Tyrosine Kinase Inhibitors. 9. Synthesis and Evaluation of Fused Tricyclic Quinazoline Analogues as ATP Site Inhibitors of the Tyrosine Kinase Activity of the Epidermal Growth Factor Receptor

Gordon W. Rewcastle,[†] Brian D. Palmer,[†] Alexander J. Bridges,[‡] H. D. Hollis Showalter,[‡] Li Sun,[‡] James Nelson,[‡] Amy McMichael,[‡] Alan J. Kraker,[‡] David W. Fry,[‡] and William A. Denny*,[†]

Cancer Research Laboratory, University of Auckland School of Medicine, Private Bag 92019, Auckland, New Zealand, and Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company, 2800 Plymouth Road, Ann Arbor, Michigan 48106-1047

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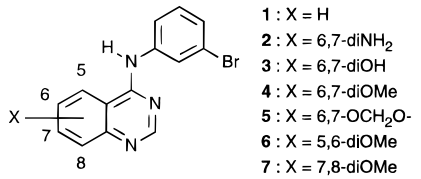
Following the discovery of 4-[(3-bromophenyl)amino]-6,7-dimethoxyquinazoline (**4**; PD 153035) as an extremely potent (IC_{50} 0.025 nM) inhibitor of the tyrosine kinase activity of the epidermal growth factor receptor (EGFR), several fused tricyclic quinazoline analogues have been prepared and evaluated for their ability to inhibit the enzyme. The most potent compound was the linear imidazo[4,5-*g*]quinazoline (**8**), which exhibited an IC_{50} of 0.008 nM for inhibition of phosphorylation of a fragment of phospholipase C-γ1 as substrate. While *N*-methyl analogues of **8** showed similar potency, analogous *N*-[2-(dimethylamino)ethyl] derivatives were less effective. The next most potent compounds were the linear pyrazoloquinazolines (**19** and **20**) (IC_{50}s 0.34 and 0.44 nM) and pyrroloquinazoline (**21**) (IC_{50} 0.44 nM), while several other linear tricyclic ring systems of similar geometry to **8** (triazolo-, thiazolo-, and pyrazinoquinazolines) were less effective. In the imidazo[4,5-*g*]quinazoline and pyrroloquinazoline series, the corresponding angular isomers were also much less effective than the linear ones. These results are consistent with structure−activity relationship studies previously developed for the 4-[(3-bromophenyl)amino]quinazolines, which suggested that small electron-donating substituents at the 6- and 7-positions were desirable for high potency. Cellular studies of the linear imidazoloquinazoline **8** show that it can enter cells and rapidly and very selectively shut down EGF-stimulated signal transmission by binding competitively at the ATP site of the EGFR.

Introduction

4-Anilinoquinazolines have been shown[1−5] to be potent and highly selective inhibitors of the tyrosine kinase activity of the epidermal growth factor receptor (EGFR), via a mechanism competitive with the binding of ATP.[1] These compounds are of potential interest as anticancer drugs, because EGFR is known to be overexpressed in a large percentage of clinical cancers of various types,[6−8] and this overexpression is associated with poor prognosis.[9,10] We have previously demonstrated structure−activity relationships (SAR) for 4-anilinoquinazolines which suggest the utility of electron-donating substituents in the 6- and 7-positions.[2,5] Thus 4-(3-bromophenyl)quinazoline (**1**) has an IC_{50} for inhibition of phosphorylation of a PLCγ-based substrate of 27 nM, whereas the 6,7-dihydroxy and diamino analogues (**2** and **3**) were much more potent (IC_{50}s of 0.17 and 0.12 nM, respectively). The 6,7-dimethoxy derivative **4** was much more potent again (IC_{50} 0.025 nM), while the 6,7-methylenedioxy derivative **5** was less active (IC_{50} 15 nM).[5] It is not clear whether these structure−activity relationships are related to oxidative instability of the bisamino- or hydroxy-substituted derivatives, to different electron density patterns, or to steric requirements. It was therefore decided to explore the effects of incorporating the electron-donating amino substituents into a fused 5- or 6-membered ring which is part of the aromatic system. The present paper reports on the synthesis and evaluation of a series of fused tricyclic analogues of **1** as EGFR inhibitors.



1 : X = H
2 : X = 6,7-diNH_2
3 : X = 6,7-diOH
4 : X = 6,7-diOMe
5 : X = 6,7-OCH_2O-
6 : X = 5,6-diOMe
7 : X = 7,8-diOMe

Chemistry

The majority of the imidazoquinazolines were prepared by the condensation of 3-bromoaniline and 3-bromoaniline hydrochloride with the appropriate methylthioquinazoline (method A; Scheme 1), or by the reaction of the appropriate 6,7-diaminoquinazoline derivative with formic acid (method B; Scheme 1). With method A, because of precipitation of the products as their hydrochloride salts, the addition of a full equivalent of HCl, in the form of 3-bromoaniline hydrochloride, was found necessary in order to ensure complete reaction. The methylthio compounds required for this procedure were prepared from the analogous quinazolinethiones, by reaction with KOH/MeI in aqueous methanol, while the thiones were prepared from the appropriate quinazolinones by thiation with P_2S_5 in pyridine.

The unsubstituted 1*H*-imidazo[4,5-*g*]quinazoline **8** was initially prepared in moderate overall yield from the known[11] (methylthio)quinazoline **25** (method A; Scheme 1). A more flexible and higher-yielding route was therefore developed from the known[12] 7-fluoroquinazoline (**26**). Nitration of **26**, followed by removal of the unwanted 8-nitro isomer by recrystallization from acetic acid, gave 7-fluoro-6-nitroquinazolinone **27**. This was converted to the corresponding 4[(3-bromophenyl)-

[†] University of Auckland School of Medicine.
[‡] Parke-Davis Pharmaceutical Research.
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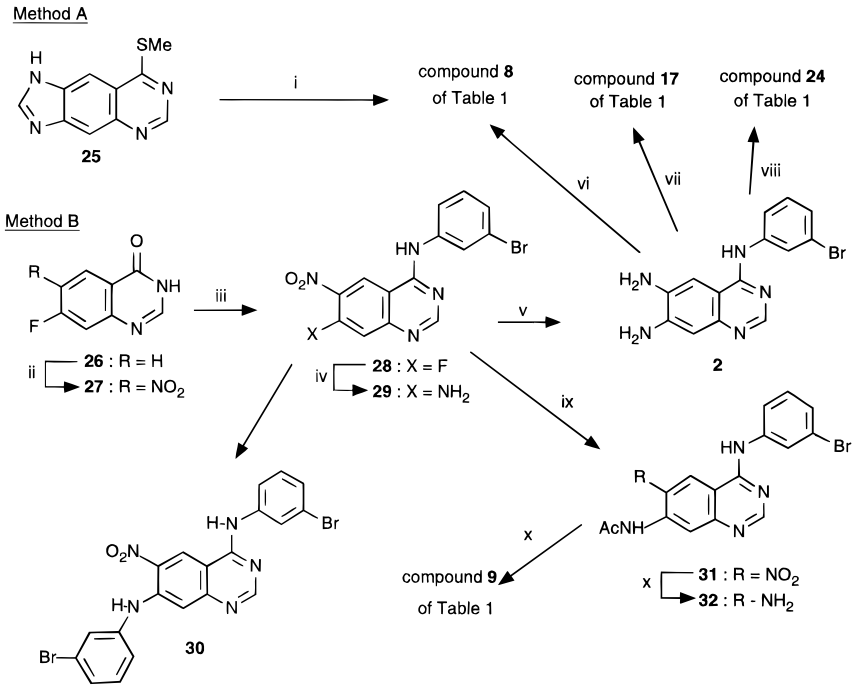
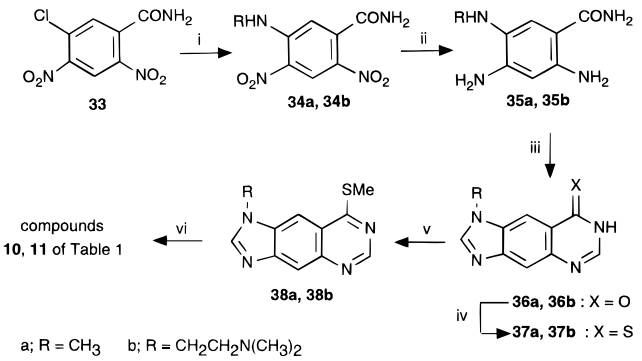
Scheme 1[a]



[a] (i) 3-Bromoaniline/3-bromoaniline hydrochloride/*i*-PrOH/reflux/1 h; (ii) c. H_2SO_4/f. HNO_3/100 °C/1 h; (iii) $SOCl_2$/DMF/reflux/3 h, then 3-bromoaniline/*i*-PrOH/20 °C; (iv) NH_3/*i*-PrOH/100 °C/8 h (pressure vessel); (v) Fe/H^+; (vi) HCO_2H/reflux/1 h; (vii) $NaNO_2$/HCl/0 °C, then NH_4OH; (viii) 1,4-dioxane-2,3-diol/20 °C/12 h; (ix) AcOH/Ac_2O/reflux/12 h; (x) Fe/AcOH/reflux/30 min (*in situ* reaction: **31** to **9** directly).

