m, 1 H, quinazoline H), 1.92 (m, 3 H, quinazoline CH_2), 2.30–2.39 (m, 3 H, quinazoline CH_2), 2.71 (s, 3 H, NCH_3), 2.91–3.09 (m, 2 H, 9-CH_2), 3.67 (s, 3 H, OCH_3), 3.68 (s, 3 H, OCH_3), 5.66 (s, 2 H, NH_2, exch), 6.13 (s, 2 H, NH_2, exch), 6.41 (dd, J = 2.85 and 8.63 Hz, 1 H, 4'-H), 6.46 (d, J = 2.85 Hz, 1 H, 6'-H), 6.79 (d, J = 8.63 Hz, 1 H, 3'-H). Anal. ($C_{18}H_{25}N_5O_2 \cdot 0.5H_2O \cdot 0.1CH_3COOH$) C, H, N.

(6*R*,6*S*)-2,4-Diamino-6-[[(2',5'-dimethoxyphenyl)ethylamino]methyl]-5,6,7,8-tetrahydroquinazoline (6). This compound was synthesized by the procedure described above, using **26** (0.55 g, 2 mmol) and *N*-ethyl-2,5-dimethoxyaniline (2.17 g, 12 mmol). Purification of the crude product was carried out by column chromatography using $CHCl_3$/EtOAc/MeOH (2:2:1) as eluent. The product was triturated with ether to afford 0.07 g (11%) of **6** from **26**: mp 135–138 °C; TLC (a) $CHCl_3$/MeOH/NH_4OH (5:1:1 drop)/silica gel, R_f 0.56, (b) $CHCl_3$/EtOAc/MeOH/NH_4OH (2:2:1:1 drop)/silica gel, R_f 0.41; IR (KBr) 3400, 3330, 3150, 2920, 1580, 1440, 1220, 1050, 780 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 0.93 (t, 3 H, $N-CH_2CH_3$), 1.24 (m, 1 H, quinazoline H), 1.84 (m, 3 H, quinazoline CH_2), 2.30 (m, 3 H, quinazoline CH_2), 2.96–3.07 (m, collapses to br d on D_2O addition, 2 H, 9-CH_2), 3.09–3.17 (m, collapses to q on D_2O addition, 2 H, NCH_2CH_3), 3.65 (s, 3 H, OCH_3), 3.69 (s, 3 H, OCH_3), 5.61 (s, 2 H, NH_2, exch), 6.05 (s, 2 H, NH_2, exch), 6.43 (dd, J = 2.70 and 8.68 Hz, 1 H, 4'-H), 6.48 (d, J = 2.70 Hz, 1 H, 6'-H), 6.80 (d, J = 8.68 Hz, 1 H, 3'-H). Anal. ($C_{19}H_{27}N_5O_2 \cdot 2H_2O \cdot 0.5CH_3CH_2OH$) C, H, N.

(6*R*,6*S*)-2,4-Diamino-6-[[(2',5'-diethoxyphenyl)methylamino]methyl]-5,6,7,8-tetrahydroquinazoline (8). This compound was synthesized by the procedure described above, using **26** (0.55 g, 2 mmol) and *N*-methyl-2,5-diethoxyaniline (2.58 g, 12 mmol). Purification of the crude product was performed by column chromatography using $CHCl_3$/MeOH (4:1) as eluent to afford 0.025 g (4%) of **8** from **26**; mp 160–162 °C; TLC $CHCl_3$/MeOH/NH_4OH (4:1:2 drops)/silica gel, R_f (0.58; IR (KBr) 3340, 3170, 2930, 1650, 1500, 1450, 1380, 1190, 1020, 750 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.28 (m, 7 H, quinazoline H, OCH_2CH_3), 1.87 (m, 3 H, quinazoline CH_2), 2.35 (s, 3 H, quinazoline CH_2), 2.75 (s, 3 H, NCH_3), 2.98–3.11 (m, 2 H, 9-CH_2), 3.92 (m, 4-H, OCH_2CH_3), 5.73 (s, 2 H, NH_2, exch), 6.20 (s, 2 H, NH_2, exch), 6.37 (dd, J = 2.81 and 8.69 Hz, 1 H, 4'-H), 6.44 (d, J = 2.81 Hz, 1 H, 6'-H), 6.75 (d, J = 8.69 Hz, 1 H, 3'-H). Anal. ($C_{20}H_{29}N_5O_2 \cdot 0.5H_2O \cdot 0.1CH_3COOH$) C, H, N.

