Benzoquinazoline Inhibitors of Thymidylate Synthase: Enzyme Inhibitory Activity and Cytotoxicity of Some 3-Amino- and 3-Methylbenzo[*f*]quinazolin-1(2*H*)-ones

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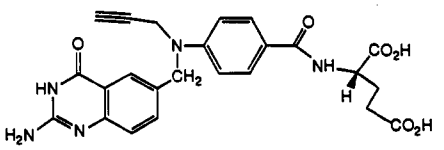
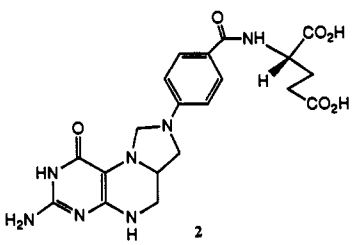
The synthesis and thymidylate synthase (TS) inhibitory activity of a series of simple benzo[*f*]-quinazolin-1(2*H*)-ones are described. Fully aromatic 3-amino compounds with compact lipophilic substituents in the 9-position were found to have I_{50} values as low as 20 nM on the isolated enzyme, and represent the first examples of potent, folate-based TS inhibitors that completely lack any structural feature corresponding to the (p-aminobenzoyl)glutamate moiety of the cofactor. A number of the compounds also showed moderate growth inhibitory activity against a human colon adenocarcinoma cell line (SW480), with IC_{50} values as low as 2 μM.

Introduction

Jones et al. described the synthesis of the potent thymidylate synthase (TS) inhibitor *N*-[4-[*N*-[(2-amino-3,4-dihydro-4-oxo-6-quinazolinyl)methyl]-*N*-prop-2-ynylamino]benzoyl]-L-glutamic acid, CB3717 (1),[1] a compound structurally related to the folate cofactor for this enzyme, 5,10-methylenetetrahydrofolic acid (2). The inhibitor showed significant clinical activity in a variety of tumor types[2-4] and was withdrawn only because of non-mechanism-based renal and hepatic toxicities caused by the limited solubility of the compound.[5] Subsequent structure/activity studies led *via* 2-desamino analogs[6] through a series of inhibitors containing small lipophilic groups at C-2[7-9] to the second generation TS inhibitor, ICI D1694 (3).[10] Compound 3 was more soluble than CB3717, lacked the renal and hepatic toxicity of the latter, and was a more potent inhibitor of cell growth due not only to its excellent TS inhibitory activity but also its substrate activity for the reduced folate transport system and susceptibility to intracellular polyglutamylation.[11]



1, CB 3717



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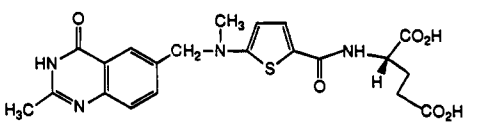
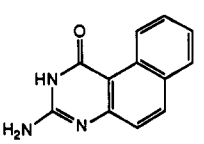


3, ICI D1694



4a

Our interest in thymidylate synthase was initially as an antimicrobial target and, because of the absence of any active folate uptake mechanism in microbes,[12] was therefore limited to molecules lacking the highly polar (*p*-aminobenzoyl)glutamate side chain common to folate cofactors and inhibitors of types 1–3. A subset of simple heterocycles containing the 2-amino-4-oxopyrimidine substructure of the cofactor was chosen from our compound database and examined for TS activity. The benzoquinazoline **4a** (I_{50}(*Escherichia coli* TS) = 7 μM) was identified as a lead compound, and a number of analogs were synthesized. Several of the inhibitors reported here showed submicromolar levels of activity against bacterial and fungal enzymes. However a TS-based antibacterial or antifungal agent should have a high degree of selectivity for microbial *vs* human TS, whereas inhibitory activities of compounds of type 4 ranged from roughly equipotent on all three enzymes to about 2 orders of magnitude more potent on human TS, with *Candida* enzyme generally having less affinity for these compounds than the *E. coli* enzyme. The development of the initial lead into a series of compounds selective for bacterial (*E. coli*) enzyme will be described in a later paper. The main aim of the present study, however, was to maximize the inhibitory activity of these simple benzoquinazolines on human TS, with two divergent applications. On the one hand a relatively lipophilic compound without a glutamate residue would not depend for its cytotoxic activity on active folate transport and polyglutamylation, and thus would avoid at least two mechanisms of resistance.[13-15] On the other hand, we felt that a suitably substituted derivative of the lead compound **4a**, itself an unusually potent TS inhibitor compared with other simple pterin-like heterocycles commonly used as the basis of folate-like inhibitors, would serve as an excellent substrate for attachment of a folate-like side chain to probe for synergy in the (*p*-aminobenzoyl)glutamate binding region of the enzyme.

We here describe the synthesis of a number of simple benzoquinazolines structurally related to **4a**, some of which have potent inhibitory activity against human TS and

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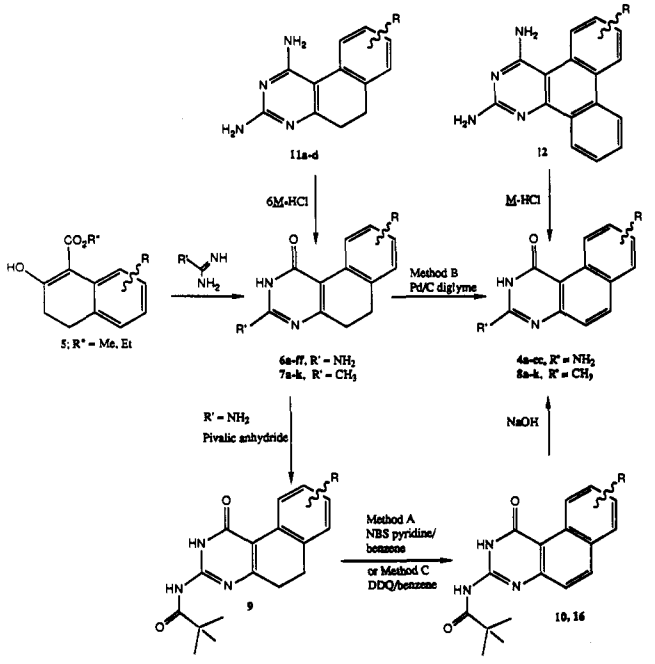
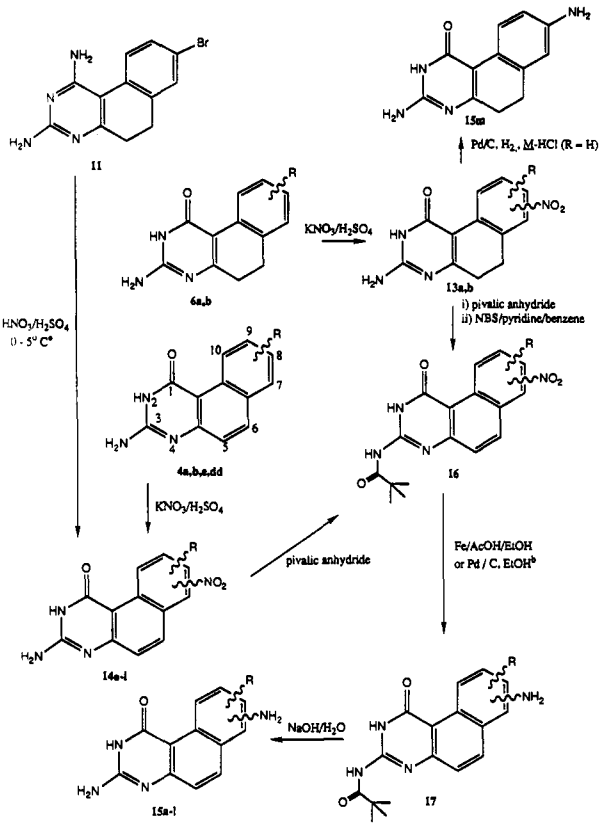
Scheme I



Scheme II [a]



[a] Treatment of 11 with HNO_3/H_2SO_4 gave **14i**, the product of concomitant nitration, hydrolysis, and oxidation of the starting material.[b] In **16**, when R = Br, reduction of NO_2 with Fe/AcOH resulted in retention of Br; reduction with $Pd/C/H_2$ led to its removal.

which showed tumor cell growth inhibitory activity in the micromolar range. These are the first reported examples of potent, folate-based TS inhibitors completely lacking any moiety corresponding to the (*p*-aminobenzoyl)-glutamate region of the cofactor.

Chemistry

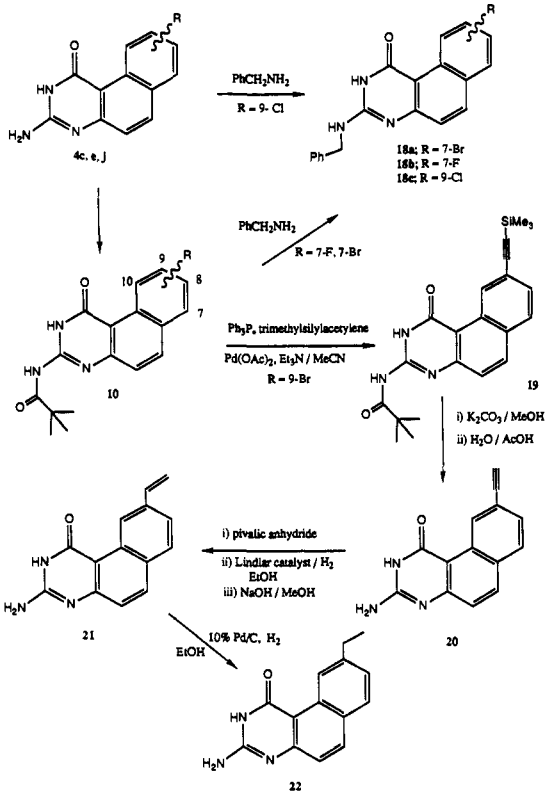
5,6-Dihydrobenzoquinazolines (**6** and **7**) were normally prepared by cyclization of an ethyl or methyl 3,4-dihydro-2-hydroxy-1-naphthoate **5** with guanidine or acetamidine in a modification of a procedure previously described for tetrahydroquinazolines[16] to yield the corresponding 3-amino or 3-methyl-5,6-dihydro compounds of types **6** or **7**, respectively (Scheme I). Four examples (**6cc–ff**) were also made by acid hydrolysis of the corresponding 1,3-diamino derivatives;[17] the neutral species of the products were identical with samples prepared by cyclization of the requisite 3,4-dihydro-2-hydroxy-1-naphthoates as above.

The 5,6-dihydro compounds were oxidized to the fully aromatic derivatives **4** or **8** (Scheme I), with the 3-amino substituent protected as the pivaloyl derivative as necessary, by one of three methods: (i) a bromination/dehydrobromination sequence with *N*-bromosuccinimide (NBS) (method A), (ii) catalytic dehydrogenation with palladium/charcoal (Pd/C) in diglyme (method B), or (iii) reaction with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in benzene (method C).

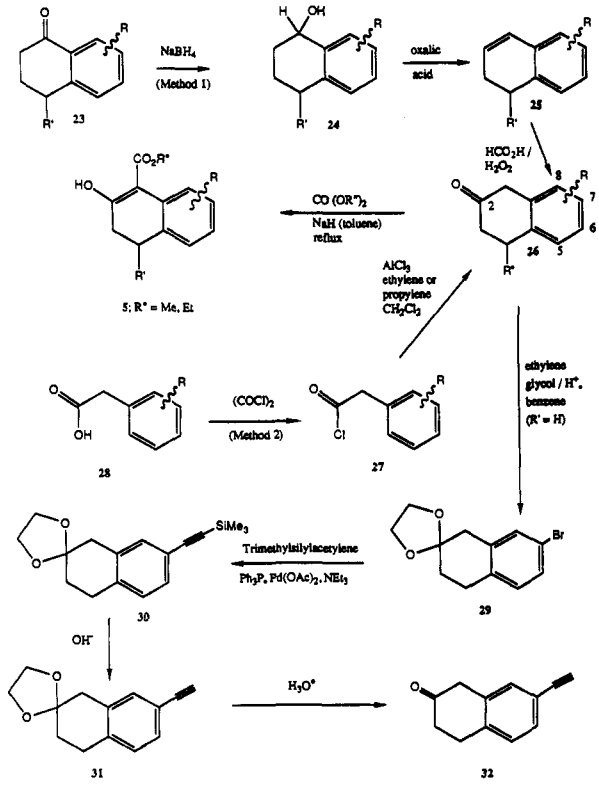
The 3-aminodibenzoquinazolinone **4z** was obtained *via* acid hydrolysis of the corresponding fully aromatic 1,3-diamino derivative **12**. The diamine precursor was prepared by cyclization of 9-aminophenanthrene with sodium dicyanamide, with isolation, but not characterization of the presumed N^1,N^5-bis(9-phenanthryl)biguanide intermediate. In this case, hydrolysis of the fully aromatic derivative proceeded smoothly to the 1-oxo compound in dilute acid (hydrolyses of the 5,6-dihydro derivatives **11a–d** were more difficult, required strongly acidic conditions, and gave rise to mixtures of the products with the corresponding 3-oxo-1-amino isomers). The single isomer isolated from the hydrolysis of **12** was assigned the 2-amino-4-oxo structure **4z** on the basis of the similarity of the chemical shift of the strongly deshielded aromatic proton adjacent to the carbonyl group (9.75–9.83 ppm) to that of the 10-proton of similar aromatic 3-amino-1-oxobenzoquinazolines such as **4b** (9.83 ppm), prepared by the unambiguous route described above from **5** (R = 7-Br). Although the 3-oxo-1-amino compound from **12** was not available for comparison, the chemical shift of the proton adjacent to the carbonyl in **4z** was ~1 ppm downfield from the corresponding proton in the diamine **12**. Furthermore, hydrolysis of the analogous (fully aromatic) 1,3-diaminobenzo[*f*]quinazoline proceeded much more readily than that of its 5,6-dihydro analogues and gave only the 3-amino-1-oxo isomer **4a**, which was also synthesised via its 5,6-dihydro derivative **6a** by the unambiguous guanidine cyclization route from **5** (R = H). Demethylation of the 9-methoxy compounds **4r** and **6ff** with HBr gave the corresponding phenolic derivatives **4y** and **6gg**. Free radical bromination of the pivaloyl derivative of **4w** gave the bromomethyl compound (**10**, R = 6-CH_2Br) which was converted into the 6-hydroxymethyl derivative **4aa** and the methoxymethyl derivative **4bb** with sodium hydroxide and methoxide respectively.