Scheme 2[a]



[a] (i) 40% aqueous $MeNH_2$/EtOH/100 °C/2 h (pressure vessel), or $H_2N(CH_2)_2NMe_2$/EtOH/reflux/15 min; (ii) Pd−C/H_2/EtOH/HCO_2H/20 °C; (iii) HCO_2H/reflux/2 h; (iv) P_2S_5/pyridine/reflux/16 h; (v) MeI/KOH/MeOH/20 °C/16 h; (vi) 3-bromoaniline/3-bromoaniline hydrochloride/*i*-PrOH/reflux/6 h.

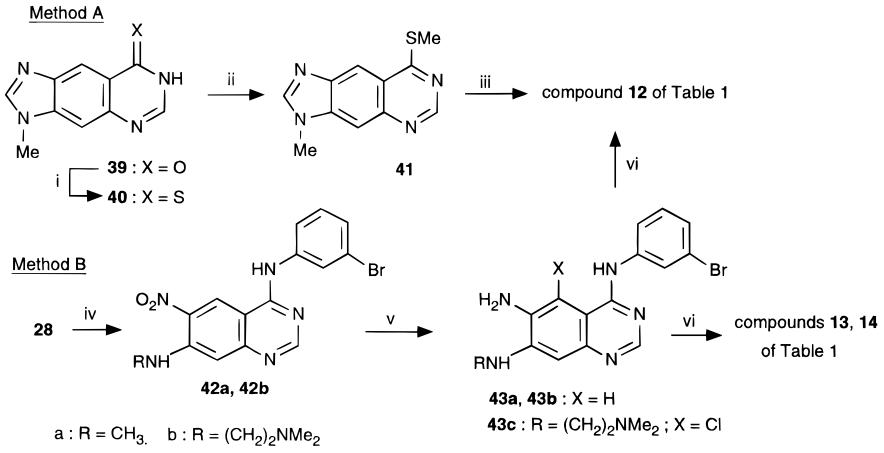
amino]quinazoline (**28**), which reacted readily with ammonia to give the 7-amino derivative **29**. Reduction then gave the diamine **2**, which on treatment with refluxing formic acid gave **8** in good yield. Compound **2** was also a key intermediate for the preparation of the 1,2,3-triazolo[4,5-*g*]quinazoline **17** and the pyrazino[2,3-*g*]quinazoline **24**, by reaction with HNO_2 or 1,4-dioxane-2,3-diol[13] respectively (Scheme 1). Acetylation of **29**, followed by reduction of the resulting nitroacetamide **31** and *in situ* ring closure of the resultant aminoacetamide **32**, gave 2-methylimidazo[4,5-*g*]quinazoline **9** (Scheme 1).

The 1-substituted 1*H*-imidazo[4,5-*g*]quinazolines **10** and **11** were prepared as shown in Scheme 2. Addition of methylamine or *N*,*N*-dimethylethylenediamine to 5-chloro-2,4-dinitrobenzamide[14] (**33**) gave the amino dinitro amides **34a** and **34b**, which were reduced to the analogous triamines (**35a** and **35b**) and converted directly to the imidazoquinazolones **36a** and **36b** via a double-ring-closure reaction with formic acid. Thiation to **37a** and **37b**, followed by conversion to the thiomethyl compounds **38a** and **38b**, followed by condensation with 3-bromoaniline, then gave the 1-substituted derivatives **10** and **11**.

The 3-methyl-3*H*-imidazo[4,5-*g*]quinazoline **12** was initially prepared from the known[15] quinazolinone (**39**), via the analogous thione and methylthio compounds (**40** and **41**) (Scheme 3), but a superior route was found to be via the known[5] 7-methylamino compound (**42a**). Reduction of **42a** gave the known[5] diamine **43a**, which reacted readily with formic acid to give **12**. Preparation of **42a** was much more facile using the fluoroquinazoline **28** (Scheme 1) than the analogous chloro compound which was used previously.[5] The 3-[2-(dimethylamino)-ethyl] derivative **13** was prepared similarly, via intermediates **42b** and **43b**, although complications were experienced with the nitro reduction step. Reduction of **42b** either with Fe dust or by hydrogenation over Pt on activated carbon when HCl was present (to improve solubility) gave significant incorporation of chlorine at the quinazoline 5-position, yielding **43c**, which could be isolated pure due to its lower solubility. Reduction of **42b** to the diamine **43b** was achieved cleanly with Na_2S under basic conditions. Reaction of **43b** and **43c** with formic acid then gave compounds **13** and **14**, respectively.

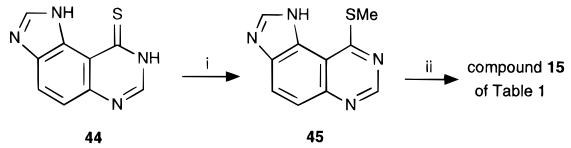
The nonlinear imidazo[4,5-*f*]quinazoline **15** was prepared by method A, following conversion of the known[16] thione **44** to the thiomethyl compound **45** (Scheme 4). The isomeric imidazo[4,5-*h*]quinazoline **16** was similarly prepared from the known[16] thione **51**. However, the latter compound was prepared by a different method to that reported, beginning with nitration of the known[17] 6-bromo-7-chloroquinazolin-4(3*H*)-one (**46**) (Scheme 5), instead of 7-chloroquinazolin-4(3*H*)-one.[11] The advantage of using the 6-bromo precursor was that the desired

Scheme 3[a]



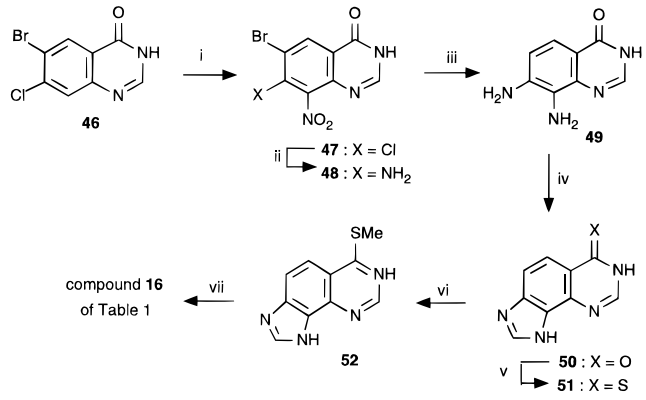
[a] (i) P_2S_5/pyridine/reflux/16 h; (ii) MeI/KOH/MeOH/20 °C/16 h; (iii) 3-bromoaniline/3-bromoaniline hydrochloride/*i*-PrOH/reflux/1 h; (iv) 40% aqueous $MeNH_2$/*i*-PrOH/100 °C/2 h (pressure vessel); (v) Fe/H^+ or H_2/Pt/C or Na_2S; (vi) HCO_2H/reflux/1 h.

Scheme 4[a]



[a] (i) MeI/KOH/MeOH/20 °C/12 h; (ii) 3-bromoaniline/3-bromoaniline hydrochloride/*i*-PrOH/reflux/16 h.