(6*R*,6*S*)-2,4-Diamino-6-[[(3',4'-dichlorophenyl)methylamino]methyl]-5,6,7,8-tetrahydroquinazoline (10). This compound was obtained by the procedure described above, using **26** (1 g, 3.6 mmol) and *N*-methyl-3,4-dichloroaniline (3.83 g, 21.70 mmol). The product was purified by column chromatography using CH_2Cl_2/MeOH (5:1) as eluent to afford 0.11 g of **10** as an off-white solid, which was washed with ether and dried, to obtain an analytically pure sample. The overall yield from **26** (10%); mp 212–214 °C; TLC CH_2Cl_2/MeOH (5:1)/silica gel, R_f 0.42; IR (KBr) 3420, 3300, 3160, 1630, 1580, 1490, 1430, 820, 780 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.39 (m, 1 H, quinazoline H), 1.76–2.05 (m, 3 H, quinazoline CH_2), 2.30–2.49 (m, 3 H, quinazoline CH_2), 2.96 (s, 3 H, $N-CH_3$), 3.29 (m, 2 H, 9-CH_2), 5.66 (s, 2 H, NH_2, exch), 6.12 (s, 2 H, NH_2, exch), 6.66 (dd, J = 2.62 and 8.96 Hz, 1 H, 6'-H), 6.79 (d, J = 2.62 Hz, 1 H, 2'-H), 7.28 (d, J = 8.96 Hz, 1 H, 5'-H). Anal. ($C_{16}H_{19}N_5Cl_2 \cdot 0.15HCl \cdot 0.1C_2H_5OC_2H_5$) C, H, N, Cl.

(6*R*,6*S*)-2,4-Diamino-6-[(2',5'-dichloroanilino)methyl]-5,6,7,8-tetrahydroquinazoline (11). This compound was synthesized by the procedure described above, using **26** (0.55 g, 2 mmol) and 2,5-dichloroaniline (1.94 g, 12 mmol). Purification of the crude product was performed by column chromatography using $CHCl_3$/MeOH (3:1) as eluent to afford 0.11 g (17%) of 11 from **26**: mp 211–213 °C; TLC $CHCl_3$/MeOH (3:

1)/silica gel, R_f 0.32; IR (KBr) 3420, 3320, 3140, 1650, 1570, 1490, 1420, 1080, 1035, 810, 780 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.32 (m, 1 H, quinazoline H), 1.90 (m, 3 H, quinazoline CH_2), 2.41 (m, 3 H, quinazoline CH_2), 3.13 (s, 2 H, 9-CH_2), 5.63 (s, 1 H, NH, exch), 5.69 (s, 2 H, NH_2, exch), 6.16 (s, 2 H, NH_2, exch), 6.57 (dd, J = 1.74 and 8.34 Hz, 1 H, 4'-H), 6.70 (d, J = 1.74 Hz, 1 H, 6'-H), 7.24 (d, J = 8.34 Hz, 1 H, 3'-H). Anal. ($C_{15}H_{17}N_5Cl_2$·0.5CH_3CH_2OH) C, H, N, Cl.