Additional examples of novel 3-aminobenzoquinazolines (**13a,b**, **14a–i**) were obtained by nitration, both before and after aromatization (Scheme II). Treatment of 1,3-diamino-8-bromo-5,6-dihydrobenzo[*f*]quinazoline with nitric and sulfuric acids resulted not only in nitration at the 9-position but also hydrolysis of the 1-amino substituent and oxidation across the 5,6-bond to yield the fully aromatic derivative **14i**. The 3-methyl-8-nitro derivative **13c** was also obtained by nitration of **7a**. Amino derivatives **15a–m** were obtained by reduction of the nitro compounds,

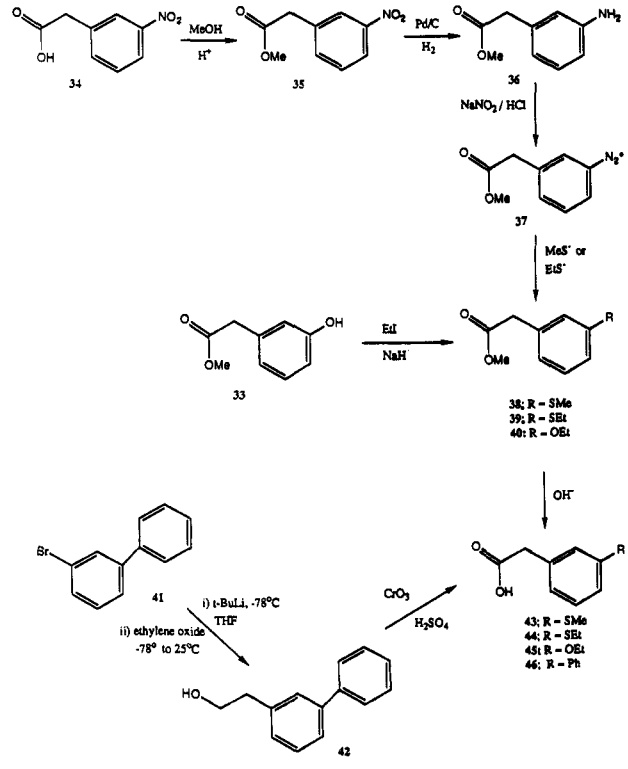
Scheme III



Scheme IV. Synthesis of Tetralones



Scheme V

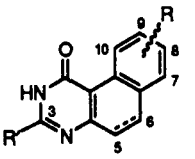


and one example (**15m**) was subjected to further bromination with concomitant oxidation across the 5,6-bond to yield the fully aromatic 7,9-dibromo-8-amino compound **15n**. In 3-amino-5,6-dihydro derivatives, electrophilic substitution tended to occur in an unsubstituted 8-position, but directly could be altered by blocking the 8-position with a bromo substituent followed by catalytic debromination. Thus the pivaloyl derivative **16** of the 8-bromo-9-nitro compound **14i** was hydrogenated over palladium on carbon to yield ultimately the 9-aminobenzoquinazoline **15e**. Pivaloylation of the 3-amino derivatives was frequently employed both as a protecting group and as an aid to solubility.

Three examples of 3-(benzylamino)benzoquinazolines (**18a–c**) were prepared by nucleophilic displacement of a 3-amino or 3-(pivaloylamino) group with benzylamine (Scheme III). Acylation of the 3-amino-9-bromo derivative **4b** with acetic/formic anhydride yielded the corresponding 3-formamido compound **18d**. The 3-methylamino analogue (**18e**) of **4a** was made by cyclization of methyl 3,4-dihydro-2-hydroxy-1-naphthoate (**5**, R = H) with *N*-methylguanidine. 9-Ethynyl-, 9-vinyl-, and 9-ethyl derivatives **20** and **21** were obtained via alkylation of the pivaloylated 9-bromo derivative with (trimethylsilyl)-acetylene, subsequent deprotection, and stepwise reduction as indicated in Scheme III.

Scheme IV outlines syntheses of the 2-tetralones used in each of the above routes, with the exception of 2-tetralone itself, its 5-, 6-, and 7-methoxy derivatives, and its 6,7-dimethoxy derivative which were commercially available. The 2-tetralones were made either by annelation of phenylacetic acids with ethylene[18] or propylene, or by transposition of the carbonyl group of 1-tetralones.[19] In addition to the commercial compounds mentioned above, several other tetralones have been described previously.[17-30] 7-Ethynyl-2-tetralone was made *via* palladium catalysed coupling of a protected 7-bromo-2-tetralone with trimethylsilylacetylene. In most cases the alkyl 3,4-dihydro-2-hydroxy-1-naphthoate precursors of the benzoquinazolines were prepared by treatment of the anion of the appropriate tetralone with diethyl or dimethyl carbonate. Occasionally (e.g. in preparations of **6cc–ff**) the tetralones were cyclized directly to the diaminobenzoquinazolines with dicyandiamide[17] prior to hydrolysis to the oxo compounds. Phenylacetic acid precursors of the tetralones were generally commercially available; in the case of 7-ethoxy-, 7-(methylthio)-, 7-(ethylthio)- and 7-phenyl-

Table I. Thymidylate Synthase Enzyme Inhibition Data and Human Tumor Cell Culture Cytotoxicity Data for Benzo[*f*]quinazolin-1(2*H*)-ones



no.	R	thymidylate synthase inhibitory activity[a] I_{50} (μM) or % I at stated concentration (μM)				tumor cell culture cytotoxicity: IC_{50} (μM) SW480
		human	calf thymus	bacterial (*E. coli*)	fungal (*C. albicans*)	
		3-Aminobenzo[*f*]quinazolin-1(2*H*)-ones (fully aromatic, R′ = NH_2)				
4a	H	1.08	5.0	7	20	52
4b	9-Br	0.022	0.158	0.267	0.322	10
4c	7-F	25		208	16.5% at 110	30
4d	7-Cl	26		40% at 56.8	6.1% at 56	25
4e	7-Br	8.9		47% at 16.8	10.7% at 300	10
4f	7-I	1.31		6.3	19.6% at 300	10
4g	8-F	44		231	23.4% at 168	50
4h	8-Cl	45.4		45% at 59.6	22.9% at 208	>100
4i	9-F	0.50		2.4	17.4	10
4j	9-Cl	0.025	0.12	0.52	1.0	3
4k	9-I	0.022		0.323	77.8% at 14	5
4l	6-Me-8-Cl	6.9		18% at 6.8	17.8% at 6.6	
4m	6-Me-9-Cl	0.02		0.17	36.9% at 1.2	2
4n	8,9-DCl_2	0.71		5.4	61.5% at 10	20
4o	8-Br-9-OEt	34% at 29.2		14% at 29.2	15.9% at 28.8	
4p	8-NO_2-9-Br	3.12		31.0	22.8% at 10	2.5
4q	9-Me	0.178		1.47	2.6	30
4r	9-OMe		1.6	5.0	15.5	20
4s	9-OEt	4.2		40% at 44.0	8.% at 10.8	20
4t	9-SMe	0.46		1.6	25.5% at 10 73.3% at 100	
4u	9-SEt	3.28		4.3		
4v	7,9-Me_2		6.0	5.0	66	
4w	6-Me		2.8	1.0	15	
4x	7-Me	7.5		18.1	44.3% at 240	35
4y	9-OH	0.48		1.84		40
4z	5,6-benzo	24		25% at 60.8	22.3% at 92	4
4aa	6-CH_2OH	8.6		101.9		>100
4bb	6-CH_2OMe	15		5% at 11.88		60
4cc	8-Br	37% at 74.8		32% at 18.8	32.3% at 192	
14a	7-NO_2	23% at 63		29% at 63.2	0% at 63.2	
14b	8-NO_2	10% at 5.6		0% at 5.6	13.1% at 204	
14c	10-NO_2	2.31		9.8	79	>100
14d	8,10-$(NO_2)_2$	145.5		104.4	7.1% at 456	
14e	7-NO_2-8-Br	68.3% at 7.8		103.7		25
14f	9-Br-10-NO_2	0.23				20
14g	7-NO_2-8-F	552		403	7.5% at 29	30
14h	8-F-10-NO_2	34.5		41% at 764.0		50
14i	8-Br-9-NO_2		27	28		
15a	9-Br-10-NH_2	0.36		0.64		30
15b	7-NH_2-8-Br	16.8		46% at 123.2		20
15c	8-NH_2-9-Br	0.34		2.8		15
15e	9-NH_2	0.63		0.6 ± 0.05		80
15g	7-NH_2	15.2		39.0		>100
15h	8-NH_2	7.5		36% at 5.76	47.9% at 131	100
15i	10-NH_2	15.6		33% at 6.08	46% at 147	>100
15j	8,10-$(NH_2)_2$	7.8		5.12		>100
15k	7-NH_2-8-F	29% at 19		119		30
15l	8-F-10-NH_2	73.8		47.1		70
15n	8-NH_2-7,9-Br_2		21	25		
20	9-ethynyl	0.6		14	50.7% at 16.2	20
21	9-ethenyl	0.12		1.1	85.0% at 86	6
22	9-Et	0.49		7.7	47.0% at 72	20
		3-Amino-5,6-dihydrobenzo[*f*]quinazolin-1(2*H*)-ones (R′ = NH_2)				
6a	H	9.82		7	127	>100
6b	9-Br		1.0	2.0	8.8	25
6c	6-Me		22	23	250	
6d	7-F	83.6		99.0	11.3% at 100	>100
6e	7-Cl	38% at 96.8		368.7	23.1% at 211	
6f	7-Br		154	109	510	
6g	7-I	54.9		40% at 47[a]	32.1% at 417	
6h	7-Me		51	59	47% at 1700	>100
6i	7-Ph		41% at 220	0% at 0.22	2.8% at 100	

Table I (Continued)

no.	R	thymidylate synthase inhibitory activity[a] I_{50} (μM) or % I at stated concentration (μM)				tumor cell culture cytotoxicity: IC_{50} (μM) SW480
		human	calf thymus	bacterial (*E. coli*)	fungal (*C. albicans*)	
		3-Amino-5,6-dihydrobenzo[*f*]quinazolin-1(2*H*)-ones (R′ = NH_2)				
6j	8-F	107		750	0% at 100	80
6k	8-Cl		52.5	334	41.3% at 100	
6l	8-Br		9	23		40
6m	9-F	1.30	3.0	4.0	73	80
6n	9-I	0.102	4.0	5.0	13	15
6o	9-Me	0.72	2.6	5.8	36.4	>100
6p	9-ethynyl	3.0		26.3	97	35
6q	9-Ph		25% at 400	0% at 0.5	4.8% at 100	
6r	9-OEt	40.4		24% at 148	10% at 120	70
6s	9-SMe	1.8		1.2	47.6% at 67	60
6t	9-SEt	17.0		31.7	34.0% at 100	40
6u	10-Cl		16% at 600	358	770	
6v	6,6-Me_2	43.9		49.6	48.8% at 1840	
6w	6-Me-8-Cl	58.9		40% at 432	214	
6x	6-Me-9-Cl	0.37		3.6	34.8% at 8.6	
6y	7,8-benzo		19% at 59	36	28.7% at 100	30
6z	7,9-Me_2		34	13	560	>100
6aa	8.9-Cl_2	2.96	6.5	6.7	21.7% at 10	24
6bb	8,9-$(OMe)_2$		25% at 765	762		
6cc	9-Cl	0.343	0.66	1.6	1.92	25
6dd	8-OMe		220	240		
6ee	7-OMe		146	250		
6ff	9-OMe	3.6	7	6		25
6gg	9-OH	8.4		12	19.7% at 10	>100
13a	8-NO_2		19	43		
13b	8-NO_2-9-Br	28.7		97.5		12
15c	8-NH_2-9-Br	1.55		2.9		15
15f	9-NH_2	13.49		16.9		>100
15m	8-NH_2		156	89		
		3-Methyl-5,6-dihydrobenzo[*f*]quinazolin-1(2*H*)-ones (R′ = CH_3)				
7a	H	35.6		118.7	18.2% at 100	>100
7b	9-Br	1.15		8.69		65
7c	7-Cl	192.8		0% at 1528	0% at 225	>100
7d	7-Br	49% at 496		0% at 496		50
7e	7-I	154		0% at 832	10.2% at 88	80
7f	8-F	24% at 168		18% at 168	0% at 100	>100
7g	8-Br	16% at 105		0% at 105		65
7h	9-F	7.16		32.8	62.2% at 168	>100
7i	9-Cl	3.1		18.8	43.3% at 20.6	>100
7j	9-I	1.98		19.75	28.2% at 112	25
13c	8-NO_2	20% at 440		4% at 440	11.9% at 100	100
		3-Methylbenzo[*f*]quinazolin-1(2*H*)-ones (fully aromatic, R′ = CH_3)				
8a	9-Br	0.29		6.9		6
8b	7-Cl	3.9			32% at 108	50
8c	7-Br					50
8d	7-I	8.8				50
8e	8-F	25% at 47.6		8.5% at 47.6	4.8% at 84	15
8f	8-Br	20% at 18		0% at 18		30
8g	9-F	1.6		29.6 ± 2.8	60% at 136	100
8h	9-Cl	0.44			23.1% at 10.1	10
8i	9-I	0.157		28% at 6.0	29.1% at 12	>100
8j	H	5.4		30.1	44.6% at 300	>100
		Benzoquinazolines Modified on the 3-Amino Substituent				
18a	7-Br (R′ = 3-$NHCH_2Ph$)	0.52		0.63		60
18b	7-F (R′ = 3-$NHCH_2Ph$)	12.5% at 5.6		0 at 5.6	22.5% at 92	0.8
18c	9-Cl (R′ = 3-$NHCH_2Ph$)	0.27			44% at 10.4	12
18d	9-Br (R′ = 3-NHCHO)	0.54				7
18e	H (R′ = 3-$NHCH_3$, 5,6-H_2)	98.4		40 at 64.8	0 at 48	>100

[a] Assayed by liberation of ^3H_2O from [5-^{3}H]dUMP. Kinetic parameters determined for human, calf thymus, *E. coli, and C. albicans* TS varied by less than 3-fold; K_m for dUMP was ~3 μM and for 5,10-methylenetetrahydrofolate was ~15–40 μM. Reaction mixture was 20 μM in dUMP and 40 μM in 5,10-methylenetetrahydrofolate.

tetralones, the requisite phenylacetic acids were made as indicated (Scheme V).