Scheme 5[a]



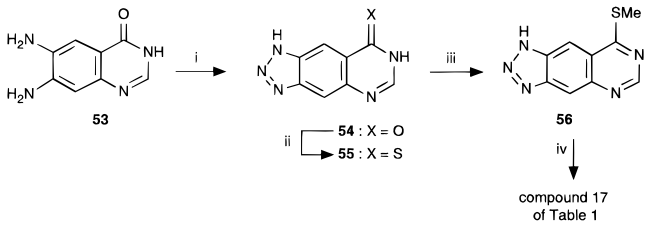
[a] (i) c. H_2SO_4/f. HNO_3/100 °C/3 h; (ii) NH_3/*n*-BuOH/175 °C/36 h (pressure vessel); (iii) Pd/C/H_2/MeOH/KOH; (iv) HCO_2H/reflux/3 h; (v) P_2S_5/pyridine/reflux/16 h; (vi) MeI/KOH/MeOH/20 °C/16 h; (vii) 3-bromoaniline/3-bromoaniline hydrochloride/*N*-methylpyrrolidone/120 °C/2 h.

8-nitro derivative (**47**) was obtained exclusively, rather than as the minor product.[11] Selective substitution of the chloro group with ammonia gave **48**, which was reacted with hydrogen over 5% palladium/activated carbon to simultaneously remove the bromine blocking group and reduce the nitro group to give **49**. This was then converted via **50** to the thione **51** by standard techniques.

Although the 1,2,3-triazoloquinazoline **17** was best prepared directly from the 6,7-diaminoquinazoline **2** by reaction with HNO_2 (Scheme 1), it could also be prepared from the known[11] 6,7-diaminoquinazolinone **53** (scheme 6). Treatment of **53** with HNO_2 gave the triazoloquinazolinone **54**, which was then converted to the thione **55** and the methylthio compound **56**, before reaction with 3-bromoaniline which finally yielded **17**.

The thiazolo[5,4-*g*]quinazoline **18** was obtained from 5-chloro-2,4-dinitrobenzamide[14] (**33**) by the method

Scheme 6[a]



[a] (i) $NaNO_2$/HCl/0 °C, then KOH; (ii) P_2S_5/pyridine/reflux/16 h; (iii) MeI/KOH/MeOH/20 °C/16 h; (iv) 3-bromoaniline/3-bromoaniline hydrochloride/*N*-methylpyrrolidone/120 °C/2 h.

outlined in Scheme 7. Reaction with an excess of NaSH resulted in chloride displacement followed by nitro reduction, affording the amino thiol **58** as the major initial product. Purification of **58** was conveniently achieved by allowing it to spontaneously dimerize to the highly insoluble disulfide **57**, from which it could be quantitatively regenerated by reduction with $NaBH_4$. Reaction of **58** with formic acid gave the benzothiazole **59**, from which the thiazoloquinazolone **60** was obtained by nitro group reduction followed by reaction with triethyl orthoformate. Conversion of **60** to the corresponding 4-chloroquinazoline **61**, followed by reaction with 3-bromoaniline, gave **18**.

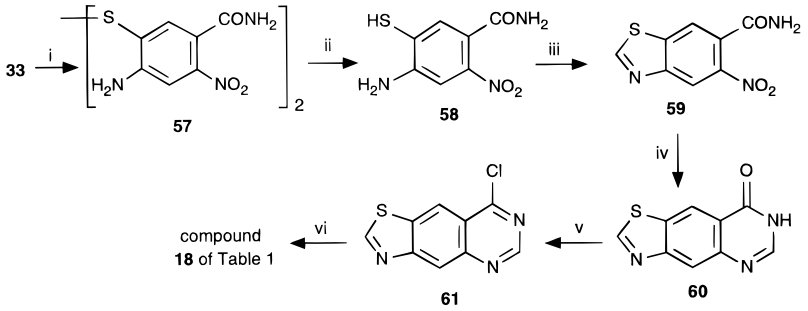
The 1*H*-pyrazoloquinazolines **19** and **20**, the pyrroloquinazolines **21** and **22**, and the benzo[*g*]quinazoline **23** were prepared from the known[18−21] pyrazoloquinazolinones **62** and **63**, pyrroloquinazolinones **64** and **65**, and benzo[*g*]quinazolin-4(3*H*)-one (**66**) by reaction with $POCl_3$, to give the corresponding 4-chloroquinazolines in poor yields, followed by usual condensation with 3-bromoaniline (Scheme 8).

Results and Discussion

The structures and physicochemical properties of the compounds prepared are given in Table 1. All the analogues were evaluated for their ability to inhibit tyrosine phosphorylation of a polypeptide (a portion of phospholipase C-γ1) by EGF-stimulated full-length EGFR enzyme isolated from A431 cells.[1] Full dose−response curves were determined for each compound, and the resulting IC_{50}s listed in Table 1 are the average of at least two such determinations.

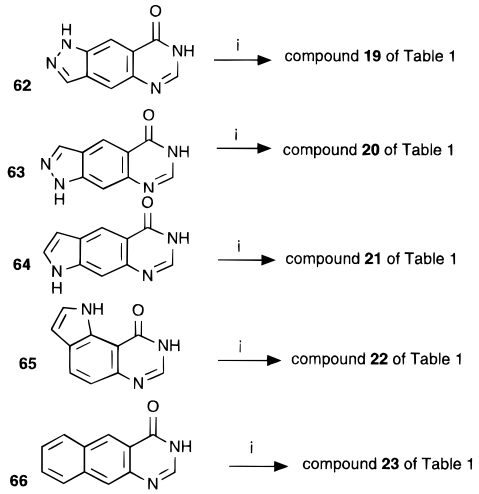
SAR previously derived[2,5] for substituted quinazolines suggested the utility of electron-donating substituents

Scheme 7[a]



[a] (i) NaSH/MeOH/THF/20 °C; (ii) $NaBH_4$/MeOH/20 °C/10 min; (iii) HCO_2H/reflux/2 h; (iv) Pd/C/H_2/MeOH, then $CH(OEt)_3$/reflux/18 h; (v) $POCl_3$/reflux/3 h; (vi) 3-bromoaniline/HCl (trace)/*i*-PrOH−THF/reflux/45 min.

Scheme 8[a]



[a] (i) $POCl_3$ (reflux/18 h for **62**, **63**, 105 °C/4 h for **64**, 60 °C/5 h for **65**, reflux/3 h for **66**), then 3-bromoaniline/HCl (trace)/*i*-PrOH/reflux/30 min.

at the 6- and/or 7-positions, with both 6,7-$(OH)_2$ (**6**) and 6,7-$(NH_2)_2$ (**7**) analogues showing high potency (IC_{50}s ca. 0.1 nM) (Table 1). However, the 6,7-$(OMe)_2$ derivative (**4**) was even more potent (IC_{50} 0.025 nM), raising the issue of whether protection of the amino functions of **2** without increasing steric bulk (which has been shown[5] to be disadvantageous in the quinazoline series) would also result in increased potency. Thus the first class of tricyclic analogues studied here were the imidazoquinazolines, where the amino groups are bridged to form the third ring. Although these nitrogen atoms are not as powerfully electron-donating as free amino groups, parent compound (**8**) was indeed a very potent inhibitor, with an IC_{50} of 0.008 nM. The isomeric methyl derivatives (**10** and **12**) were much less water-soluble but only slightly less active (IC_{50}s 0.01 and 0.025 nM respectively), suggesting some bulk tolerance at these positions. The corresponding *N*-[(dimethylamino)-ethyl] derivatives **11** and **13** were therefore also prepared, as potentially more soluble analogues. While these compounds were substantially less effective (IC_{50}s 1.3 and 22 nM, respectively) they were of the same rank order. It is not known whether this is due to simple bulk intolerance to these much larger groups, or to the presence of the cationic side chain. An analogue of **13** bearing a 9-chloro substituent (**14**) was 10-fold less potent, bearing out previous SAR for 5-substituted quinazolines.[2] The 2-methyl analogue **9** was considerably less potent than either the 1- or 3-methyl analogues (IC_{50} 0.29 nM), suggesting less bulk tolerance at this position.