(6*R*,6*S*)-2,4-Diamino-6-[(2',6'-dichloroanilino)methyl]-5,6,7,8-tetrahydroquinazoline (12). This compound was synthesized by the procedure described above, using **26** (0.55 g, 2 mmol) and 2,6-dichloroaniline (1.94 g, 12 mmol). Purification of the crude product was done by column chromatography using $CHCl_3$/MeOH (3:1) as eluent to afford 0.03 g (4.5%) of **12** from **26**: mp 175 °C; TLC $CHCl_3$/MeOH/NH_4OH (3:1:2 drops)/silica gel, R_f 0.45; IR (KBr) 3390, 3180, 2930, 1620, 1570, 1440, 1240, 1080, 750 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.37 (m, 1 H, quinazoline H), 1.93 (m, 3 H, quinazoline CH_2), 2.41 (m, 3 H, quinazoline CH_2), 3.15–3.42 (m, 2 H, 9-CH_2), 4.76 (t, 1 H, NH, exch), 5.97 (s, 2 H, NH_2, exch), 6.46 (s, 2 H, NH_2, exch), 6.85 (t, J = 8.02 Hz, 1 H, 4'-H), 7.33 (d, J = 8.02 Hz, 2 H, 3', 5'-H). Anal. ($C_{15}H_{17}N_5Cl_2$·0.5H_2O) C, H, N, Cl.

(6*R*,6*S*)-2,4-Diamino-6-[[(4'-chlorophenyl)methylamino]methyl]-5,6,7,8-tetrahydroquinazoline (14). This compound was synthesized by the procedure described above, using **26** (0.55 g, 2 mmol) and *N*-methyl-4-chloroaniline (1.70 g, 12 mmol). Purification of the crude product was performed by column chromatography using CH_2Cl_2/MeOH (9:1) as eluent to yield 0.078 g (12%) of **14** from **26**: mp 214–215 °C; TLC (a) CH_2Cl_2/MeOH/NH_4OH (9:1:1 drop)/silica gel, R_f 0.20, (b) $CHCl_3$/EtOAc/MeOH (1:1:1)/silica gel, R_f 0.30; IR (KBr) 3380, 3160, 2920, 1570, 1500, 1430, 1360, 790 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.35 (m, 1 H, quinazoline H), 1.76–2.03 (m, 3 H, quinazoline CH_2), 2.29–2.38 (m, 3 H, quinazoline CH_2), 2.94 (s, 3 H, NCH_3), 3.29 (m, collapses to br d on D_2O addition, 2 H, 9-CH_2), 5.57 (s, 2 H, NH_2, exch), 6.05 (s, 2 H, NH_2, exch), 6.65 (ABq, 2 H, 2',6'-H), 7.13 (ABq, 2 H, 3',5'-H). Anal. ($C_{16}H_{20}N_5Cl$·0.5H_2O·0.2CH_3COOH) C, H, N, Cl.

(6*R*,6*S*)-2,4-Diamino-6-[(3'-bromoanilino)methyl]-5,6,7,8-tetrahydroquinazoline (15). This compound was synthesized by the procedure described above, using **26** (0.55 g, 2 mmol) and 3-bromoaniline (2.06 g, 12 mmol). Purification of the crude product was performed by column chromatography using $CHCl_3$/MeOH (3:1) as eluent. The product was triturated with ether and dried to afford an analytical sample. The overall yield from **26** was 0.05 g (10%): mp 218–220 °C; TLC (a) $CHCl_3$/MeOH (3:1)/silica gel, R_f 0.24, (b) $CHCl_3$/EtOAc/MeOH/NH_4OH (2:2:1:1 drop)/silica gel, R_f 0.36; IR (KBr) 3400, 3340, 3100, 2870, 2820, 1635, 1550, 1430, 1320, 970 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.40 (m, 1 H, quinazoline H), 1.89 (m, 3 H, quinazoline CH_2), 2.40–2.49 (m, 3 H, quinazoline CH_2), 2.97 (m, 2 H, 9-CH_2), 5.52 (s, 2 H, NH_2, exch), 6.00 (br s, 3 H, NH_2, NH, exch), 6.54 (d, J = 7.94 Hz, 1 H, 6'-H), 6.61 (d, J = 7.94 Hz, 1 H, 4'-H), 6.71 (s, 1 H, 2'-H), 6.98 (t, J = 7.94 Hz, 1 H, 5'-H). Anal. ($C_{15}H_{18}N_5Br$·0.15H_2O·0.15CH_3COOH) C, H, N, Br.