Biological Testing

The target compounds were tested as inhibitors of purified human thymidylate synthase (TS) isolated from an *E. coli* harboring a plasmid with *thy*A gene cloned from SV40 transformed human fibroblast cells.[31] Prior to the availability of the human enzyme, compounds were tested against TS isolated from calf thymus. Fungal TS from *Candida albicans* was cloned in *E. coli* and purified as described previously.[32] Bacterial TS from *E. coli* was isolated as described previously.[33] The enzymes were assayed, and the extent of inhibition of the enzyme by the

various compounds was determined by the tritium release assay of Roberts[34] as modified by Dev *et al.*[33] The inhibitor concentration producing 50% inhibition and the standard error of the mean (SEM) were obtained by fitting data to the Hill equation as described in ref 33. SEM values ranged from ±2 to ±17%. Inhibition of the growth of the human tumor cell line SW480 (colon adenocarcinoma) was determined as described previously.[35]

Discussion

A comparison of the thymidylate synthase (TS) enzyme inhibitory activities of 5,6-dihydrobenzoquinazolines of type **6** or **7** with those of the corresponding fully aromatic derivatives **4** or **8** shows a general increase in enzymic potency upon aromatization (Table I). For example the I_{50} value for inhibition of human TS by the prototypical 3-(aminobenzo)quinazoline **4a** was 9-fold lower than that of the corresponding dihydro compound **6a**. In those cases where the I_{50} values of dihydro compounds of type **6** can be compared directly with those of the corresponding fully aromatic derivatives **4**, the increases in level of human TS inhibition range from 2.6- to 42-fold, with an average increase of 10.9-fold. Similar increases in human TS inhibitory potency were observed on comparison of the 3-methyl-5,6-dihydro derivatives **7** with the corresponding aromatic derivatives **8** (4–49-fold, average increase 14.5-fold). The bacterial and fungal enzymes discriminated similarly between corresponding pairs of dihydro and aromatic derivatives; enhancements of TS inhibition upon aromatization of the benzoquinazolines averaged 7-fold for *E. coli* and 8.6-fold for *C. albicans*.

Replacement of the 3-amino substituent with 3-methyl resulted in significant attenuation of TS inhibitory activity (and cytotoxic activity) in most cases. For example, on the human enzyme the 3-amino compound **4a** was 5-fold more potent than its 3-methyl analogue **8j**. On average, fully aromatic 3-amino compounds of type **4** were 7.6-fold more inhibitory *vs* human TS and their 3-methyl counterparts of type **8**, and 5,6-dihydro-3-amino compounds (type **6**) were on average 11.3-fold more inhibitory than the corresponding 3-methyl derivatives of type **7**. Qualitatively similar trends are evident for the bacterial and fungal enzymes, though in many cases, where percent inhibition was determined at a single concentration for each compound, direct comparison of I_{50} values could not be made. Substitution with compact lipophilic moieties in the 9-position of the benzoquinazoline nucleus offered optimum TS inhibitory activity, at least in monosubstituted derivatives, compared with the unsubstituted derivative or the corresponding 7- and 8-isomers. Substitution in the 7- and 8-positions was generally detrimental to TS inhibition. Thus, for example, the 9-chloro derivative **4j** was 43-fold more inhibitory *vs* human TS than the corresponding 9-unsubstituted compound **4a**, while the 7- and 8-isomers **4d** and **4h** were respectively 24- and 42-fold less inhibitory than **4a**. Tight steric requirements were noted for the 9-substituents; for example, diminution of human TS inhibition accompanied an increase in size from methoxy to ethoxy (**6ff** to **6r**, 11-fold), methylthio to ethylthio (**6s** to **6t**, 9-fold), or methyl to ethyl (**4q** to **22**, 3-fold). Steric restrictions also apply around the region of the 6-position. In the 6-methyl compounds **4l**, **4m**, **4w**, **6c**, **6w**, and **6x** the 6-methyl group either had no effect or marginally increased inhibitory activity, and some minor differences between the enzymes were noted. Thus the 6-methyl-9-chloro derivative **4m** was 3-fold more potent against bacterial TS (and equipotent on human TS) than the 6-unsubstituted-9-chloro compound **4j**. Similarly the 6-methyl compound **4w** was 7-fold more potent than the unsubstituted compound **4a** against bacterial TS, but only 2-fold more potent against the calf thymus enzyme. Increased steric bulk around the 6-position above the level of a single methyl group, however, resulted in diminution of the TS inhibition; for example with bacterial enzyme, the 6,6-dimethyl derivative (**6v**) was 2-fold less potent than the corresponding 6-methyl compound **6c**, and the 6-hydroxymethyl compound **4aa** was over 100-fold less potent than the corresponding 6-methyl compound **4w** (though the increased hydrophilicity of the hydroxymethyl substituent could be responsible for some of the loss in activity; see below). For human enzyme, the 6-methoxymethyl compound **4bb** was almost 2-fold less potent than the hydroxymethyl compound **4aa**. Similarly the 5,6-benzo compound **4z** was 22-fold less potent against human TS than was the 5,6-unsubstituted compound **4a**.

Hydrogen-bond donors were less effective than compact lipophilic groups in elevating TS inhibition in the 9-position, but were similarly detrimental in the 7-, 8-, and 10-positions. For example the order of human TS inhibitory activity for compounds of type **4** and **6** was 9-Hal ≫ 9-NH2 ~ 9-OH ~ H, while H > Hal ~ NH_2 in other positions.

In general, the effect on inhibition of human TS of addition of a second substituent in a particular position in the distal benzene ring was qualitatively similar to its effect as a monosubstituted derivative in that position. For example, addition of a small lipophilic 9-substituent generally improved TS inhibitory activity of 7-, 8-, or 10-substituted derivatives (e.g. introduction of a 9-bromo substituent into the 10-nitro derivative **14c** to yield **14f** gave a 10-fold increase in potency); correspondingly an additional substituent in 7-, 8-, or 10-positions generally lowered inhibitory activity relative to the corresponding monosubstituted derivative (*cf.* the 9-chloro derivative **4j** with the corresponding 8,9-dichloro analogue **4n**, a 28-fold decrease in potency).

Modification of the 3-amino substituent (compounds **18b–e**) had a generally detrimental effect on human TS inhibition; the single exception was the 3-(benzylamino)-7-bromo derivative **18a**, which showed an unexpected 17-fold increase relative to the corresponding 3-amino compound **4e**. The enhanced cytotoxic potency of the 3-(benzylamino)-7-fluoro derivative **18b**, 38-fold over the corresponding 3-amino compound **4c**, might be explained in terms of better cell penetration of the more lipophilic derivative, but it is not clear at present that TS inhibition is the sole mechanism for cytotoxicity of these compounds (see below).

In all of the benzoquinazolines examined, inhibitory activity of a given compound against bacterial or fungal TS was never significantly greater, and usually considerably less than that against human enzyme; furthermore the compounds showed no significant *in vitro* antibacterial or antifungal activity. In contrast, several of the more potent inhibitors of human thymidylate synthase showed inhibition of the growth of a human colon cell line (SW480) in culture, with IC_{50} values in the low micromolar range. However, the level of TS inhibition did not correlate well with cell culture cytotoxicity data; addition of thymidine to the medium did not completely reverse the cytotoxicity

of the compounds, which indicates the involvement of mechanisms of cytotoxicity other than TS inhibition.

Conclusion

Benzo[*f*]quinazolin-1(2*H*)-ones, especially those with compact lipophilic sustituents in the 9-position, have been shown to be potent pharmacophores for inhibition of thymidylate synthase (I_{50} values as low as 20 nM), and represent the first reported examples of analogues of the folate cofactor completely lacking any structural feature equivalent to the (*p*-aminobenzoyl)glutamate region of methylenetetrahydrofolate that inhibit TS to this extent. While the simple quinazolines described here do not themselves penetrate cells particularly efficiently, their potency against the target enzyme makes them desirable substrates for attachment of (*p*-aminobenzoyl)glutamate and analogous folate-like side chains with a view to exploiting active uptake and polyglutamylation mechanisms.

Experimental Section

^{1}H NMR spectra were recorded on Varian XL-200 and XL-300 spectrometers; chemical shifts are in parts per million downfield from tetramethylsilane, and coupling constants (*J*) are measured in hertz (Hz). Mass spectra were determined by Oneida Research Services (Whitesboro, NY) on a Finnegan 4500 instrument. Analytical samples of intermediates moved as single spots on TLC, and were run on Whatman MK6F silica gel plates. Column chromatography was carried out on silica gel 60 (E. Merck, Darmstadt, Germany). The benzoquinazolinones generally did not have sharp melting points, but decomposed gradually above 220 °C. They were also very tenacious of water and other hydroxylic solvents of crystallization, and in cases where the analysis indicated the presence of these substances, the ^{1}H NMR spectrum in rigorously-dried DMSO-d_6 also confirmed their presence. Analyses were performed by Atlantic Microlab, Inc.; all values were within 0.4% of theory.

General Procedures for Preparation of 5,6-Dihydrobenzo[*f*]quinazolin-1(2*H*)-ones. 3-Amino-9-bromo-5,6-dihydrobenzo[*f*]quinazolin-1(2*H*)-one (6b). Guanidine hydrochloride (11.3 g, 118 mmol) was added to a solution of sodium (2.72 g, 118 mmol) in absolute ethanol (350 mL) and the mixture stirred and heated to reflux under a nitrogen atmosphere. Ethyl 7-bromo-3,4-dihydro-2-hydroxy-1-naphthoate (11.72 g, 39.4 mmol) in absolute ethanol (75 mL) was added dropwise over 2.5 h. The mixture was heated under reflux for 21.5 h, cooled to room temperature, and filtered. Evaporation under reduced pressure gave a yellow foam which was dissolved in 0.1 N NaOH (100 mL). The basic solution was extracted with ether and neutralized with acetic acid/water (1:9). The precipitate was collected, washed with water and ether, and dried to give **6b** as an off-white powdery solid (6.45 g, 53%). ^{1}H NMR (DMSO-d_6, 80 MHz): δ 2.45–2.90 (m, 4H, CH_2CH_2), 6.80 (br s, 2H, NH_2), 7.03–7.29 (m, 2H, Ar,H^6), 8.60–8.75 (m, 1H, Ar), 11.0 (br s, 1H, NH). Anal. ($C_{12}H_{10}BrN_3O\cdot H_2O$) C, H, Br, N.

3-Amino-5,6-dihydrobenzo[*f*]quinazolin-1(2H)-ones **6a–ff** were prepared similarly.

3-Amino-9-chloro-5,6-dihydrobenzo[*f*]quinazolin-1(2*H*)-one Hydrochloride (6cc). 1,3-Diamino-9-chloro-5,6-dihydrobenzo[f]quinazoline[17] (4.0 g) was heated under reflux with 6 M HCl (400 mL) for 2.5 h. The solution was filtered to remove the 1-amino-3-oxo isomer of the title compound (0.6 g) and the filtrate heated for a further 1.5 h. The product was collected by filtration from the cooled reaction mixture, washed with water, and dried under vacuum (0.508 g, 11.1%). ^{1}H NMR (DMSO-d_6, 250 MHz): δ 2.82 (m, 4H, CH_2CH_2), 4.0 (v br s, 1H), 7.26 (m, 2H, Ar), 8.27 (br s, 2H, NH_2), 8.38 (s, 1H, Ar). Anal. ($C_{12}H_{10}ClN_3O\cdot HCl$) C, H, N.

Also prepared from the corresponding diamines[17] by an essentially similar procedure were the following.

3-Amino-5,6-dihydro-8-methoxybenzo[*f*]quinazolin-1(2*H*)-one Hydrochloride (6dd). Yield: 9.5%. ^{1}H NMR (DMSO-d_6, 250 MHz): δ 2.77 (m, 4H, CH_2CH_2), 3.76 (s, 3H, OCh_3), 6.81 (m, 1H), 8.27 (m, 2H), 8.10 (br s, 1H). Mass spectrum (EI): *m/z* 243, (M^+), 100%. Anal. ($C_{13}H_{13}N_3O_2\cdot HCl\cdot 0.44H_2O$) C, H, N.

3-Amino-5,6-dihydro-7-methoxybenzo[*f*]quinazolin-1(2*H*)-one Hydrochloride (6ee). Yield: 24.7%. ^{1}H NMR (DMSO-d_6, 80 MHz): δ 2.75 (m, 4H, CH_2CH_2), 3.80 (s, 3H, OCH_3), 7.08 (m, 2H, Ar), 8.00 (m, 1H, Ar), 8.21 (br s, 1H, NH). Anal. ($C_{13}H_{13}N_3O_2\cdot HCl\cdot 0.8H_2O$) C, H, N.

3-Amino-5,6-dihydro-9-methoxybenzo[*f*]quinazolin-1(2*H*)-one Hydrochloride (6ff). Yield: 15.6%. ^{1}H NMR (DMSO-d_6, 80 MHz): δ 2.76 (m, 4H, CH_2CH_2), 3.73 (s, 3H, OCH_3), 6.76 (dd, *J* = 8, 2.5Hz, 1H, Ar), 7.14 (d, *J* = 8Hz, 1H, Ar), 8.00 (d, *J* = 2.5Hz, 1H, Ar), 8.19 (br s, 1H, NH). Anal. ($C_{13}H_{13}N_3O_2\cdot HCl$) C, H, N.