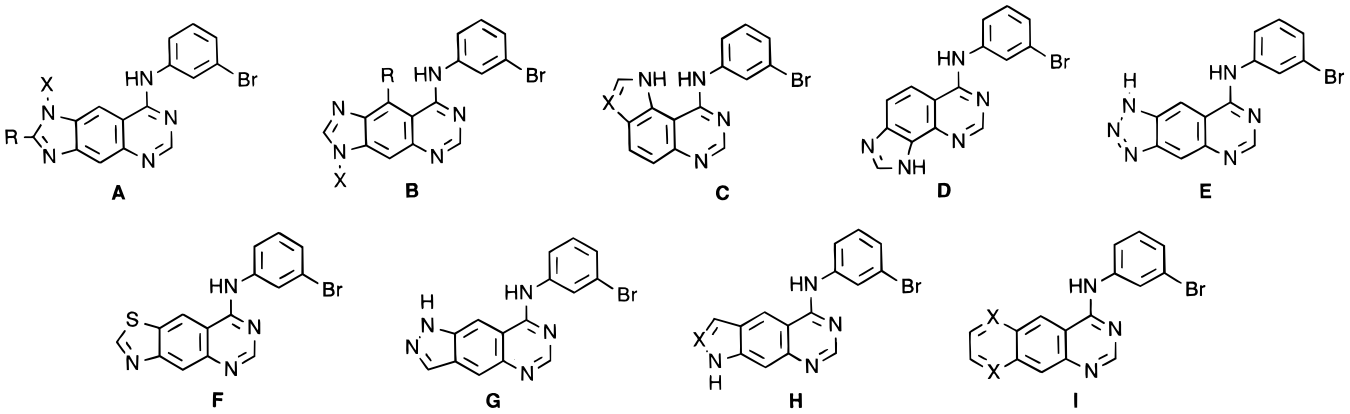
The two angular imidazoquinazolines (**15** and **16**) were also much less effective inhibitors (IC_{50}s 29 and 272 nM) than the linear isomer. Overall, the SAR of the imidazoquinazolines is similar to that of the related dimethoxyquinazolines.[5] The linear imidazo[4,5-*g*]-quinazoline **8** and the 6,7-dimethoxyquinazoline **4** are the most potent members of each series (IC_{50}s 0.008 and 0.025 nM respectively), with the imidazo[4,5-*f*] and 5,6-dimethoxy isomers (**15** and **6**) (IC_{50}s 29 and 1370 nM, respectively) being much less effective, and the imidazo-[4,5-*h*] and 7,8-dimethoxy isomers **16** and **7** a further 10-fold less potent (IC_{50}s 272 and $>10^4$ nM, respectively). However, within each geometrical isomer pattern the imidazoquinazolines are more potent than the analogous dimethoxyquinazolines, suggesting that the planarity and/or aromaticity of the molecule also appears to be important.

Two other linear tricyclic ring systems of similar geometry to **8** were also studied (the triazolo- and thiazoloquinazolines **17** and **18**) but were much less effective (IC_{50}s 4 and 41 nM, respectively). In these compounds the third ring is more electron-deficient than the imidazoloquinazolines, suggesting that the degree of electron release to the B ring is relevant to activity. This is consistent with other data[22] showing that pyrido-[4,3-*d*]pyrimidines (6-azaquinazolines), also possessing more electron-deficient B rings, are generally less potent inhibitors of the EGFR than the analogous quinazolines. The linear pyrazoloquinazolines (**19** and **20**) and the pyrroloquinazoline (**21**) (the latter of which at least also has a more electron-rich B ring) were in contrast much more potent (IC_{50}s of 0.3−0.4 nM). In the case of the pyrroloquinazoline **21**, the isomeric angular analogue (**22**) was significantly less effective, paralleling the results seen above with the angular imidazoquinazoline **15**.

Finally, two compounds (**23** and **24**) with 6-membered C rings were also evaluated. The benzoquinazoline **23** appeared to be a very potent compound (IC_{50} ca 0.003 nM), but was very insoluble. It showed a nearly flat dose−response curve, and test results were difficult to duplicate. However, the more soluble pyrazino analogue was also a potent inhibitor (IC_{50} 1.7 nM), albeit much less effective than **8**.

In order to evaluate the selectivity of these compounds for EGFR, the linear imidazoquinazoline **8** was examined for its ability to inhibit a panel of kinases. The data in Table 2 show that **8** is *more than 10^6-fold*

Table 1. Physicochemical and Enzyme Inhibitory Data for Tricyclic Anilinoquinazoline Derivatives



no.	form.	X	R	mp (°C)	formula	analyses	IC_{50}[a] (nM)
				Anilinoquinazolines			
1		H		ref 2			27
2		6,7-$(NH_2)_2$		ref 2			0.12
3		6,7-$(OH)_2$		ref 2			0.17
4		6,7-$(OMe)_2$		ref 2			0.025
5		6,7-OCH_2O		ref 5			15
6		5,6-$(OMe)_2$		ref 5			1370
7		7,8-$(OMe)_2$		ref 5			>10000
				Imidazoquinazolines			
8	A	H	H	369	$C_{15}H_{11}BrClN_5$	C,H,N,Br	0.008
9	A	H	Me	332−335	$C_{16}H_{12}BrN_5$	C,H,N	0.29
10	A	Me	H	322−325	$C_{16}H_{12}BrN_5 \cdot HCl$	C,H,N,Cl	0.010[b]
11	A	$(CH_2)_2NMe_2$	H	220−230 dec	$C_{19}H_{19}BrN_6 \cdot 2HCl \cdot H_2O$	C,H,N	1.32
12	B	Me	H	312−313.5	$C_{16}H_{12}BrN_5$	C,H,N	0.025
13	B	$(CH_2)_2NMe_2$	H	274−275.5	$C_{19}H_{19}BrN_6$	C,H,N	22
14	B	$(CH_2)_2NMe_2$	Cl	182−183	$C_{19}H_{18}BrClN_6$	C,H,N	203
15	C	N		335−337	$C_{15}H_{10}BrN_5$	C,H,N	29
16	D			327−331	$C_{15}H_{12}BrN_5 \cdot HCl$	C,H,N,Cl	272
				Triazoloquinazoline			
17	E			>390	$C_{14}H_9BrN_6 \cdot HCl$	C,H,N,Cl	4.1
				Thiazoloquinazoline			
18	F			302−304	$C_{15}H_9BrN_4S$	C,H,N,S	44
				Pyrazoloquinazolines			
19	G			328−330	$C_{15}H_{10}BrN_5$	C,H,N	0.34
20	H	N		305−306	$C_{15}H_{10}BrN_5 \cdot H_2O$	C,H,N	0.44
				Pyrroloquinazolines			
21	H	CH		273	$C_{16}H_{11}N_4Br$	C,H,N	0.44
22	C	CH		130−134	$C_{16}H_{11}N_4Br$	C,H,N	1.24
				Benzoquinazoline			
23	I	CH		233	$C_{18}H_{12}N_3Br \cdot 0.25H_2O$	C,H,N	0.003[b]
				Pyrazinoquinazoline			
24	I	N		242.5−244.5	$C_{16}H_{10}BrN_5$	C,H,N	1.7

[a] IC_{50}: concentration of drug (nM) to inhibit the phosphorylation of a 14-residue fragment of phospholipase C-γ1 by EGFR (prepared from human A431 carcinoma cell vesicles by immunoaffinity chromatography). See the Experimental Section for details. Values are the averages from at least two independent dose−response curves; variation was generally ±15%. [b] Value approximate due to insolubility of compound.

selective for EGFR compared with all the other kinases tested. This is remarkable for compounds which inhibit at the ATP binding site, which is not only one of the most conserved areas in the kinases, but also a ubiquitous structural feature of all ATP-utilizing enzymes. We also examined both the potency and the selectivity of **8** in cellular assays. As found previously with the quinazolines,[1] **8** is a potent inhibitor of autophosphorylation of the EGFR in EGF-stimulated A431 cells (IC_{50} 46 nM) (albeit much less potent than against the isolated enzyme), showing instantaneous inhibition and requiring no preincubation (Figure 1).

Compound **8** shows a similar level of potency in blocking EGF-induced mitogenesis mediated in Swiss 3T3 cells, and a similarly high level of selectivity for EGF compared with blockade of EGF compared with PDGF or FGF stimulus (Table 3). This enormous selectivity for blockade of EGF-stimulated mitogenesis demonstrates that **8** has essentially no effect on any of the many other components of the mitogenic pathway at its effective dose.

Conclusions

These studies show that the linear imidazolo-, pyrazolo-, and pyrroloquinazolines (**8** and **19**−**21**) are the most potent of a series of tricyclic analogues of the 4-[(3-bromophenyl)amino]quinazolines developed as inhibitors of the tyrosine kinase activity of the EGFR. Other linear tricyclic nuclei (triazolo-, thiazolo-, and pyrazinoquinazolines), which result in less electron-rich B rings, were less effective. In the imidazolo- and pyrroloquinazoline series, the corresponding angular iso-

Table 2. Inhibition of Protein Kinase Enzymes by **8**

kinase	IC_{50}[a] (nM)	kinase	IC_{50}[a] (nM)
EGFR	0.008	v-*src*	>50000
PDGFR	>50000	c-*src*	>50000
FGFR	>50000	PKC	>50000
insulin receptor	>50000		

[a] For details of IC_{50} determination, see the Experimental Section.