(6*R*,6*S*)-2,4-Diamino-6(1-indolinomethyl)-5,6,7,8-tetrahydroquinazoline (18). This compound was synthesized by the procedure described above using **26** (0.55 g, 2 mmol) and indoline (1.43 g, 12 mmol). The product was purified by column chromatography using $CHCl_3$/MeOH (3:1) as eluent to yield 0.23 g (38%) of **18** from **26**: mp 182–184 °C; TLC $CHCl_3$/MeOH/NH_4OH (4:1:2 drops)/silica gel, R_f 0.48; IR (KBr) 3440, 3300, 3140, 2900, 2820, 1595, 1570, 1560, 1430, 1250, 735 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.40 (m, 1 H, quinazoline H), 1.93 (m, 3 H, quinazoline CH_2), 2.47 (m, 3 H, quinazoline CH_2), 2.90 (t, 2 H, indoline 3'-CH_2), 2.99 (d, 2 H, 9-CH_2), 3.37 (m, 2 H, indoline 2'-CH_2), 5.56 (s, 2 H, NH_2, exch), 6.03 (s, 2 H, NH_2, exch), 6.51 (m, 2 H, indoline ArH), 6.97 (m, 2 H, indoline ArH). Anal. ($C_{17}H_{21}N_5$·0.7CH_3CH_2OH) C, H, N.

(6*R*,6*S*)-2,4-Diamino-6-[(1'-naphthylanilino)methyl]-5,6,7,8-tetrahydroquinazoline (19). This compound was synthesized by the procedure described above, using **26** (0.55 g, 2 mmol) and 1-naphthylamine (1.72 g, 12 mmol). Purification of the crude product was carried out by column chromatography using $CHCl_3$/MeOH (4.5:1) as eluent to afford 0.08 g (12%) of **19** from **26**: mp 217–218 °C; TLC (a) $CHCl_3$/MeOH/NH_4OH (5:1:1 drop)/silica gel, R_f 0.43, (b) $CHCl_3$/EtOAc/MeOH/NH_4OH (2:2:1:1 drop)/silica gel, R_f 0.38; IR (KBr) 3300, 3150, 2930, 1620, 1570, 1520, 1440, 1270, 1120, 770 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.49 (m, 1 H, quinazoline H), 1.90–2.02 (m, 3 H, quinazoline CH_2), 2.47 (m, 3 H, quinozoline CH_2), 3.22 (m, 2 H, 9-CH_2), 5.76 (s, 2 H, NH_2, exch), 6.17 (t, 1 H, NH, exch), 6.27 (s, 2 H, NH_2, exch), 6.50 (d, 1 H, ArH), 7.09 (d, 1 H, ArH), 7.28 (t, 1 H, ArH), 7.39 (m, 2 H, ArH), 7.74 (t, 1 H, ArH), 8.23 (d, 1 H, ArH). Anal. ($C_{19}H_{21}N_5$·0.5H_2O·0.2CH_3COOH) C, H, N.

(6*R*,6*S*)-2,4-Diamino-6-[(1'-naphthylmethylamino)methyl]-5,6,7,8-tetrahydroquinazoline (20). This compound was synthesized by the procedure described above, using **26** (0.55 g, 2 mmol) and *N*-methyl-1-naphthylamine (2.00 g, 12 mmol). Purification of the crude product was performed by column chromatography using $CHCl_3$/MeOH (5:1) as eluent to afford 0.06 g (9%) of **20** from **26**: mp 185–186 °C; TLC (a) $CHCl_3$/MeOH/NH_4OH (5:1:2 drops), R_f 0.52, (b) $CHCl_3$/EtOAc/MeOH/NH_4OH (2:2:1:1 drop), R_f 0.42; IR (KBr) 3400, 3150, 2920, 1600, 1570, 1430, 1260, 1070, 980, 770 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.39 (m, 1 H, quinazoline H), 2.00 (m, 3 H, quinazoline CH_2), 2.44 (m, 3 H, quinazoline CH_2), 2.80 (s, 3 H, NCH_3), 3.03 (m, 2 H, 9-CH_2), 5.64 (s, 2 H, NH_2, exch), 6.16 (s, 2 H, NH_2, exch), 7.21 (d, 1 H, ArH), 7.40–7.50 (m, 3 H, ArH), 7.58 (d, 1 H, ArH), 7.87 (d, 1 H, ArH), 8.27 (d, 1 H, ArH). Anal. ($C_{20}H_{23}N_5$·0.2H_2O·0.2CH_3COOH) C, H, N.