9-Bromo-5,6-dihydro-3-methylbenzo[*f*]quinazolin-1(2*H*)-one (7b). Acetamidine hydrochloride (3.2 g, 34 mmol) was added to a solution of sodium (0.73 g, 32 mmol) in absolute ethanol (40 mL) and the mixture stirred and heated to reflux under a nitrogen atmosphere. A solution of methyl 7-bromo-3,4-dihydro-2-hydroxy-1-naphthoate (2.98 g, 10.5 mmol) in a small volume of absolute ethanol was added rapidly. The mixture was heated for 20 h, cooled, and neutralized with glacial acetic acid. The precipitate was collected, washed with water and ethanol, and dried to give **7b** as a white solid (2.21 g, 72%). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 2.30 (s, 3H, CH_3), 2.65–2.85 (m, 4H, CH_2CH_2), 7.17 (d, *J* = 8.0 Hz, 1H, Ar), 7.35 (dd, *J* = 8.0, 2.2 Hz, 1H, Ar), 8.76 (d, *J* = 2.2 Hz, 1H, Ar), 12.67 (br s, 1H, NH). Anal. ($C_{13}H_{11}BrN_2O$) C, H, Br, N. 5,6-Dihydro-3-methylbenzo[*f*]quinazolin-1(2*H*)-ones **7a–k** were similarly prepared from appropriately substituted methyl or ethyl 3,4-dihydro-2-hydroxy-1-naphthoates.

Aromatization of 5,6-Dihydrobenzo[*f*]quinazolin-1(2*H*)-ones. Method A. 3-Amino-9-bromobenzo[*f*]quinazolin-1-(2*H*)-one (4b). (i) *N*-(9-Bromo-1,2,5,6-tetrahydro-1-oxobenzo[*f*]quinazolin-3-yl)pivalamide (9, R = 9-Br). A suspension of **6b** (5.83 g, 20 mmol) in pivalic anhydride (200 mL) was stirred and heated to 185 °C under a nitrogen atmosphere for 1 h. The pivalic anhydride was evaporated from the cooled solution under reduced pressure and the residue triturated with ether/hexanes (1:1) (200 mL), filtered, and dried to give **9** (R = 9-Br) as an off-white solid (6.1 g, 81%). ^{1}H NMR (DMSO-d_6, 300 MHz): δ. 1.23 (s, 9H, t-Bu), 2.73–2.85 (m, 4H, CH_2CH_2); 7.18 (d, *J* = 8.1 Hz, 1H, Ar), 7.34 (dd, *J* = 7.8, 2.1 Hz, 1H, Ar), 8.70 (d, *J* = 2.0 Hz, 1H, Ar), 11.35 (br s, 1H, NH). Anal. ($C_{17}H_{18}BrN_3O_2$) C, H, N.

(ii) *N*-(9-Bromo-1,2-dihydro-1-oxobenzo[*f*]quinazolin-3-yl)pivalamide (10, R = 9-Br). A mixture of **9**, (R = 9-Br) (1.09 g, 2.9 mmol) and pyridine (0.28 mL, 3.5 mmol) in dry benzene (100 mL) was stirred and heated to reflux under a nitrogen atmosphere. *N*-Bromosuccinimide (0.57 g, 3.2 mmol) was added in a single portion, and the mixture was vigorously stirred and refluxed for 1.5 h. After cooling, benzene and excess pyridine were removed under reduced pressure, leaving a light yellow residue which was then triturated with methanol/methylene chloride (1:1), filtered, and dried to give **10**, (R = 9-Br) (0.4 g, 37%). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 1.26 (s, 9H, t-Bu), 7.58 (d, *J* = 9.0 Hz, 1H, Ar), 7.74 (dd, *J* = 8.7, 2.1 Hz, 1H, Ar), 7.98 (d, *J* = 8.8 Hz, 1H, Ar), 8.25 (d, *J* = 9.0 Hz, 1H, Ar), 9.92 (d, *J* = 2.0 Hz, 1H, Ar), 11.35 (br s, 1H, NH), 12.35 (br s, 1H, NH). Anal. ($C_{17}H_{18}BrN_3O_2$) C, H, N.

(iii) 3-Amino-9-bromobenzo[*f*]quinazolin-1-(2*H*)-one (4b). A solution of **10** (R = 9-Br) (0.15 g, 0.4 mmol) in 0.75 N NaOH (7 mL) was stirred and heated to 75 °C under a nitrogen atmosphere for 10.5 h. The solution was cooled and made slightly acidic with acetic acid to cause precipitation of the product. The precipitate was collected, washed successively with water, methanol, and ether, and dried to give **4b** as an off-white solid (0.115 g, 99%). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 6.64 (br s, 2H, NH_2), 7.31 (d, *J* = 8.8 Hz, 1H, Ar), 7.57 (dd, *J* = 8.5, 1.9 Hz, 1H, Ar), 7.83 (d, *J* = 8.6 Hz, 1H, Ar), 8.02 (d, *J* = 9.0 Hz, 1H, Ar), 9.83 (s, 1H, Ar), 11.28 (br s, 1H, NH). Anal. ($C_{12}H_8BrN_3O$) C, H, N.

Fully aromatic 3-aminobenzo[*f*]quinazolin-1(2*H*)-ones **4c–p** were prepared similarly; fully aromatic 3-methylbenzo[*f*]-quinazolin-1(2*H*)-ones **8a–i** were obtained from the corresponding 5,6-dihydro derivatives of type **7** essentially as above, but without the necessity for pivaloyl protection.

Method B. 3-Amino-7,9-dimethylbenzo[*f*]quinazolin-1-(2*H*)-one (4v). A mixture of **6z** (0.25 g, 1.04 mmol) and 10% palladium on carbon (0.5 g) in diglyme (25 mL) was vigorously stirred and refluxed under nitrogen for 2.5 h and then filtered while still hot through a bed of Celite. Diglyme was removed from the filtrate under reduced pressure, and the residue was triturated with hot methanol, filtered, washed with methanol and ether, and dried to give **4v** as an off-white solid (0.14 g, 55%). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 2.43 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 6.48 (s, 2H, NH_2), 7.14 (s, 1H, Ar), 7.25 (d, J = 9.2 Hz, 1H, Ar), 8.11 (d, J = 9.1 Hz, 1H, Ar), 9.38 (s, 1H, Ar), 11.07 (s, 1H, NH). Anal. ($C_{14}H_{13}N_3O\cdot0.25H_2O$) C, H, N.

Fully aromatic benzo[*f*]quinazolin-1(2*H*)-ones **4a**, **4j**, **4k**, **4w**, and **4x** were obtained as above from the corresponding 5,6-dihydro compounds. For the 2-amino-9-methyl derivative **4q**, the corresponding 5,6-dihydro derivative **6o** was pivaloylated, the *N*-pivalamide derivative dehydrogenated as for **4v** above, and the pivaloyl group removed with NaOH as described for **4b**.

Method C. 3-Amino-9-methoxybenzo[*f*]quinazolin-1(2*H*)-one (4r). The 3-amino dihydro derivative **6ff** was pivaloylated as described for **4b** under method A. The crude pivalamide (0.93 g, ~2.84 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (0.8 g, 3.5 mmol) in dry benzene (60 mL) were refluxed under a nitrogen atmosphere for 3 h. The mixture was cooled, the benzene removed under reduced pressure, and the residue purified on a silica gel column eluting with chloroform to give *N*-(1,2-dihydro-9-methoxy-1-oxobenzo[*f*]-quinazolin-3-yl)pivalamide (0.9 g). The *N*-pivaloyl protecting group was removed with aqueous NaOH as described in method A to yield **4r** as a white solid (0.58 g, 85%). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 3.86 (s, 3H, CH_3), 6.51 (s, 2H, NH_2), 7.08 (dd, J = 8.8, 2.5 Hz, 1H, Ar), 7.12 (d, J = 8.9 Hz, 1H, Ar), 7.77 (d, J = 8.8 Hz, 1H, Ar), 7.93 (d, J = 8.8 Hz, 1H, Ar), 9.18 (d, J = 2.5 Hz, 1H, Ar), 11.03 (s, 1H, NH). Anal. ($C_{13}H_{11}N_3O_2$) C, H, N.

Aromatization of the 5,6-dihydro compounds **6r**, **6s**, and **6t**, respectively, with DDQ as above gave the derivatives **4s**, **4t**, and **4u**.

2-Aminodibenzo[*f*,*h*]quinazolin-4(3*H*)-one (4z). (i) 2,4-Diaminodibenzo[*f*,*h*]quinazoline (12). 9-Aminophenanthrene (1.0 g, 5.2 mmol) (Aldrich) and sodium dicyanamide (0.90 g, 10 mmol) were dissolved in glacial acetic acid (50 mL) at 50 °C, then stirred at room temperature for 1 h. The solution was diluted with water (~200 mL), adjusted to pH 6 with NH_4OH, and extracted with methylene chloride (200 mL). The organic phase was dried (K_2CO_3) and concentrated *in vacuo*, and the residue was purified by chromatography on silica gel eluting with ethyl acetate/methylene chloride (1:1) to give an uncyclized adduct (0.82 g). A solution of this solid in diglyme (20 mL) was stirred at reflux under nitrogen for 1 h and then concentrated *in vacuo*. The solid was suspended in methylene chloride, filtered, and then eluted on silica gel (15 g) with methanol/methylene chloride (1:9). A solid precipitated upon concentration *in vacuo* of the eluent and was filtered and dried at 85 °C under reduced pressure to give **12** (0.26 g). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 6.24 (brs, 2H, NH_2), 6.92 (brs, 2H, NH_2), 7.42–7.80 (m, 4H, Ar), 8.57 (dd, J = 8, 2 Hz, 1H, Ar), 8.67 (d, J = 8 Hz, 2H, Ar), 8.94 (dd, J = 8, 2 Hz, 1H, Ar). Anal. ($C_{16}H_{12}N_4\cdot0.25H_2O$) C, H, N.

(ii) 2-Aminodibenzo[*f*,*h*]quinazolin-4(3*H*)-one (4z). A suspension of 2,4-diaminodibenzo[*f*,*h*]quinazoline (0.20 g, 0.76 mmol) in 1 N HCl (150 mL) was stirred at reflux for 24 h, and then neutralized with NH_4OH. The resulting solid was filtered, washed with water and methanol, then suspended in warm methanol (50 mL) for 20 min, filtered, and dried at 90 °C under reduced pressure. The solid was dissolved in ethanol (100 mL) and 1 N NaOH (~1.5 mL) and filtered, and the filtrate was neutralized with acetic acid to give a precipitate which was filtered, washed with ethanol, and dried at 90 °C under reduced pressure. The solid was briefly heated to reflux in pivalic anhydride (4 mL), the solution concentrated *in vacuo*, and the residue subjected to chromatography on silica gel, eluting with methylene chloride containing a small percentage of ethyl acetate. The pivalamide (not characterized) was hydrolyzed in a solution of methanol (9 mL) and 1 N NaOH (1 mL) at reflux for 1.5 h. The solution was neutralized with acetic acid, and the precipitate was filtered, washed with methanol, and dried at 90 °C under reduced pressure to give **4z** as a beige solid (0.10 g). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 6.69 (br s, 2H, NH_2), 7.47–7.84 (m, 4H, Ar), 8.66–8.80 (m, 2H, Ar), 8.96 (dd, J = 8, 1 Hz, 1H, Ar), 9.75–9.83 (m, 1H, Ar), 11.26 (br s, 1H, NH). Mass spectrum (CI-CH_4): m/z 262 (M + 1, 100). Anal. ($C_{16}H_{11}N_3O$) C, H, N.

Similarly, **3-aminobenzo[*f*]quinazolin-1(2*H*)-one hydrochloride (4a)** (78%) was prepared by hydrolysis of corresponding diamine.[17] ^{1}H NMR (DMSO-d_6, 80 MHz): δ 7.58 (d, J = 9 Hz, 1H, Ar), 7.59–7.86 (m, 2H, Ar), 7.99–8.11 (m, 1H, Ar), 8.35 (d, J = 9 Hz, 1H, Ar), 8.40 (br s, 2H NH_2), 9.52 (dd, J = 8, 1.5Hz, 1H, Ar). Mass spectrum (EI): m/z 211 (M^+, 100). Anal. ($C_{12}H_9N_3O\cdot HCl\cdot0.67H_2O$): C, H, N.

3-Amino-9-hydroxybenzo[*f*]quinazolin-1(2*H*)-one (4y). A solution of **4r** (0.33 g, 1.37 mmol) in 48% HBr (8 mL) was stirred and heated at 110 °C for 50 h. The cooled mixture was neutralized by careful addition of solid NaOH to cause precipitation of the product. The precipitate was collected, washed with water, and dried. The crude product was converted to the *N*-pivalamide derivative by reaction with pivalic anhydride as described for **4b** (method A) and purified on a silica gel column eluting with 0–0.8% methanol/chloroform.

The pivaloyl group was removed with base as in method A above to give **4y** as a tan solid (0.22 g, 65%). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 6.45 (br s, 2H, NH_2), 6.93 (dd, J = 8.6, 2.2 Hz, 1H, Ar), 7.03 (d, J = 8.8 Hz, 1H, Ar), 7.67 (d, J = 8.6 Hz, 1H, Ar), 7.86 (d, J = 8.8 Hz, 1H, Ar), 9.01 (d, J = 2.2 Hz, 1H, Ar), 9.77 (s, 1H, OH), 11.02 (br s, 1H, NH). Anal. ($C_{12}H_9N_3O_2\cdot1.15H_2O$) C, H, N.