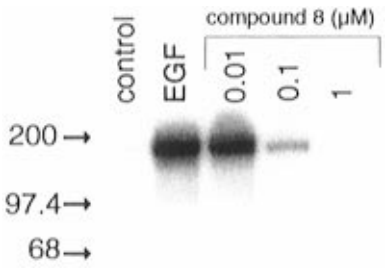


Figure 1. Effect of **8** on EGF receptor autophosphorylation in A431 human epidermoid cells (see the Experimental Section for details).

Table 3. Blockade of Growth Factor Mediated Mitogenesis in Swiss 3T3 Cells by **8**

mitogen	cellular IC_{50}[a] (nM)
EGF	46
PDGF	>50000
b-FGF	>50000

[a] For details of IC_{50} determination, see the Experimental Section.

mers were much less effective than the linear ones. These results are consistent with SAR studies previously developed for the 4-[(3-bromophenyl)amino]quinazolines, which suggested that small electron-donating substituents at the 6- and 7-positions were desirable for high potency, as exemplified by the 6,7-dimethoxy derivative **7**. During the course of this work, a series of related compounds was reported, some of which are also potent inhibitors of the EGFR enzyme.[23] Cellular studies of the linear imidazoloquinazoline **8** show that it is an immediate, potent, and very selective inhibitor of EGFR autophosphorylation and EGF-stimulated mitogenesis. Its potency, selectivity, onset, and mechanism of action strongly distinguishes it from other classes of EGFR inhibitors such as the tyrphostins.

Experimental Section

Analyses were performed by the Microchemical Laboratory, University of Otago, Dunedin, NZ, or by Parke-Davis Pharmaceutical Research Analytical Department. Melting points were determined using Electrothermal Model 9200 or Gallenkamp digital melting point instruments, and are as read. NMR spectra were measured on Bruker AC-200 or DRX-400 or Varian Unity 400 NMR spectrometers, and referenced to Me_4Si. Mass spectra were recorded on a Varian VG 7070 spectrometer at nominal 5000 resolution or a Fisons VG Trio-2A spectrometer. Reaction solvents were reagent grade or distilled-in-glass and were stored over activated 3A (for lower alcohols) or 4A molecular sieves.

8-[(3-Bromophenyl)amino]-1*H*-imidazo[4,5-*g*]quinazoline (8): Scheme 1. Method A. A mixture of 8-(methylthio)-1*H*-imidazo[4,5-*g*]quinazoline[11] (**25**) (0.5 g, 2.31 mmol), 3-bromoaniline (0.35 g, 2.0 mmol), and 3-bromoaniline hydrochloride (0.4 g, 1.9 mmol) in 2-propanol (200 mL) was heated under reflux for 1 h to give a precipitate of 8-[(3-bromophenyl)amino]-1*H*-imidazo[4,5-*g*]quinazoline hydrochloride (**8**) (0.63 g, 72%): mp (MeOH) 369 °C dec; ^{1}H NMR [$(CD_3)_2SO$] δ 9.93 (br s, 1 H, NH), 9.01 (s, 1 H), 8.66 (s, 2 H), 8.39 (s, 1 H), 8.04 (m, 2 H, H-2′,6′), 7.39 (t, J = 7.9 Hz, 1 H, H-5′), 7.31 (br d, J = 8.0 Hz, 1 H, H-4′). Anal. ($C_{15}H_{11}BrClN_5$) C, H, N, Br, Cl.

Method B. A mixture of 2-amino-4-fluorobenzoic acid[24] (6.3 g, 41 mmol) and formamidine acetate (8.5 g, 82 mmol) in 2-methoxyethanol (40 mL) was heated under reflux for 18 h, and the solution was concentrated. The residue was diluted with 0.01 M ammonia, and the product was collected, washed with water, and dried to give 7-fluoroquinazolin-4(3*H*)-one[12] (**26**) (6.0 g, 90%): mp 235−237 °C (lit.[12] mp 230−233 °C); ^{1}H NMR [$(CD_3)_2SO$] δ 12.4 (br s, 1 H, NH), 8.20 (dd, J = 8.8, 6.3 Hz, 1 H, H-5), 8.17 (s, 1 H, H-2), 7.46 (dd, J = 10.1, 2.5 Hz, 1 H, H-8), and 7.40 (td, J = 8.8, 2.6 Hz, 1 H, H-6); ^{13}C NMR δ 165.5 (ds, J_{C-F} = 250.9 Hz, C-7), 160.0 (s, CO), 150.9 (d, J_{C-F} = 13.1 Hz), 146.8 (s, C-2), 128.9 (dd, J_{C-F} = 11.0 Hz, C-5), 119.6 (s, C), 115.2 (dd, J_{C-F} = 23.5 Hz), 112.2 (dd, J_{C-F} = 21.6 Hz).

A solution of **26** (47.4 g, 0.29 mmol) in concentrated H_2SO_4 (100 mL) and fuming HNO_3 (100 mL) was heated at 100 °C for 1 h. After cooling the solution was poured onto ice−water (1.5 L) to give a mixture of 6- and 8-nitroquinazolin-4(3*H*)-ones (54.5 g, 90%). Recrystallization from AcOH gave pure 7-fluoro-6-nitroquinazolin-4(3*H*)-one (**27**) (33.7 g, 56%): mp 283−285 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 12.80 (br s, 1 H, NH), 8.73 (d, J_{H-F} = 8.3 Hz, 1 H, H-5), 8.32 (s, 1 H, H-2), 7.78 (dd, J_{H-F} = 12.4 Hz, 1 H, H-8); ^{13}C NMR δ 159.2 (s, CO), 157.5 (d, J_{C-F} = 265.7 Hz, C-7), 154.0 (d, J_{C-F} = 13.3 Hz, C), 149.9 (d), 135.3 (d, J_{C-F} = 9.7 Hz), 125.4 (d), 119.2 (d, J_{C-F} = 1.6 Hz), 115.6 (d, J_{C-F} = 21.4 Hz, C-8). Anal. ($C_8H_4FN_3O_3$) C, H, N, F.

A suspension of **27** (10.45 g, 50 mmol) in $SOCl_2$ (200 mL) containing 3 drops of DMF was heated under reflux for 3 h to give a clear solution. The $SOCl_2$ was removed under reduced pressure to give crude 4-chloro-7-fluoro-6-nitroquinazoline, which was used directly [^{1}H NMR ($CDCl_3$) δ 9.18 (s, 1 H, H-2), 9.05 (d, J_{H-F} = 7.6 Hz, 1 H, H-5), and 7.96 (d, J_{H-F} = 10.7 Hz, 1 H, H-8)]. The crude chloro compound was dissolved in 100 mL of CH_2Cl_2, and a solution of 3-bromoaniline (10.5 g, 55 mmol) in *i*-PrOH (250 mL) was added. The resulting mixture was stirred at room temperature for 15 min when a precipitate of product hydrochloride formed. After a further 15 min sufficient hexane was added to ensure complete precipitation, and the solid was collected by filtration and dissolved in aqueous MeOH. Neutralization with Et_3N and further dilution with water gave 4-[(3-bromophenyl)amino]-7-fluoro-6-nitroquinazoline (**28**) (16.0 g, 88%): mp (MeOH) 197−199 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.48 (br s, 1 H, NH), 9.61 (d, J_{H-F} = 8.0 Hz, 1 H, H-5), 8.75 (s, 1 H, H-2), 8.15 (br s, 1 H, H-2′), 7.87 (dd, J = 8.9, 2.2 Hz, 1 H, H-6′), 7.84 (d, J_{H-F} = 12.5 Hz, 1 H, H-8), 7.41−7.35 (m, 2 H, H-4′,5′). Anal. ($C_{14}H_8BrN_4O_2$) C, H, N.