General Procedure for the Synthesis of N^{10}-Methyl Analogues 2 and 17. To a solution of the bis(acetamido) condensed intermediates **27** (2 mmol) in 5 mL of CH_3CN, at room temperature, was added (0.82 mL) of a 37% HCHO solution (10 mmol) and $NaCNBH_3$ (3.2 mmol). The pH was adjusted to 6–7 by the dropwise addition of glacial AcOH. The solution was stirred for 24 h, at room temperature with the occasional addition of glacial AcOH to maintain pH near neutrality. The solution was then evaporated to dryness and deprotected with Na/EtOH by the procedure described for 1.

(6*R*,6*S*)-2,4-Diamino-6-[[(3',4',5'-trimethoxyphenyl)methylamino]methyl]-5,6,7,8-tetrahydroquinazoline (2). The compound was synthesized using **27** (0.19 g, 4.5 mmol). The crude product was purified by column chromatography using EtOAc/$CHCl_3$/MeOH (1:1:1) as eluent to afford 0.05 g (30%) of **2** from **27**; mp 199–200 °C; TLC (a) EtOAc/$CHCl_3$/MeOH (1:1:1)/silica gel, R_f 0.15, (b) $CHCl_3$/MeOH/NH_4OH (2:1:2 drops)/silica gel, R_f 0.67; IR (KBr) 3420, 1630, 1570, 1500, 1120 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.39 (m, 1 H, quinazoline H), 1.81–2.40 (m, 6 H, quinazoline CH_2), 2.93 (s, 3 H, NCH_3), 3.24 (d, 2 H, 9-CH_2), 3.53 (s, 3 H, OCH_3), 3.72 (s, 6 H, OCH_3), 5.58 (s, 2 H, NH_2, exch), 5.89 (s, 2 H, 2',6'-H), 6.07 (s, 2 H, NH_2, exch). Anal. ($C_{19}H_{27}N_5O_3$·0.4H_2O) C, H, N.

(6*R*,6*S*)-2,4-Diamino-6-[[(3',4',5'-trimethoxybenzyl)methylamino]methyl]-5,6,7,8-tetrahydroquinazoline (17). This compound was obtained by the procedure described above using **27** (0.084 g, 2 mmol). Purification by chromatography was performed using $CHCl_3$/MeOH (3:1) as eluent to yield 0.09 g (11%) of **17** from **27**: mp 100–102 °C; TLC $CHCl_3$/MeOH (3:1)/silica gel, R_f 0.41; IR (KBr) 3310, 3160, 1640, 1580, 1490, 1440, 1225, 1115 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.26 (m, 1 H, quinazoline H), 1.82–2.49 (m, 9 H, quinazoline CH_2, NCH_3), 3.44–3.61 (m, 7 H, OCH_3, 9-CH_2, NCH_2Ar), 3.74 (s, 6 H, OCH_3), 5.85 (s, 2 H, NH_2, exch), 6.33 (s, 2 H, NH_2, exch), 6.64 (d, 2 H, 2',6'-H). Anal. ($C_{20}H_{29}N_5O_3$·0.7H_2O) C, H, N.

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Supporting Information Available: National Cancer Institute's *in vitro* tumor screening data for compounds 1, 11, 12, 15, 18, and 19 (1 page). Ordering information is given on any current masthead page.

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