In a similar manner, **3-amino-9-hydroxy-5,6-dihydrobenzo-[*f*]quinazolin-1(2*H*)-one (6gg)** was prepared from **6ff** (53%). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 2.40–2.70 (m, 4H, CH_2CH_2), 6.41 (dd, J = 8.2, 2.5 Hz, 1H, Ar), 6.59 (br s, 2H, NH_2), 6.88 (d, J = 8.2 Hz, 1H, Ar), 7.96 (d, J = 2.5 Hz, 1H, Ar), 8.91 (s, 1H, ArOH), 10.87 (br s, 1H, NH). Anal. ($C_{12}H_{11}N_3O_2\cdot0.3H_2O\cdot1.25CH_3OH$) C, H, N.

3-Amino-6-(methoxymethyl)benzo[*f*]quinazolin-1(2*H*)-one (4bb). (i) *N*-[6-(Bromomethyl)-1,2-dihydro-1-oxobenzo-[*f*]quinazolin-3-yl]pivalamide (10, R = 6-CH_2Br). The 6-methyl derivative **4w** was pivaloylated as described for **6b** under method A above. To a solution of the pivalamide (1.76 g, 5.7 mmol) in dry benzene (150 mL) was added *N*-bromosuccinimide (1.01 g, 5.7 mmol) and dibenzoyl peroxide (15 mg). The mixture was heated to reflux under a nitrogen atmosphere for 2.5 h. Benzene was evaporated from the cooled solution under reduced pressure, and the residue purified on a silica gel column eluting with chloroform to give (**10**, R = 6-CH_2Br) as an off-white solid (1.4 g, 57%). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 1.27 (s, 9H, t-Bu), 5.26 (s, 2H, CH_2Br), 7.63–7.81 (m, 3H, Ar), 8.26 (dd, J = 7.6, 2.0 Hz, 1H, Ar), 9.81 (dd, J = 7.8, 2.0 Hz, 1H, Ar), 11.27 (s, 1H, NH), 12.33 (s, 1H, NH). Anal. ($C_{16}H_{18}BrN_3O_2$) C, H, N.

(ii) 3-Amino-6-(methoxymethyl)benzo[*f*]quinazolin-1-(2*H*)-one (4bb). A solution of *N*-[6-(bromomethyl)-1,2-dihydro-1-oxobenzo[*f*]quinazolin-3-yl]-pivalamide (0.28 g, 0.72 mmol) in 0.3 M sodium methoxide (25 mL) was stirred and heated at 65 °C under a nitrogen atmosphere for 4 h. After cooling, the mixture was acidified to pH 6 with glacial acetic acid, and then all the solvent was removed under reduced pressure. The residue was triturated with water (20 mL), then filtered, washed with water and acetone, and dried to give **4bb** as an off-white solid (0.12 g, 58%). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 3.39 (s, 3H, OCH_3), 4.85 (s, 2H, CH_2), 6.54 (br s, 2H, NH_2), 7.33 (s, 1H, Ar), 7.44 (dt, J = 6.9, 1.4 Hz, 1H, Ar), 7.59 (dt, J = 6.9, 1.4 Hz, 1H, Ar), 7.96 (dd, J = 8.2, 1.0 Hz, 1H, Ar), 9.69 (d, J = 8 Hz, Ar), 11.11 (br s, 1H, NH), 11.91 (br s, <1H, pyr-NH^+). Anal. ($C_{14}H_{13}N_3O_2\cdot0.5HOAc\cdot0.1H_2O$) C, H, N.

Similarly **3-amino-6-(hydroxymethyl)benzo[*f*]quinazolin-1(2*H*)-one acetate (4aa)** (32%) was prepared by using 0.6 N aqueous NaOH in place of sodium methoxide in the foregoing procedure. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 4.95 (d, J = 4.2 Hz, 2H, CH_2), 5.44 (t, J = 4.2 Hz, 1H, OH), 6.52 (br s, 2H, NH_2), 7.40 (s, 1H, Ar), 7.43 (dt, J = 7.9, 1.5 Hz, 1H, Ar), 7.57 (dt, J = 7.9, 1.5 Hz, 1H, Ar), 7.94 (dd, J = 7.9, 1.5 Hz, 1H, Ar), 9.70 (d, J = 7.9 Hz, 1H, Ar), 11.10 (br s, 1H, NH). Anal. ($C_{13}H_{11}N_3O_2\cdot CH_3COOH$) C, H, N.

General Procedure for Nitration of Benzo[*f*]quinazolin-1(2*H*)-ones. 3-Amino-9-bromo-10-nitrobenzo[*f*]quinazolin-1(2*H*)-one (14f). To a stirred solution of **4b** (3.0 g, 10.3 mmol)

in 98% sulfuric acid (125 mL) at 0–5 °C was added finely divided potassium nitrate (1.05 g, 10.3 mmol) in several portions over 20 min. After stirring at 0 °C for 2 h more, the mixture was poured onto 1000 mL of crushed ice and allowed to stand until all the ice melted. A fine, light yellow precipitate was then filtered, washed with water, and resuspended in 2 N NaOH with stirring for 3 h. The suspension was filtered and the solid resuspended in dilute aqueous acetic acid with vigorous stirring and sonication. The bright yellow solid was filtered, washed with water, dried, and triturated with boiling ethanol (500 mL) to give **14f** (2.74 g, 72%). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 6.91 (br s, 2H, NH_2), 7.42 (d, J = 9 Hz, 1H, Ar), 7.86 (d, J = 7 Hz, 1H, Ar), 8.06 (d, J = 9 Hz, 1H, Ar), 8.13 (d, J = 7 Hz, 1H, Ar), 11.25 (br s, 1H, NH). Anal. ($C_{12}H_7BrN_4O_3$) C, H, Br, N.

Similar nitrations of the appropriate 3-aminobenzo[*f*]quinazolin-1(2*H*)-ones gave the nitro derivatives **14a-e,g,h** and **13a,b**. The 3-methyl derivative **13c** was isolated by adjusting the aqueous solution of the reaction mixture after treatment with ice to pH 7 with solid NaOH.

3-Amino-8-bromo-9-nitrobenzo[*f*]quinazolin-1(2*H*)-one (14i). To a mixture of fuming nitric acid (7 mL) and sulfuric acid (6 mL) at 0 °C was added 1,3-diamino-8-bromo-5,6-dihydrobenzo[*f*]quinazoline[17] (1.0 g, 3.4 mmol) in a single portion. The reaction mixture was stirred at 0–5 °C for 45 min, and then slowly poured onto ice (15 g). The resulting precipitate was filtered, washed with water (10 mL) and ether (10 mL), and resuspended in boiling 1 N HCl (100 mL) for 1 h. After cooling, the solid was filtered, triturated with hot ethanol, filtered again, washed with ethanol and ether, and dried to give **14i** as a pale yellow solid (0.59 g, 45%). ^{1}H NMR (DMSO-d_6, 80 MHz): δ 7.67 (d, J = 9 Hz, 1H, Ar), 7.77 (s, 3H, NH_3^+), 8.23–8.34 (d, J = 9 Hz, 1H, Ar), 8.59 (s, 1H, Ar), 10.08 (s, 1H, Ar). Anal. ($C_{12}H_7BrN_4O_3 \cdot 0.5HNO_3 \cdot H_2O$) C, H, N.

General Procedure for Reduction of Nitrobenzo[*f*]quinazolin-1(2*H*)-ones in Fe/AcOH. 3,10-Diamino-9-bromobenzo[*f*]quinazolin-1(2*H*)-one (15a). The 3-amino-group of **14f** was pivaloylated as described in method A above (55%). A mixture of the pivalamide (0.8 g, 1.9 mmol) and iron powder (0.44 g, 7.8 mmol) in ethanol/glacial acetic acid (1:1) (25 mL) was stirred and heated to reflux under a nitrogen atmosphere for 3 h. The reaction mixture was poured into chloroform/water (2:1) (150 mL) and neutralized by addition of solid sodium bicarbonate. The chloroform layer was separated, and the aqueous phase was washed twice with chloroform (50 mL of each). The combined chloroform layers were dried over sodium sulfate, filtered, and evaporated under reduced pressure. The crude product was purified on a silica gel column eluting with chloroform to give *N*-(10-amino-9-bromo-1,2-dihydro-1-oxobenzo[*f*]quinazolin-3-yl)pivalamide as a bright yellow solid (0.66 g, 89%). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 1.27 (s, 9H, t-Bu), 6.51 (s, 2H, NH_2), 7.22 (d, J = 8.4 Hz, 1H, Ar), 7.51 (br d, J = 9 Hz, 1H, Ar), 7.72 (d, J = 8.4 Hz, 1H, Ar), 8.12 (d, J = 9.0 Hz, 1H, Ar), 11.40 (br s, 1H, NH), 12.45 (br s, 1H, NH). Anal. ($C_{17}H_{17}BrN_4O_2$) C, H, Br, N.

The pivalamide (0.58 g, 1.5 mmol) was deprotected with aqueous sodium hydroxide as described for **4b** (method A) to yield **15a** as a yellow solid. (0.36 g, 80%). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 6.49 (br s, 2H, NH_2), 6.69 (br s, 2H, NH_2), 7.09 (d, J = 8.4 Hz, 1H, Ar), 7.22 (d, J = 8.9 Hz, 1H, Ar), 7.56 (d, J = 8.4 Hz, 1H, Ar), 7.90 (d, J = 8.9 Hz, 1H, Ar), 11.47 (br s, 1H, NH). Anal. ($C_{12}H_8BrN_4O$) C, H, Br, N. Amino bromo derivative **15b–d** were prepared by similar Fe/AcOH reductions of the corresponding pivaloylamino bromo nitro compounds.

General Procedure for Catalytic Reduction of Nitro- or Bromonitrobenzo[*f*]quinazolin-1(2*H*)-ones. 3,9-Diaminobenzo[*f*]quinazolin-1(2*H*)-one (15e). (i) *N*-(8-Bromo-1,2-dihydro-9-nitro-1-oxobenzo[*f*]quinazolin-3-yl)pivalamide (16). *N*-(8-Bromo-1,2,5,6-tetrahydro-9-nitro-1-oxobenzo[*f*]quinazolin-3-yl)-pivalamide (0.23 g, 0.5 mmol), prepared from **61** as above, was treated with *N*-bromosuccinimide (0.12 g, 0.7 mmol) and pyridine (0.06 mL, 0.8 mmol) in dry benzene (150 mL) as in method A. The crude product was purified by trituration with methanol/water (1:9), filtered, washed (water and methanol), and dried under vacuum to give **16** as a pale yellow solid. (0.20 g, 94%). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 1.27 (s, 9H, t-Bu), 7.76 (d, J = 9.0 Hz, 1H, Ar), 8.32 (d, J = 9.0 Hz, 1H, Ar), 8.65 (s, 1H, Ar), 10.21 (s, 1H, Ar), 11.40 (s, 1H, NH), 12.45 (br s, 1H, NH). Anal. ($C_{17}H_{15}BrN_4O_4 \cdot 0.85H_2O$) C, H, N.

(ii) *N*-(9-Amino-1,2-dihydro-1-oxobenzo[*f*]quinazolin-3-yl)pivalamide (17). The foregoing pivalamide **16** (0.18 g, 0.43 mmol) was dissolved in ethanol (200 mL) in a 500-mL Parr hydrogenation flask. A slurry of 10% palladium on carbon (0.13 g) in a small volume of ethanol was added, and the reduction was begun with 42.5 psi of hydrogen pressure. When uptake of hydrogen had ceased (3.5 h), the reaction mixture was filtered through Celite, and the solvent was removed under reduced pressure to leave a yellow solid. The product was purified on a silica gel column eluting with methanol/chloroform (1:99) to give *N*-(9-amino-1,2-dihydro-1-oxobenzo[*f*]quinazolin-3-yl)pivalamide as a tan solid (0.09 g, 63%). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 1.25 (s, 9H, t-Bu), 5.75 (br s, 2H, NH_2), 6.92 (dd, J = 8.7, 2.2 Hz, 1H, Ar), 7.10 (d, J = 8.5 Hz, 1H, Ar), 7.64 (d, J = 8.6 Hz, 1H, Ar), 7.91 (d, J = 8.8 Hz, 1H, Ar), 8.77 (d, J = 1.4 Hz, 1H, Ar), 11.10 (br s, 1H, NH), 12.10 (br s, 1H, NH). Anal. ($C_{17}H_{18}N_4O_2 \cdot 0.8H_2O \cdot 0.3CH_3OH$) C, H, N.

(iii) 3,9-Diaminobenzo[*f*]quinazolin-1(2*H*)-one (15e). *N*-(9-Amino-1,2-dihydro-1-oxobenzo[*f*]quinazolin-3-yl)pivalamide (0.065 g, 0.2 mmol) was treated with aqueous sodium hydroxide as described for **4b** (method A). The product was precipitated from the basic reaction mixture with acetic acid, filtered, and washed with water to give **15e** as a tan solid (0.04 g, 84%). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 5.54 (br s, 2H, NH_2), 6.35 (br s, 2H, NH_2), 6.80 (dd, J = 8.5, 2.3 Hz, 1H, Ar), 6.87 (d, J = 8.6 Hz, 1H, Ar), 7.52 (d, J = 8.6 Hz, 1H, Ar), 7.73 (d, J = 8.6 Hz, 1H, Ar), 8.73 (s, 1H, Ar), 10.91 (br s, 1H, NH). Anal. ($C_{12}H_{10}N_4O \cdot 0.5H_2O \cdot 0.05CH_3OH$) C, H, N.

Amino compounds **15f–l** were prepared by catalytic reduction of the *N*-pivalamide derivatives of the corresponding nitro-substituted compounds **13d** and **14a–h** as above.

3,8-Diamino-5,6-dihydrobenzo[*f*]quinazolin-1(2*H*)-one (15m). A suspension of **13a** sulfate monohydrate (2.0 g, 5.3 mmol) and 5% palladium on carbon (10 mg) in 1 N HCl (20 mL) was shaken with hydrogen in a Parr apparatus. When uptake of hydrogen ceased, the mixture was filtered and the filtrate evaporated, leaving a white residue which was stirred in water (20 mL) and filtered. The crude product was recrystallized from 2 M H_2SO_4 and dried to yield **15m** sulfate as a white solid (1.1 g, 61%). ^{1}H NMR (DMSO-d_6, 80 MHz): δ 2.60–2.65 (m, 4H, CH_2CH_2), 4.99–5.69 (br s, 2H, NH_2), 6.75–6.79 (m, 4H, NH_2 + Ar,H[9]), 8.24–8.35 (d, J = 9 Hz, 1H, Ar). Anal. ($C_{12}H_{12}N_4O \cdot H_2SO_4 \cdot 0.5H_2O$) C, H, N, S.