When the above reaction mixture was heated, or allowed to stir at room temperature for a longer period of time, it was possible to isolate a less soluble byproduct which was identified as 4,7-bis[(3-bromophenyl)amino]-6-nitroquinazoline (**30**): mp (MeOH) 251−252 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.30 (br s, 1 H, NH), 9.52 (s, 1 H, H-5), 9.29 (s, 1 H, NH), 8.52 (s, 1 H, H-2), 8.18 (br s, 1 H, H-2′), 7.88 (br d, 1 H, H-6′), 7.61 (br s, 1 H, H-2″), 7.89−7.32 (m, 5 H, H-4′,5′,4″,5″,6″), 7.22 (s, 1 H, H-8). Anal. ($C_{20}H_{13}Br_2N_5O_2$) C, H, N, Br.

A suspension of **28** (1.82 g, 5 mmol) in 2-propanol (150 mL) was saturated with NH_3 gas, and the mixture was heated in a sealed pressure vessel at 100 °C for 8 h. After cooling, the solid was collected and washed with MeOH to give 7-amino-4-[(3-bromophenyl)amino]-6-nitroquinazoline (**29**) (1.74 g, 96%), identical with an authentic sample.[2] Reduction of **29** with Fe/HCl as previously described [2] gave 4-[(3-bromophenyl)amino]-6,7-diaminoquinazoline (**2**).

A solution of **2** (0.10 g, 0.30 mmol) in formic acid (5 mL) was heated under reflux for 1 h, and the excess formic acid was removed under reduced pressure. The residue was dissolved in EtOH, and the solution was basified with concentrated ammonia, diluted with water, concentrated, and cooled to give 8-[(3-bromophenyl)amino]-1*H*-imidazo[4,5-*g*]quinazoline (**8**) (0.07 g, 68%): mp (MeOH) 334−335 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 12.93 (br s, 1 H, NH), 9.90 (br s, 1 H, NH), 8.99 (br s, 1 H, H-4 or H-9), 8.63 (s, 2 H, H-2 and H-6), 8.38 (br s, 1 H, H-2′), 8.03 (d, J = 8.0 Hz, 1 H, H-6′), 7.98 (br s, 1

H, H-4 or H-9), 7.38 (t, J = 8.0 Hz, 1 H, H-5′), 7.30 (d, J = 7.9 Hz, 1 H, H-4′); ^{13}C NMR δ 158.0 (s), 152.0 (d), 147.6 (d), 145.2 (s), 142.8 (br s), 141.4 (s), 138.3 (br s), 130.3 (d), 125.5 (d), 123.83 (d), 121.1 (d), 120.4 (d), 111.9 (br s), 111.1 (s), 107.7 (br d). Anal. ($C_{15}H_{10}BrN_5$) C, H, N.

8-[(3-Bromophenyl)amino]-2-methyl-1*H*-imidazo[4,5-*g*]quinazoline (9): Scheme 1. A solution of **29** (1.62 g, 4.5 mmol) in a mixture of AcOH (100 mL) and Ac_2O (50 mL) was heated under reflux for 12 h. After cooling the excess Ac_2O was hydrolyzed by the addition of water (50 mL), and the mixture was evaporated to dryness. The solid residue was washed with water and recrystallized from EtOH/water to give 7-acetamido-4-[(3-bromophenyl)amino]-6-nitroquinazoline (**31**) (1.46 g, 81%), identical with an authentic sample.[2] A mixture of **31** (1.21 g, 3 mmol) and Fe powder (0.5 g, 9 mmol) in AcOH (50 mL) was heated under reflux for 30 min, and the mixture was filtered to remove insolubles. The AcOH was removed under reduced pressure, the residue was dissolved in EtOH, and the solution was basified with concentrated ammonia solution. After filtering through Celite, the solution was concentrated and diluted with water to give a solid which was collected, dried, and extracted with EtOAc/EtOH to remove remaining Fe residues and give 8-[(3-bromophenyl)amino]-2-methyl-1*H*-imidazo[4,5-*g*]quinazoline (**9**) (0.66 g, 62%): mp (MeOH) 332−335 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 12.67 (br, 1 H, NH), 9.81 (s, 1 H, NH), 8.78 (br, 1 H, H-4 or H-9), 8.57 (s, 1 H, H-6), 8.33 (br s, 1 H, H-2′), 7.99 (br d, J = 7.9 Hz, 1 H, H-6′), 7.79 (br, 1 H, H-4 or H-9), 7.36 (t, J = 8.0 Hz, 1 H, H-5′), 7.28 (br d, J = 8.9 Hz, 1 H, H-4′). Anal. ($C_{16}H_{12}BrN_5$) C, H, N.

8-[(3-Bromophenyl)amino]-1-methyl-1*H*-imidazo[4,5-*g*]quinazoline (10): Scheme 2. A solution of 5-chloro-2,4-dinitrobenzamide[14] (**33**) (6.14 g, 25 mmol) and 40% aqueous methylamine (20 mL) in EtOH (80 mL) was heated in a sealed pressure vessel at 100 °C for 2 h. After cooling, dilution with water gave 2,4-dinitro-5-(methylamino)benzamide (**34a**) (5.89 g, 98%): mp (EtOH), 278−280.5 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.88 (q, J = 4.9 Hz, 1 H, NH), 8.76 (s, 1 H, H-3), 8.07 & 7.77 (2xs, 2 H, NH_2), 6.98 (s, 1 H, H-6), 3.07 (d, J = 5.0 Hz, NCH_3); ^{13}C NMR δ 166.7 (s, CO), 147.9 (s), 140.0 (s), 132.5 (s), 128.8 (s), 124.6 (d), 114.0 (d), 30.2 (q). Anal. ($C_8H_8N_4O_5$), C, H, N.

A suspension of **34a** (4.80 g, 20 mmol) in EtOH containing formic acid (2.5 mL, 66 mmol) was hydrogenated over 5% Pd/C, and the solvent was removed under reduced pressure. The resulting crude salt of the triamine **35a** was dissolved in formic acid (100 mL), and the mixture was heated under reflux for 2 h. The formic acid was removed under reduced pressure, and the residue was dissolved in the minimum volume of 0.1 M HCl. After clarification with charcoal and filtration through Celite, the aqueous solution was neutralized with dilute aqueous ammonia and allowed to stand overnight to give 1-methyl-1*H*-imidazo[4,5-*g*]quinazolin-8(7*H*)-one (**36a**) (2.99 g, 75%): mp (EtOH), 345−352 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.91 (br s, 1 H, NH), 8.50 (s, 1 H), 8.33 (s, 1 H), 8.00 (s, 1 H), 7.89 (s, 1 H), 3.95 (s, 3 H, NCH_3). Anal. ($C_{10}H_8N_4O$) C, H, N.

A mixture of **36a** (2.50 g, 12.5 mmol) and P_2S_5 (5.55 g, 25 mmol) in pyridine (30 mL) was heated under reflux for 16 h, and the pyridine was removed under reduced pressure. The residue was treated with boiling water (50 mL), and the resulting yellow precipitate was collected by filtration and dissolved in 0.1 M KOH solution. After filtration to remove insolubles, the solution was neutralized with NH_4Cl to give 1-methyl-1*H*-imidazo[4,5-*g*]quinazoline-8(7*H*)-thione (**37a**) (1.58 g, 59%): mp (EtOH) 376 °C dec; ^{1}H NMR [$(CD_3)_2SO$] δ 13.65 (br s, 1 H, NH), 8.76 (s, 1 H), 8.61 (s, 1 H), 8.11 (s, 1 H), 7.98 (s, 1 H), 3.99 (s, 3 H, NCH_3); ^{13}C NMR δ 185.7 (s, CS), 151.0 (d), 149.0 (s), 140.8 (d), 139.3 (s), 135.7 (s), 124.5 (s), 116.6 (d), 109.9 (d), 31.2 (q). Anal. ($C_{10}H_8N_4S$) C, H, N, S.

A solution of **37a** (1.08 g, 5 mmol) and KOH (0.40 g, 7 mmol) in 50% aqueous MeOH (100 mL) was treated with MeI (0.33 mL, 5.3 mmol), and the resulting mixture was stirred at room temperature for 1 h. The methanol was then removed under reduced pressure, and the residual aqueous solution was kept at 5 °C overnight to give crystals of 1-methyl-8-(methylthio)-1*H*-imidazo[4,5-*g*]quinazoline (**38a**) (0.62 g, 54%): ^{1}H NMR [$(CD_3)_2SO$] δ 8.93 (s, 1 H), 8.67 (s, 1 H), 8.22 (s, 1 H), 8.21 (s, 1 H), 4.01 (s, 3 H, NCH_3), 2.74 (s, 3 H, SCH_3). Anal. ($C_{11}H_{10}N_4S$) C, H, N.

A mixture of **38a** (0.3 g, 1.3 mmol), 3-bromoaniline (0.34 g, 1.95 mmol), and 3-bromoaniline hydrochloride (0.41 g, 1.95 mmol) in *i*-PrOH (400 mL) was heated under reflux for 6 h. After cooling the precipitated solid was collected by filtration and recrystallized from EtOH to give 8-[(3-bromophenyl)-amino]-1-methyl-1*H*-imidazo[4,5-*g*]quinazoline (**10**) as the hydrochloride salt (0.43 g, 85%): mp 322−325 °C; ^{1}H NMR [free base in $(CD_3)_2SO$] δ 9.86 (br s, 1 H, NH), 8.77 (s, 1 H), 8.60 (s, 2 H), 8.30 (br s, 1 H), 8.06 (s, 1 H), 8.00 (d, J = 7.9 Hz, H, H-6′), 7.39 (t, J = 8.0 Hz, 1 H, H-5′), 7.32 (d, J = 8.4 Hz, 1 H, H-4′), 3.99 (s, 3 H, CH_3); ^{13}C NMR δ 157.7 (s), 151.6 (d), 150.6 (d), 147.6 (s), 144.5 (s), 141.3 (s), 134.8 (s), 130.4 (d), 125.8 (d), 124.0 (d), 121.2 (s), 120.5 (d), 115.7 (d), 111.4 (s, 102.6 (d), 31.18 (q)). Anal. ($C_{16}H_{12}BrN_5$·HCl) C, H, N, Cl.

8-[(3-Bromophenyl)amino]-1-[2-(dimethylamino)ethyl]-1*H*-imidazo[4,5-*g*]quinazoline (11): Scheme 2. A mixture of **33** (6.14 g, 25 mmol) and *N*,*N*-dimethylethylenediamine (5.5 mL) in EtOH (100 mL) was heated under reflux for 15 min, cooled, and diluted with water to give 5-{[2-(dimethylamino)-ethyl]amino}-2,4-dinitrobenzamide (**34b**) (6.38 g, 86%): mp (EtOH) 185−187 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.90 (t, J = 4.6 Hz, 1 H, NH), 8.76 (s, 1 H, H-3), 8.08 (br s, 1 H, NH), 7.06 (s, 1 H, H-6), 3.54 (q, J = 5.8 Hz, 2 H, CH_2), 2.56 (t, J = 6.1 Hz, 2 H, CH_2), 2.23 (s, 6 H, CH_3); ^{13}C NMR δ 166.6 (s), 147.1 (s), 140.0 (s), 132.7 (s), 128.8 (s), 124.7 (d), 114.6 (d), 56.3 (t), 44.8 (q), 40.4 (q). Anal. ($C_{11}H_{15}N_5O_5$) C, H, N.

A mixture of **34b** (5.95 g (20 mmol) and HCO_2H (5 mL) in MeOH (100 mL) was hydrogenated over Pd/C for 2 days to give a colorless solution. The MeOH was removed under reduced pressure, the residue was dissolved in HCO_2H (200 mL), and the resulting solution was heated under reflux for 4 h. The HCO_2H was removed under reduced pressure, and the oily residue was dissolved in water, decolorized with charcoal, filtered through Celite, and basified with concentrated ammonia. The solution was evaporated to dryness, and the residue was extracted with hot EtOAc to give 1-[2-(dimethylamino)ethyl]-1*H*-imidazo[4,5-*g*]quinazolin-8(7*H*)-one (**36b**) (4.38 g, 85%): mp (EtOAc) 238−239 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 12.06 (br s, 1 H, NH), 8.53 (s, 1 H), 8.39 (s, 1 H), 8.00 (s, 1 H), 7.90 (s, 1 H), 4.47 (t, J = 6.1 Hz, 2 H, CH_2), 2.67 (t, J = 6.1 Hz, 2 H, CH_2), 2.19 (s, 6 H, CH_3); ^{13}C NMR δ 161.4 (s), 149.4 (d), 148.0 (s), 143.3 (s), 142.5 (d), 133.5 (s), 118.1 (s), 116.1 (d), 107.0 (s), 57.9 (t), 45.1 (q), 42.4 (t). Anal. ($C_{13}H_{15}N_5O$) C, H, N.

A mixture of **36b** (2.57 g, 10 mmol) and P_2S_5 (4.44 g, 20 mmol) in pyridine (25 mL) was heated under reflux for 18 h. The pyridine was removed under reduced pressure, and the residue was treated with boiling water, basified with Et_3N, and filtered. The solid precipitate was extracted with 1 M HCl, and the resulting solution was then basified with Et_3N and combined with the original filtrate. The mixture was evaporated, and the oily residue was extracted with hot EtOAc. Evaporation of the solvent gave 1-[2-(dimethylamino)ethyl]-1*H*-imidazo[4,5-*g*]quinazoline-8(7*H*)-thione (**37b**) as an oil (1.50 g, 55%) which was used without further purification: ^{1}H NMR [$(CD_3)_2SO$] δ 13.64 (br s, 1 H, NH), 8.83 (s, 1 H), 8.63 (s, 1 H), 8.10 (s, 1 H), 7.98 (s, 1 H), 4.50 (t, J = 6.0 Hz, 2 H, CH_2), 2.73 (t, J = 6.0 Hz, 2 H, CH_2), 2.22 (s, 6 H, CH_3). Hydrochloride salt, mp (MeOH) 292 °C dec. Anal. ($C_{13}H_{15}N_5S$·HCl·0.5H_2O) C, H, N.

Crude **37b** (1.40 g, 5 mmol) was treated with KOH/MeI in 50% aqueous MeOH to give 1-[2-(dimethylamino)ethyl]-8-(methylthio)-1*H*-imidazo[4,5-*g*]quinazoline (**38b**) (0.18 g, 12%) which was used without further purification. A sample was chromatographed on silica gel, eluting with CH_2Cl_2/MeOH (98:2), to give pure material as an oil: ^{1}H NMR [$(CD_3)_2SO$] δ 8.92 (s, 1 H), 8.68 (s, 1 H), 8.33 (s, 1 H), 8.20 (s, 1 H), 4.54 (t, J = 5.9 Hz, 2 H, CH_2), 2.74 (s, 3 H, SCH_3), 2.70 (t, J = 5.9 Hz, 2 H, CH_2), 2.21 (s, 6 H, NCH_3); HREIMS found M^+ 287.1195, calculated for $C_{14}H_{17}N_5S$ 287.1205.

Reaction of crude **38b** (0.18 g, 0.63 mmol) with 3-bromoaniline and 3-bromoaniline hydrochloride in 2-propanol as above, followed by chromatography on SiO_2, eluting with CH_2Cl_2/MeOH (95:5), gave 8-[(3-bromophenyl)amino]-1-[2-(dimeth-

ylamino)ethyl]-1*H*-imidazo[4,5-*g*]quinazoline (**11**) (0.18 g, 70%). Dihydrochloride salt: mp (EtOH) 220−230 °C dec; ^{1}H NMR [free base in $(CD_3)_2SO$] δ 9.80 (br s, 1 H, NH), 8.81 (s, 1 H), 8.63 (s, 1 H), 8.60 (s, 1 H), 8.25 (br s, 1 H, H-2′), 8.06 (s, 1 H), 7.97 (br d, J = 7.3 Hz, 1 H, H-6′), 7.40 (t, J = 8.0 Hz, 1 H, H-5′), 7.32 (br d, J = 8.3 Hz, 1 H, H-4′), 4.47 (t, J = 6.1 Hz, 2 H, CH_2), 2.79 (t, J = 6.1 Hz, 2 H, CH_2), 2.22 (s, 6 H, CH_3). Anal. ($C_{19}H_{19}BrN_6 \cdot 2HCl \cdot H_2O$) C, H, N.