3-Amino-8-bromobenzo[*f*]quinazolin-1(2*H*)-one (4dd). To a stirred suspension of **4a** (0.56 g, 2.65 mmol) in glacial acetic acid at 60 °C was added dropwise a solution of bromine (0.85 g, 5.3 mmol) in glacial acetic acid (1.1 mL) over a 20 min period. When the addition was complete, the mixture was heated to reflux for 4 h, and then allowed to cool before filtering. The solid was dissolved into 1 N NaOH and reprecipitated with acetic acid, filtered, washed with water and methanol, and dried. The crude product was acylated with pivalic anhydride; the resulting *N*-pivalamide was purified by recrystallization from ether and then hydrolyzed with base as described in method A. The product was precipitated from aqueous base with acetic acid, filtered, washed with water, and dried to give **4dd** as a tan solid (0.25 g, 32%). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 6.60 (s, 2H, NH_2), 7.33 (d, J = 9.0 Hz, 1H, Ar), 7.70 (dd, J = 9.2, 2.2 Hz, 1H, Ar), 8.00 (d, J = 9.0 Hz, 1H, Ar), 8.13 (d, J = 2.2 Hz, 1H, Ar), 9.55 (d, J = 9.2 Hz, 1H, Ar), 11.22 (s, 1H, NH). Anal. ($C_{12}H_8BrN_3O \cdot 0.5H_2O$) C, H, N.

3,8-Diamino-7,9-dibromobenzo[*f*]quinazolin-1(2*H*)-one (15n). To a stirred mixture of **15m** sulfate hemihydrate (0.5 g, 1.5 mmol) in acetic acid (15 mL) at 60 °C under a nitrogen atmosphere was added bromine (1 mL) in one portion. The reaction mixture was heated to 90 °C for 1 h and then cooled before pouring onto ice (40 g). The precipitate was filtered, washed with water, and recrystallized from 2 M H_2SO_4 to give **15n** sulfate as an off-white solid (0.2 g, 27%). ^{1}H NMR (DMSO-d_6, 80 MHz): δ 5.0–6.5 (br s, 2H, NH_2), 7.53–7.65 (d, J = 9 Hz, 1H, Ar), 8.23–8.27 (br s, 3H, NH_3^+), 8.30–8.42 (d, J = 9 Hz, 1H, Ar), 9.78 (s, 1H, Ar). Anal. ($C_{12}H_8Br_2N_4O \cdot H_2SO_4 \cdot 1.25H_2O$) C, H, N, S.

3-(Benzylamino)-7-bromobenzo[*f*]quinazolin-1(2*H*)-one (18a). A mixture of 10 (R = 7-Br) (0.3 g, 0.8 mmol), prepared as for **4a** (method A), and benzylamine (10 mL) was stirred and heated at reflux under a nitrogen atmosphere for 18 h. The cooled reaction mixture was then mixed with 4 volumes of ether to precipitate the product. The precipitate was filtered and recrystallized from methanol to give **18a** as an off-white solid (0.11 g, 37%). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 4.62 (d, J = 5.7 Hz, 2H, CH_2), 7.02 (m, 1H, benzyl-NH), 7.20–7.55 (m, 7H, Ar), 7.79 (dd, J = 7.5, 1.1 Hz, 1H, Ar), 8.30 (d, J = 9.2 Hz, 1H, Ar), 9.74 (d, J = 8.6 Hz, 1H, Ar), 11.2 (br s, 1H, pyr-NH). Anal. ($C_{19}H_{14}BrN_3O$) C, H, N.

The corresponding 7-fluoro derivative **18b** was prepared similarly, while the 9-chloro derivative **18c** was made by the action of benzylamine directly on the 3-amino derivative **4j**.

***N*-(9-Bromo-1,2-dihydro-1-oxobenzo[*f*]quinazolin-3-yl)-formamide (18d).** To a solution of the mixed anhydride prepared by adding 96% formic acid (10 mL) to acetic anhydride (20 mL) and stirring for 45 min was added **4b** (0.20 g, 0.69 mmol). The suspension was heated until homogeneous and the solution stirred for 45 min without additional heat and then 15 min with warming until TLC (methanol/methylene chloride (1:9)) indicated complete reaction. The solution was chilled briefly in an ice bath and then allowed to stand at room temperature for 45 min. The resulting crystals were filtered, washed with water, and dried at 95 °C under reduced pressure to give **18d** (0.135 g) as a white solid. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 7.55 (d, J = 9 Hz, 1H, Ar), 7.73 (dd, J = 9 Hz, 2Hz, 1H, Ar), 7.97 (d, J = 9 Hz, 1H, Ar), 8.22 (d, J = 9 Hz, 1H, Ar), 8.97 (br s, 1H, CHO), 9.89 (s, 1H, Ar), 10.75 (br s, 1H, CONH), 11.89 (br s, 1H, NH). Anal. ($C_{13}H_6BrN_3O_2$) C, H, Br, N.

5,6-Dihydro-3-(methylamino)benzo[*f*]quinazolin-1(2*H*)-one (18e). Methyl 3,4-dihydro-2-hydroxy-1-naphthoate was heated with methylguanidine as described for the synthesis of compounds of type **6** to yield **18e**. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 2.52–2.64 (m, 2H, CH_2), 2.68–2.82 (m, 2H, CH_2), 2.81 (d, J = 5 Hz, 3H, NCH_3), 6.54 (br s, 1H, C^3NH), 7.02 (ddd, J = 8, 8, 2 Hz, 1H, Ar), 7.07–7.18 (m, 2H, Ar), 8.42 (dd, J = 8,2 Hz, 1H, Ar), 10.98 (br s, 1H, N^2H). Anal. ($C_{13}H_{13}N_3O$) C, H, N.

3-Amino-9-ethynylbenzo[*f*]quinazolin-1(2*H*)-one (20). (i) *N*-[1,2-Dihydro-1-oxo-9-[2-(trimethylsilyl)ethynyl]benzo[*f*]-quinazolin-3-yl]pivalamide (19). A suspension of 3-amino-9-bromobenzo[*f*]quinazolin-1(2*H*)-one (**4b**) (0.99 g, 3.4 mmol) in pivalic anhydride (10 mL) was stirred at reflux for 10 min and the resulting solution cooled and concentrated *in vacuo*. The solid was suspended in triethylamine/acetonitrile (1:3) (80 mL) and triphenylphosphine (0.53 g, 2.0 mmol), (trimethylsilyl)-acetylene (3.0 mL, 21 mmol) (Aldrich), and $Pd(OAc)_2$ (0.23 g, 1.0 mmol) were added, and the reaction mixture was stirred for 25 h at 65 °C. The solution was cooled and the resulting solid filtered and washed with diethyl ether to give crude product (0.84 g). This was combined with material (0.83 g) from a similar reaction and the combined crude product purified by chromatography on silica gel eluting with ethyl acetate/methylene chloride (1:99) to give *N*-(1,2-dihydro-1-oxo-9-[2-(trimethylsilyl)ethynyl]benzo[*f*]-quinazolin-3-yl)pivalamide (0.25 g). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 0.28 (s, 9H, $Si(CH_3)_3$), 1.27 (s, 9H, t-Bu), 7.56 (d, J = 9 Hz, 1H, Ar), 7.60 (dd, J = 8, 1 Hz, 1H, Ar), 8.00 (d, J = 8 Hz, 1H, Ar), 8.22 (d, J = 9 Hz, 1H, Ar), 9.81 (s, 1H, Ar), 11.27 (br s, 1H, N^2H), 12.44 (br s, 1H, C^3NH). Anal. ($C_{22}H_{25}N_3O_2Si$) C, H, N.

(ii) 3-Amino-9-ethynylbenzo[*f*]quinazolin-1(2*H*)-one (20). A solution of *N*-(1,2-dihydro-1-oxo-9-[2-(trimethylsilyl)ethynyl]-benzo[*f*]quinazolin-3-yl)pivalamide (0.24 g, 0.61 mmol) and K_2CO_3 (0.50 g, 3.6 mmol) in methanol (~50 mL) was stirred at reflux for 2.5 h. The solution was then diluted with water (~20 mL) and acidified with acetic acid, and the resulting solid was filtered and dried at 90 °C under reduced pressure. The solid was resuspended in ethanol (~20 mL), filtered, and dried to give 3-amino-9-ethynylbenzo[*f*]quinazolin-1(2*H*)-one (0.084 g, 10.1% from **4a**) as a tan solid. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 4.26 (s, 1H, ethynyl CH), 6.63 (br s, 2H, NH_2), 7.32 (d, J = 9 Hz, 1H, Ar), 7.47 (dd, J = 8.2 Hz, 1H, Ar), 7.87 (d, J = 8 Hz, 1H, Ar), 8.02 (d, J = 9 Hz, 1H, Ar), 9.78 (s, 1H, Ar), 11.34 (br s, 1H, NH). Mass spectrum (Cl-CH_4): m/z 236 (M + 1, 100). Anal. ($C_{14}H_9N_3O$) C, H, N.

3-Amino-9-vinylbenzo[*f*]quinazolin-1(2*H*)-one (21). A solution of 3-amino-9-ethynyl benzo[*f*]quinazolin-1(2*H*)-one (0.19 g, 0.18 mmol) in pivalic anhydride (4 mL) was stirred at reflux for 10 min and then concentrated *in vacuo*. A solution of the residual solid and Lindlar catalyst (50 mg) in ethanol (50 mL) was shaken under hydrogen (~10 psi) for 30 min and then filtered through Celite and concentrated *in vacuo*. The residue was purified by chromatography on silica gel eluting with ethyl acetate/hexane (1:4) to give *N*-(1,2-dihydro-1-oxo-9-vinylbenzo-[*f*]quinazolin-3-yl)pivalamide. A solution of the solid in methanol (9 mL) and 1 N NaOH (1 mL) was stirred at reflux for 1.5 h and, after cooling, was neutralized with acetic acid. The resulting precipitate was filtered and dried at 85 °C under reduced pressure to give 3-amino-9-vinylbenzo[*f*]quinazolin-1(2*H*)-one (0.067 mg) as a white solid. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 5.36 (d, J = 12 Hz, 1H, vinyl CH), 5.94 (d, J = 18 Hz, 1H, vinyl CH), 6.54 (br s, 2H, NH_2), 6.89 (dd, J = 18, 12 Hz, 1H, vinyl CH), 7.26 (d, J = 9 Hz, 1H, Ar), 7.64 (dd, J = 8, 2 Hz, 1H, Ar), 7.83 (d, J = 8 Hz, 1H, Ar), 7.98 (d, J = 9 Hz, 1H, Ar), 9.63 (s, 1H, Ar), 11.13 (br s, 1H, NH). Mass spectrum (Cl-CH_4): m/z 238 (M + 1, 100). Anal. ($C_{14}H_{11}N_3O$) C, H, N.

3-Amino-9-ethylbenzo[*f*]quinazolin-1(2*H*)-one (22). A solution of 3-amino-9-vinylbenzo[*f*]quinazolin-1(2*H*)-one (0.060 g, 0.25 mmol) and 10% palladium on carbon (0.10 g) (Aldrich) in ethanol (200 mL) was shaken under hydrogen (40 psi) for 1 h and then filtered through Celite and concentrated *in vacuo*. The residue was suspended in ethanol, filtered, and dried at 85 °C under reduced pressure to give 3-amino-9-ethylbenzo[*f*]quinazolin-1(2*H*)-one (0.039 g) as a white solid. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 1.26 (t, J = 7 Hz, 3H, CH_3), 2.76 (q, J = 7 Hz, 2H, CH_2), 6.49 (br s, 2H, NH_2), 7.21 (d, J = 9 Hz, 1H, Ar), 7.31 (dd, J = 8, 2Hz, 1H, Ar), 7.77 (d, J = 8Hz, 1H Ar), 7.96 (d, J = 9 Hz, 1H, Ar), 9.47 (s, 1H, Ar), 11.08 (br s, 1H, NH). Mass spectrum (Cl-CH_4): m/z 240 (M + 1, 100). Anal. ($C_{14}H_{13}N_3O \cdot 0.1H_2O$) C, H, N.

General Procedures for Preparation of Tetralone Precursors. Methyl 7-Bromo-3,4-dihydro-2-hydroxy-1-naphthoate (5, R = 7-Br). To a stirred suspension of sodium hydride (5.6 g of 80% in oil, 187 mmol) in dry dimethyl carbonate (120 mL) at reflux under a nitrogen atmosphere was added a solution of 7-bromo-2-tetralone (14 g, 62 mmol) in dry dimethylcarbonate (60 mL), dropwise over 40 min. After a further 45 min, the reaction mixture was cooled to room temperature, carefully quenched with glacial acetic acid, diluted with 1 volume of water, and extracted with ethyl acetate (150 mL). The organic phase was dried over magnesium sulfate, filtered, and evaporated under reduced pressure to leave a residue which was purified using silica gel column chromatography eluting with ethyl acetate/hexane (3:97) to give methyl 7-bromo-3,4-dihydro-2-hydroxy-1-naphthoate as a white solid. (15.2 g, 86%).

The 3,4-dihydro-2-hydroxy-1-naphthoates used in the synthesis of benzoquinazolines were prepared using the procedure described above without significant modification: methyl 5-methoxy-,[29] methyl 6-methoxy-,[25] methyl[27] and ethyl 7-methoxy-,[28] and methyl 4-methyl-3,4-dihydro-2-hydroxy-4-methyl-1-naphthoates[26] have been described previously.

2-Tetralone and its 5-methoxy, 6-methoxy, 7-methoxy, and 6,7-dimethoxy derivatives were commercially available. Other 2-tetralones were obtained by one of two methods: (1) from the corresponding 1-tetralones by a four-step carbonyl transposition sequence[19] or (2) from appropriately substituted phenylacetic acids by cyclization of the corresponding acid chlorides with ethylene or propylene under Friedel–Crafts conditions.[18]

General Procedures for Preparation of 2-Tetralones. Method 1. 4,4-Dimethyl-2-tetralone (26, R = 4,4-Me_2). To a stirred suspension of sodium borohydride (3.5 g, 93 mmol) in dry methanol (50 mL) at 0 °C under a nitrogen atmosphere was added a solution of 4,4-dimethyl-1-tetralone (10 g, 57.4 mmol) in dry methanol/toluene (1:3) (100 mL) dropwise over a 45-min period. The mixture was allowed to warm to room temperature, 2 volumes of water added, and the mixture stirred for 1 h. The organic layer was separated, dried over magnesium sulfate, filtered, and evaporated under reduced pressure to leave a light yellow oil, which was purified by silica gel column chromatography eluting with ethyl acetate/hexane (1:9) to give 1,2,3,4-tetrahydro-4,4-dimethyl-1-naphthol as a colorless oil (9.89 g, 98%).

A mixture of 1,2,3,4-tetrahydro-4,4-dimethyl-1-naphthol (9.6 g, 54.5 mmol) in 20% aqueous oxalic acid (60 mL) was stirred and heated to reflux for 5 h. The reaction mixture was cooled, diluted with 1 volume of water, and extracted with 2 volumes of ether. The aqueous layer was extracted again with 1 volume of ethyl acetate, and the combined organic phases were dried over magnesium sulfate, filtered, and evaporated under reduced pressure to leave an oil which was purified using silica gel column chromatography, eluting with ethyl acetate/hexane (0.1:49.9) to give 1,2-dihydro-1,1-dimethylnaphthalene as a colorless oil (4.76 g, 55%).

To a stirred mixture of 30% hydrogen peroxide (5 mL) and 97% formic acid (20 mL) was added 1,2-dihydro-1,1-dimethylnaphthalene (4.5 g, 28 mmol) dropwise at 5 °C under a nitrogen atmosphere. When the addition was complete, the temperature of the reaction was maintained between 30 and 35 °C for 45 min, with cooling as necessary. When the exothermic phase of the reaction subsided, the mixture was allowed to cool to room temperature. A solution of 10% aqueous ferric sulfate was added in portions of a few milliliters each until cloudiness persisted in the stirred mixture, then all the solvent was removed under reduced pressure. The viscous brown residue was heated under reflux with 20% H_2SO_4 (20 mL) for 4 h and then cooled and extracted with ether (3 × 75 mL). The extracts were dried over magnesium sulfate, filtered, and evaporated to leave a brown oil, which was subjected to silica gel column chromatography, eluting with ethyl acetate/hexane (7:93) to give 4,4-dimethyl-2-tetralone (3.4 g, 74%). Overall yield = 40%.

Also prepared by the above method were 4-methyl-2-tetralone[19] and 5,7-dimethyl-2-tetralone.

Method 2. 6-Bromo-2-tetralone (26, R = 6-Br). A mixture of oxalyl chloride (100 g) and 4-bromophenylacetic acid (25 g, 11.6 mmol) was stirred under a nitrogen atmosphere at room temperature for 2 h and then heated under reflux for 4 h. The excess of oxalyl chloride was removed from the cooled solution by evaporation under reduced pressure to give crude 4-bromophenylacetyl chloride as a light yellow oil which was not purified further.

A stirred suspension of aluminum chloride (56 g, 0.42 mol) in dry methylene chloride (1000 mL) under nitrogen was cooled to −10 °C in an ice/salt bath, and ethylene was introduced through a gas inlet tube positioned just *above* the vortex. Dropwise addition of the crude 4-bromophenylacetyl chloride in methylene chloride (75 mL) was started at a moderate rate, and adjusted periodically so that the reaction temperature stayed below 0 °C. Ethylene flow was continued for 30 min after addition of the acid chloride solution was complete. The reaction mixture was poured over ice (2000 mL), stirred vigorously for a few minutes, and set aside until the ice melted. The methylene chloride layer was separated and the aqueous layer extracted with methylene chloride (3 × 100 mL). The combined methylene chloride extracts were filtered through a short silica gel plug and then evaporated under reduced pressure to leave an amber oil, which was subjected to silica gel column chromatography, eluting with ethyl acetate/hexane (35:65) to give 6-bromo-2-tetralone as an amber crystalline solid. (25 g, 95%).

The remainder of the 2-tetralones not described under method 1 were prepared by method 2: in preparations of 6- and 7-chloro-4-methyltetralones, propylene was used in place of ethylene. 5-Chloro-,[23] 5-bromo-,[24] 5-methyl-,[17,20,21] 6-fluoro-,[30] 6-chloro-,[23] 7-fluoro-,[30] 7-chloro-,[22,23] 7-bromo-,[24] 7-methyl-,[17,21] 8-chloro-,[23] and 6,7-dichloro-2-tetralones[22] have been described previously.

3-Substituted phenylacetic acids led to mixtures of 5- and 7-substituted 2-tetralones which were separated by silica gel column chromatography or by crystallization from ether/hexane or ethyl acetate/hexane solvent mixtures.

7-Ethynyl-2-tetralone (32). (i) 7′-Bromo-3′,4′-dihydrospiro[1,3-dioxolane-2,2′(1′*H*)-naphthalene] (29). A solution of 7-bromo-2-tetralone (1.1g, 4.9 mmol), ethylene glycol (0.62 g, 10 mmol), and *p*-toluenesulfonic acid (80 mg, 0.42 mmol) in benzene (20 mL) was stirred under N_2 at reflux utilizing a Dean–Stark trap for 45 min. The cooled solution was diluted with diethyl ether (60 mL), washed with saturated $NaHCO_3$ solution (2 × 10 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give **29** as an oil (1.2 g, 90%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.95 (t, J = 7 Hz, 2H, CH_2), 2.91 (t, J = 7 Hz, 2H, CH_2), 2.95 (s, 2H, CH_2), 4.01 (s, 4H, OCH_2CH_2O), 6.97 (d, J = 8 Hz, 1H, Ar), 7.15–7.27 (m, 2H, Ar). Anal. ($C_{12}H_{13}BrO_2$·0.2H_2O) C, H, Br.

(ii) 3′,4′-Dihydro-7′-[2-(trimethylsilyl)ethynyl]spiro[1,3-dioxolane-2,2′(1′*H*)-naphthalene] (30). A solution of **29** (3.40 g, 12.6 mmol), (trimethylsilyl)acetylene (7.0 mL, 50 mmol) (Aldrich), triphenylphosphine (0.66 g, 2.5 mmol), and palladium acetate (0.28 g, 1.25 mmol) in triethylamine (18 mL) was stirred at 70 °C for 18 h and then concentrated *in vacuo*. The residue was adsorbed onto silica gel from a diethyl ether solution and partially purified by elution through silica gel (15 g) with diethyl ether/hexane (1:9). Further purification by chromatography on silica gel eluting with ethyl acetate/hexane (1:19) gave **30** (1.45 g, 40%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.23 (s, 9H, $SiMe_3$), 1.93 (t, J = 7 Hz, 2CH, CH_2), 2.92 (s, 2H, CH_2), 2.95 (t, J = 7 Hz, 2H, CH_2), 4.02 (s, 4H, OCH_2CH_2O), 7.03 (d, J = 8 Hz, 1H, Ar), 7.17 (s, 1H, Ar), 7.21 (d, J = 8 Hz, 1H, Ar). Anal. ($C_{17}H_{22}SiO_2$·0.15H_2O) C, H.

(iii) 7′-Ethynyl-3′,4′-dihydrospiro[1,3-dioxolane-2,2′(1*H*)-naphthalene] (31). A solution of **30** (1.45 g, 5.02 mmol) in methanol (20 mL) and suspended K_2CO_3 (0.50 g) was stirred at room temperature for 30 min. The mixture was then filtered and concentrated *in vacuo*. The residue was adsorbed onto silica gel (2 g) and purified by chromatography on silica gel (11 g) eluting with diethyl ether/hexane (1:9) to give **31** as a solid (0.85 g, 78%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.94 (t, J = 7 Hz, 2H, CH_2), 2.95 (s, 2H, CH_2), 2.98 (t, J = 7 Hz, 2H, CH_2), 3.01 (s, 1H, ethynyl H), 4.02 (s, 4H, OCH_2CH_2O), 7.07 (d, J = 8 Hz, 1H, Ar), 7.19 (s, 1H, Ar), 7.24 (d, J = 8 Hz, 1H, Ar). Anal. ($C_{14}H_{14}O_2$·0.17H_2O) C, H.

(v) 7-Ethynyl-2-tetralone (32). A solution of **31** (0.85 g, 3.9 mmol) in THF (15 mL) and 1 N HCl (5 mL) was stirred overnight at room temperature. Concentrated HCl (2 × 0.5 mL) was then added in two aliquots 2 h apart. After stirring a further 2 h the solution was diluted with diethyl ether, the aqueous phase was separated, and the solution dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (15 g) eluting with diethyl ether/hexane (1:9 → 1:4) to give **32** (0.31 g, 45%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.54 (t, J = 7 Hz, 2H, CH_2), 3.05 (s, 1H, ethynyl H), 3.06 (t, J = 7 Hz, 2H, CH_2), 3.56 (s, 2H, CH_2), 7.18 (d, J = 8 Hz, 1H, Ar), 7.26 (s, 1H, Ar), 7.34 (d, J = 8 Hz, 1H, Ar). Anal. ($C_{12}H_{10}O$·0.33H_2O) C, H.

3-Ethoxyphenylacetic Acid (45). (i) Methyl 3-Ethoxyphenylacetate (40). Methyl 3-hydroxyphenylacetate (132.5 g, 0.80 mol) was added dropwise to a suspension of 50% NaH (43.2 g, 0.90 mol) in DMF (1 L) at 0 °C under N_2. The solution was stirred 1 h at room temperature and cooled in an ice bath, and ethyl bromide (120 mL, 1.6 mol) was added. The reaction mixture was stirred overnight of room temperature, filtered, and concentrated *in vacuo*. A solution of the residue in diethyl ether was washed with dilute NaOH solution and saturated NaCl, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by chromatography on silica gel eluting with ethyl acetate/hexane (1:39 → 1:9) to give methyl 3-ethoxyphenylacetate (94.9 g, 61%). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 1.30 (t, J = 7 Hz, 3H, ethyl CH_3), 3.59 (s, 3H, ester CH_3), 3.61 (s, 2H, $ArCH_2$), 3.98 (q, J = 7 Hz, 2H, ethyl CH_2), 6.78–6.81 (m, 3H), 7.16–7.24 (m, 1H). Anal. ($C_{11}H_{14}O_3$) C, H. **(ii) 3-Ethoxyphenylacetic Acid (45).** A solution of methyl 3-ethoxyphenylacetate (92.6 g, 0.48 mol) in methanol (600 mL) and 6.25 N NaOH (400 mL) was stirred overnight at room temperature and then filtered and concentrated *in vacuo* to remove the methanol. The solution was adjusted to pH 1 with concentrated HCl; the resulting precipitate was filtered, washed with ice water, and dried under high vacuum to give 3-ethoxyphenyl acetic acid (74.5 g, 86%). Mp = 89–90 °C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 1.30 (t, J = 7 Hz, 3H, CH_3), 3.50 (s, 2H, $ArCH_2$), 3.98 (q, J = 7 Hz, 2H, ethyl CH_2), 6.75–6.80 (m, 3H, Ar), 7.14–7.23 (m, 1H, Ar). Anal. ($C_{10}H_{12}O_3$): C, H.

2-(3-Biphenylyl)acetic Acid (46). (i) 2-(3-Biphenylyl)-ethanol (42). To a solution of 3-bromobiphenyl (18 g, 77 mmol) in diethyl ether (150 mL) under N_2 cooled to −78 °C was added 1.6 M *tert*-butyllithium in pentane (100 mL, 0.16 mol) via cannula over a 15-min period. The solution was stirred 30 min at −78 °C, ethylene oxide (9 g, 0.2 mol) added, and the reaction mixture allowed to warm to room temperature over a 1-h period. The solution was boiled briefly to drive off excess ethylene oxide and transferred to a separatory funnel, a small volume of water added,

and the mixture neutralized with concentrated HCl. The organic solution was dried ($MgSO_4$) and concentrated *in vacuo* and the residue purified by chromatography on silica gel eluting with ethyl acetate/hexane (1:4) to give **42** as an oil (10.5 g, 69%). ^1H NMR ($CDCl_3$, 60 MHz): δ 2.81 (t, J = 7 Hz, 2H, CH_2), 3.76 (t, J = 7 Hz, 2H, CH_2), 6.95–7.70 (m, 9H, Ar). **(ii). 2-(3-Biphenylyl)acetic Acid (46).** To a stirred solution of **42** (10.5 g, 53.0 mmol) in acetone (100 mL) at 0 °C was added 3 N chromium trioxide in dilute sulfuric acid (~20 mL) portionwise over a 30-min period until the orange color persisted. The mixture was stirred for 20 min, ethanol added to destroy the excess of oxidant and the solution concentrated *in vacuo*. The residue was taken up in ethyl acetate/diethyl ether (150 mL), washed with water and saturated brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by chromatography on silica gel eluting with ethyl acetate/hexane (2:3) to give 2-(3-biphenylyl)acetic acid as a colorless glass (3.35 g, 30%). ^1H NMR ($CDCl_3$, 60 MHz): δ 3.61 (s, 2H, CH_2), 7.00–7.65 (m, 9H, Ar).

3-Ethylthiophenylacetic Acid (44). To a solution of methyl 3-aminophenylacetate (102 g, 0.62 mol) in 1 N HCl (1600 mL) cooled in an ice bath was added $NaNO_2$ (42.7 g, 0.62 mol) portionwise and the solution stirred for 20 min. A solution of potassium ethanethiolate was prepared by adding ethanethiol (202 mL, 2.73 mol) dropwise over 10 min to a solution of 87.5% KOH (159 g, 2.48 mol) in water (1.2 L) at 0 °C. The diazonium salt solution was then added via cannula to the solution of potassium ethanethiolate and the reaction mixture stirred for 30 min in an ice bath. Diethyl ether (~1500 mL) was added and the mixture was stirred for 1.5 h at room temperature. The ether layer was separated, the aqueous phase was extracted with ether (3 × 700 mL), and the combined ether extracts were concentrated. The residue was eluted from silica gel with ethyl acetate/hexane (1:19) to give a mixture of methyl 3-ethylthiophenylacetate. ^1H NMR (DMSO-d_6, 200 MHz): δ 1.21 (t, J = 7 Hz, 3H, ethyl CH_3), 2.95 (q, J = 7 Hz, 2H, ethyl CH_2), 3.60 (s, 3H, OCH_3), 3.65 (s, 2H, $ArCH_2$), 7.02–7.44 (m, Ar), and methyl phenylacetate (85.9 g). The esters (84 g) were hydrolyzed in a solution of methanol (500 mL) and 6.25 N NaOH (100 mL) and stirred overnight at room temperature. The solution was concentrated *in vacuo* to remove the methanol, the remaining solution was acidified with concentrated HCl, and the resulting solid was extracted into diethyl ether. The ether solution was washed with brine (3 × 100 mL), dried (Na_2SO_4), and concentrated. Vacuum distillation (0.5 mmHg) gave a distillate (110–115 °C) of phenylacetic acid and a residue of 3-ethylthiophenylacetic acid. The residue in the flask solidified upon cooling to give 3-ethylthiophenylacetic acid (49.8 g, 41%). Mp = 49–51 °C. ^1H NMR (DMSO-d_6, 200 MHz): δ 1.21 (t, J = 7 Hz, 3H, CH_3), 2.95 (q, J = 7 Hz, 2H, SCH_2), 3.54 (s, 2H, $ArCH_2$), 7.01–7.28 (m, 4H, Ar), 12.33 (br s, 1H, CO_2H). Mass spectrum (Cl-CH_4): m/z 197 (M + 1, 100). Anal. ($C_{10}H_{12}O_2S$) C, H, S.

3-Methylthiophenylacetic acid (43) (21.0 g, 17%) was prepared in an essentially similar fashion from methyl 3-aminophenylacetate (111 g, 0.67 mol) and potassium methanethiolate (2.68 mol). Mp = 76–77 °C. ^1H NMR (DMSO-d_6, 200 MHz): δ 2.44 (s, 3H, SCH_3), 3.53 (s, 2H, $ArCH_2$), 7.02–7.28 (m, 4H, Ar), 12.30 (br s, 1H, CO_2H). Mass spectrum (Cl-CH_4): m/z 183 (M + 1, 100). Anal. ($C_8H_{10}O_2S$) C, 59.32; H, 5.53; S, 17.59. Found: C, 59.34; H, 5.53; S, 17.49.

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Supplementary Material Available: ^1H NMR data and elemental analyses on compounds **6a–gg, 7a–k, 8a–k, 13a–c, 14a–i, 15a–n, 16, 17, 18a–e, 20–22, 30–32, 40–46,** and mass spectroscopic data on compounds **4a–g, 4j–p, 4r–x, 4z, 6b–j, 6o–x, 6bb, 6gg, 7b–j, 8a–j, 13a–c, 14a–i, 15a, 20–22, 43** and **44** (28 pages). Ordering information is given on any current masthead page.

References

(1) Jones, T. R.; Calvert, A. H.; Jackman, A. L.; Brown, S. J.; Jones, M.; Harrap, K. R. A Potent Antitumour Quinazoline Inhibitor of Thymidylate Synthetase: Synthesis, Biological Properties and Therapeutic Results in Mice. *Eur. J. Cancer* **1981**, *17*, 11–19.
(2) Calvert, A. H.; Harland, S. J.; Robinson, B. A.; Jackman, A. L.; Jones, T. R.; Newell, D. R.; Siddik, Z. H.; Wilsthaw, E.; McElwain, T. J.; Smith, I. E.; Harrap, K. R. A Phase I Evaluation of the Quinazoline Antifolate N10-Propargyl-5,8-dideazafolic Acid, CB3717. *J. Clin. Oncol.* **1986**, *4*, 1245–1252.
(3) Cantwell, B. M. J.; MacCauley, V.; Harris, A. L.; Kaye, S. B.; Smith, I. E.; Milstead, R. A. V.; Calvert, A. H. Phase II Study of the antifolate N10-Propargyl-5,8-dideazafolic Acid (CB3717) in Advanced Breast Cancer. *Eur. J. Cancer Clin. Oncol.* **1988**, *24*, 733–736.
(4) Bassendine, M. F.; Curtin, N. J.; Loose, H.; Harris, A. L.; James, O. F. W. Induction of Remission in Hepatocellular Carcinoma with a New Thymidylate Synthase Inhibitor, CB3717. A Phase II Study. *J. Heptaol.* **1987**, *4*, 349–356.
(5) Alison, D. L.; Newell, D. R.; Sessa, C.; Harland, S. J.; Hart, L. I.; Harrap, K. R.; Clavert, A. H. The Clinical Pharmacokinetics of the Novel Antifolate N10-Propargyl-5,8-dideazafolic Acid (CB3717). *Cancer Chemother. Pharmacol.* **1985**, *14*, 265–271.
(6) Jones, T. R.; Thornton, T. J.; Flinn, A.; Jackman, A. L.; Newell, D. R.; Calvert, A. H. Quinazoline Antifolates Inhibiting Thymidylate Synthase: 2-Deasamino Derivatives with Enhanced Solubility and Potency. *J. Med. Chem.* **1989**, *32*, 847–752.
(7) Marsham, P. R.; Chambers, P.; Hayter, A. J.; Hughes, L. R.; Jackman, A. L.; O'Connor, B. M.; Bishop, J. A. M.; Calvert, A. H. Quinazoline Antifolate Thymidylate Synthase Inhibitors: Nitrogen, Oxygen, Sulfur and Chlorine Substituents in the C2 Position. *J. Med. Chem.* **1989**, *32*, 569–575.
(8) Hughes, L. R.; Jackman, A. L.; Oldfield, J.; Smith, R. C.; Burrows, K. D.; Marsham, P. R.; Bishop, J. A. M.; Jones, T. R.; O'Connor, B. M.; Calvert, A. H. Quinazoline Antifolate Thymidylate Synthase Inhibitors: Alkyl, Substituted Alkyl, and Aryl Substituents in the C2 Position. *J. Med. Chem.* **1990**, *33*, 3060–3067.
(9) Jackman, A. L.; Marsham, P. R.; Thornton, T. J.; Bishop, J. A. M.; O'Connor, B. M.; Hughes, L. R.; Calvert, A. H.; Jones, T. R. Quinazoline Antifolate Thymidylate Synthase Inhibitors: 2'-Fluoro-N10-propargyl-5,8-dideazafolic Acid and Derivatives with Modifications in the C2 Position. *J. Med. Chem.* **1990**, *33*, 3067–3071.
(10) Marsham, P. R.; Hughes, L. R.; Jackman, A. L.; Hayter, A. J.; Oldfield, J.; Wardleworth, J. M.; Bishop, J. A. M.; O'Connor, B. M.; Calvert, A. H. Quinazoline Antifolate Thymidylate Synthase Inhibitors: Heterocyclic Benzoyl Ring Modifications. *J. Med. Chem.* **1991**, *34*, 1594–1605.
(11) Jackman, A. L.; Taylor, G. A.; Bishop, J. A.; O'Connor, B. M.; Bisset, G.; Hughes, L. R.; Moran, R. G.; Calvert, A. H. *Proc. Am. Assoc. Cancer Res.* **1990**, *31*, 342.
(12) Ferone, R. Folate Metabolism in Malaria. *Bull. WHO* **1977**, *55*, 291–298.
(13) Fry, D. W.; Jackson, R. C. Membrane Transport Alterations as a Mechanism of Resistance to Anticancer Agents. *Cancer Surveys* **1986**, *5*, 47–49.
(14) McNamara, D. J.; Berman, E. M.; Fry, D. W.; Werbel, L. M. Potent Inhibition of Thymidylate Synthase by Two Series of Nonclassical Quinazolines. *J. Med. Chem.* **1990**, *33*, 2045–2051.
(15) Varney, M. D.; Marzoni, G. P.; Palmer, C. L.; Deal, J. G.; Webber, S.; Welsh, K. M.; Bacquet, R. J.; Bartlett, C. A.; Morse, C. A.; Booth, C. L. J.; Herrmann, S. M.; Howland, E. F.; Ward, R. W.; White, J. Crystal-Structure-Based Design and Synthesis of Benz-[*cd*]indole-Containing Inhibitors of Thymidylate Synthase. *J. Med. Chem.* **1992**, *35*, 663–667.
(16) Kim, S. H. Antiviral compounds. Australian Pat. Appl. 23013/83, 1983.
(17) Rosowsky, A.; Chen, K. K. N.; Papathanasopoulos, N.; Modest, E. J. Quinazolines. VII. Synthesis of 1,3-Diamino-5,6-dihydrobenzo-[f]quinazolines. *J. Heterocycl. Chem.* **1972**, *9*, 263–273.
(18) Burckhalter, J. H.; Campbell, J. R. Ethylene and Phenylacetyl Chloride in the Friedel–Crafts Reaction. Novel Syntheses of 2-Tetralones and Benzofuranones. *J. Org. Chem.* **1961**, *26*, 4232–4235.
(19) Vebrel, J.; Carrie, R. *Bull. Soc. Chim. Fr.* **1982**, II-161–166.
(20) Bey, P.; Ourisson, G. enone-benzene rearrangement. III. Rearrangement of octolones under the Schmitt–Panouse conditions. *Bull. Soc. Chim. Fr.* **1968**, 2464–2468.
(21) Sims, J. J.; Cadogan, M.; Selman, L. H. Improvement of a β-Tetralone Synthesis: 5-, 6-, 7-, and 8-Methyl-β-tetralones. *Tetrahedron Lett.* **1971**, *14*, 951–954.
(22) Rosowsky, A.; Battaglia, J.; Chen, K. K. N.; Modest, E. J. Synthesis of new chlorine-substituted derivatives of 2-tetralone. *J. Org. Chem.* **1968**, *33*, 4288–4290.
(23) Molloy, B. B. Chlorinated tetrahydro-2-benzazepines. Ger. Offen. 2,827,931; *Chem. Abstr.* **1979**, *90*, 137703*j*.

(24) Carlsson, P. A. E.; Wikstrom, H. V.; Svensson, K. A. I.; Andersson, B. R.; Ekman, A. B.; Stjernloef, N. P.; Svensson, N. A. Preparation of halo (methyl)-substituted 2-tetralin- and 2-indanamines as central nervous system (CNS) agents. PCT Int. Appl. WO 9007490, 1990; *Chem. Abstr.* **1991**, *115*, 231888e.
(25) Colvin, E. W.; Martin, J.; Shroot, B. Selective carboxylation of 6-methoxy-2-tetralone. *Chem. Ind.* **1966**, *51*, 2130.
(26) Tshiamala, K.; Kitane, S.; Vebrel, J.; Laude, B. Control of the regioselectivity of cycloaddition of diphenylnitrilimine to substituted 1,2-dihydronaphthalenes. Stereospecificity of the reaction. *Bull. Soc. Chim. Belg.* **1966**, *95*, 1083–1098.
(27) Santroch, G.; Davis, M. A. Antibacterial, antifungal and trichomonacidal derivatives of 2-azido-2-hydroxy-1-naphthaleneacetic acid γ-lactones. U.S. Pat. 3621038, 1971; *Chem. Abstr.* **1972**, *76*, 59433r.
(28) Wiesner, K.; McCluskey, J. G. 1,5-Methano-3-benzazocine derivatives. U.S. Pat. 3687937; *Chem. Abstr.* **1972**, *77*, 152008r.
(29) Aristoff, P. A.; Johnson, P. D.; Harrison, A. W. Total Synthesis of a Novel Antiulcer Agent via a Modification of the Intramolecular Wadsworth-Emmons-Wittig Reaction. *J. Am. Chem. Soc.* **1985**, *107*, 7967–7974.
(30) Adcock, W.; Bettess, P. D.; Rizvi, S. Q. A. Fluorine-19 Substituent chemical shifts. *Aust. J. Chem.* **1970**, *23*, 1921–1937.
(31) Dev, I. K.; Dallas, W. S. Unpublished results.
(32) Singer, S. C., Richards, C. A., Ferone, R., Benedict, D, Ray, P. Cloning, Purification and Properties of *Candida albicans* Thymidylate Synthase. *J. Bacteriol.* **1989**, *171*, 1372–1378.
(33) Dev, I. K.; Yates, B. B.; Atashi, J.; Dallas, W. S. Catalytic Role of Histidine 147 in Escherischia Coli Thymidylate Synthase. *J. Biol. Chem.* **1989**, *264*, 19132–19137.
(34) Roberts, D. An Isotopic Assay for Thymidylate Synthetase. *Biochemistry* **1966**, *5*, 3546–3548.
(35) Patil, S. D.; Jones, C.; Nair, M. G.; Galivan, J.; Maley, F.; Kisliuk, R. L.; Gaumont, Y.; Duch, D.; Ferone, R. Folate Analogues. 32. Synthesis and Biological Evaluation of 2-Desamino-2-methyl-N10-propargyl-5,8-dideazafolic Acid and Related Compounds. *J. Med. Chem.* **1989**, *32*, 1284–1289.
(36) Rosowsky, A.; Chen, K. K. N.; Nadel, M. E.; Papathanasopoulos, N.; Modest, E. J. Quinazolines. VIII. Synthesis of 1,3-Diaminobenzo[f]quinazolines. *J. Heterocycl. Chem.* **1972**, *9*, 275–283.