8-[(3-Bromophenyl)amino]-3-methyl-3*H*-imidazo[4,5-*g*]quinazoline (12): Scheme 3. Method A. Reaction of 3-methyl-3*H*-imidazo[4,5-*g*]quinazolin-8(7*H*)-one[15] (**39**) with P_2S_5 in pyridine as above gave 3-methyl-3*H*-imidazo[4,5-*g*]quinazoline-8(7*H*)-thione (**40**) (88%): mp (AcOH) > 380 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.91 (s, 1 H), 8.53 (s, 1 H), 8.12 (s, 1 H), 7.91 (s, 1 H), 3.93 (s, 3 H, NCH_3). Anal. ($C_{10}H_8N_4S$) C, H, N, S. Treatment of **40** with MeI/KOH as above gave 3-methyl-8-(methylthio)-3*H*-imidazo[4,5-*g*]quinazoline (**41**) (82%): mp (EtOH) 286−287.5 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.96 (s, 1 H), 8.64 (s, 1 H), 8.39 (s, 1 H), 8.16 (s, 1 H), 3.98 (s, 3 H, NCH_3), 2.74 (s, 3 H, SCH_3). Anal. ($C_{11}H_{10}N_4S$) C, H, N, S. Reaction of **41** with 3-bromoaniline hydrochloride in 2-propanol as above gave 8-[(3-bromophenyl)amino]-3-methyl-3*H*-imidazo[4,5-*g*]quinazoline (**12**) (52%): mp (MeOH) 312−313.5 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.86 (s, 1 H, NH), 9.02 (s, 1 H), 8.54 (s, 1 H), 8.37 (br s, 1 H, H-2′), 8.01 (m, 2 H, H-4 and H-6′), 7.36 (t, J = 8.0 Hz, 1 H, H-5′), 7.28 (br d, 1 H, H-4′), 3.96 (s, 3 H, NCH_3); ^{13}C NMR δ 158.1 (s), 152.4 (d), 149.8 (d), 145.4 (s), 143.0 (s), 141.4 (s), 139.2 (s), 130.3 (d), 125.6 (d), 123.9 (d), 121.2 (s), 120.4 (d), 112.4 (d), 110.9 (s), 106.4 (d), 31.0 (q). Anal. ($C_{16}H_{12}BrN_5$) C, H, N.

Method B. A mixture of **28** (1.09 g, 3 mmol) and 40% aqueous methylamine (10 mL, 0.115 mol) in 2-propanol (100 mL) was heated at 100 °C in a sealed pressure vessel for 4 h to give 4-[(3-bromophenyl)amino]-7-(methylamino)-6-nitroquinazoline (**42a**) (1.05 g, 94%), identical with an authentic sample.[5] Reduction of **42a** as previously described[5] gave 6-amino-4-[(3-bromophenyl)amino]-7-(methylamino)-6-nitroquinazoline (**43a**), which was treated with refluxing HCO_2H as above, to give 8-[(3-bromophenyl)amino]-3-methyl-3*H*-imidazo[4,5-*g*]quinazoline (**12**) identical in all respects to the compound prepared above.

8-[(3-Bromophenyl)amino]-3-[2-(dimethylamino)ethyl]-3*H*-imidazo[4,5-*g*]quinazoline (13): Scheme 3. A mixture of **28** (0.91 g, 25 mmol) and *N*,*N*-dimethylethylenediamine (0.88 g, 0.1 mol) in *i*-PrOH (50 mL) was heated under reflux for 15 min when a deep-red precipitate was obtained. After cooling, the solid was collected, washed with water, and dried to give 4-[(3-bromophenyl)amino]-7-{[2-(dimethylamino)ethyl]-amino}-6-nitroquinazoline (**42b**) (1.06 g, 98%): mp (*i*-PrOH) 226.5−228 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.21 (br s, 1 H, NH), 9.49 (s, 1 H, H-5), 8.49 (s, 1 H, H-2), 8.17 (br s, 1 H, H-2′), 8.04 (t, J = 4.3 Hz, 1 H, NH), 7.88 (br d, J = 7.3 Hz, 1 H, H-6′), 7.36 (t, J = 7.9 Hz, 1 H, H-5′), 7.31 (br d, J = 7.9 Hz, 1 H, H-4′), 3.39 (q, J = 5.7 Hz, 2 H, CH_2), 2.59 (t, J = 6.0 Hz, 2 H, CH_2), 2.25 (s, 6 Hz, CH_3). Anal. ($C_{18}H_{19}BrN_6O_2$), C, H, N.

A suspension of **42b** (1.51 g, 35 mmol) in MeOH (250 mL) was combined with $Na_2S \cdot 9H_2O$ (24.0 g, 0.1 mol) in H_2O (100 mL), and the resulting dark red solution was heated under reflux for 2 h to give a clear orange solution. Concentration of the solution and cooling gave 6-amino-4-[(3-bromophenyl)-amino]-7-{[(2-(dimethylamino)ethyl]amino}quinazoline (**43b**) (0.89 g, 64%): mp (CH_2Cl_2) 172.5−173.5 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.17 (br s, 1 H, NH), 8.31 (s, 1 H, H-2), 8.22 (t, J = 1.9 Hz, 1 H, H-2′), 7.85 (br d, J = 8.2 Hz, 1 H, H-6′), 7.30 (s, 1 H, H-5), 7.27 (t, J = 8.1 Hz, 1 H, H-5′), 7.16 (br d, J = 7.9 Hz, 1 H, H-4′), 6.62 (s, 1 H, H-8), 5.60 (t, J = 5.0 Hz, 1 H, NH), 5.18 (br s, 2 H, NH_2), 3.28 (q, J = 6.4 Hz, 2 H, CH_2), 2.57 (t, J = 6.6 Hz, 2 H, CH_2, 2.23 (s, 6 H, CH_3). Anal. ($C_{18}H_{19}BrN_6$) C, H, N.

A solution of **43b** (0.401 g, 1 mmol) in formic acid (40 mL) was heated under reflux for 1 h, and the formic acid was then removed under reduced pressure. The residue was dissolved in water and filtered, and the solution was basified with concentrated ammonia to give 8-[(3-bromophenyl)amino]-3-[2-(dimethylamino)ethyl]-3*H*-imidazo[4,5-*g*]quinazoline (**13**) (0.25 g, 61%): mp (EtOH) 274−275.5 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.87 (br s, 1 H, NH), 9.02 (s, 1 H), 8.62 (s, 1 H), 8.56 (s, 1 H), 8.37 (br s, 1 H, H-2′), 8.04 (s, 1 H), 8.01 (br d, 1 H, H-6′), 7.37 (t, J = 8.1 Hz, 1 H, H-5′), 7.29 (br d, J = 8.7 Hz, 1 H, H-4′), 4.47 (t, J = 6.1 Hz, 2 H, CH_2), 2.71 (t, J = 6.1 Hz, 2 H, CH_2), 2.20 (s, 6 H, CH_3); ^{13}C NMR δ 158.1 (s), 152.3 (d), 149.6 (d), 145.3 (s), 143.0 (s), 141.4 (s), 138.5 (s), 130.3 (d), 125.6 (d), 123.8 (d), 121.2 (s), 120.3 (d), 112.4 (d, C-9), 110.9 (s), 106.5 (d), 57.7 (t), 45.1 (q), 42.3 (q). Anal. ($C_{19}H_{19}BrN_6$) C, H, N. Trihydrochloride salt, mp 294 °C dec. Anal. ($C_{19}H_{19}BrN_6 \cdot 3HCl$) C, H, N.

8-[(3-Bromophenyl)amino]-9-chloro-3-[2-(dimethylamino)ethyl]-3*H*-imidazo[4,5-*g*]quinazoline (14): Scheme 3. When the reduction of **42b** was performed with either Fe dust and dilute HCl in 65% aqueous EtOH, or by hydrogenation over Pt on charcoal in acidic (HCl) methanol, a less soluble byproduct was isolated and identified as 6-amino-4-[(3-bromophenyl)amino]-5-chloro-7-{[2-(dimethylamino)ethyl]amino}-quinazoline (**43c**): mp (EtOAc) 165−166 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.27 (br s, 1 H, NH), 8.32 (s, 1 H, H-2), 8.14 (br s, 1 H, H-2′), 7.71 (br d, J = 8.1 Hz, 1 H, H-6′), 7.29 (t, J = 8.0 Hz, 1 H, H-5′), 7.21 (br d, J = 7.9 Hz, 1 H, H-4′), 6.64 (s, 1 H, H-8), 5.97 (t, J = 4.5 Hz, 1 H, NH), 5.71 (br s, 2 H, NH_2), 3.31 (q, J = 6.1 Hz, 2 H, CH_2), 2.56 (t, J = 6.4 Hz, 2 H, CH_2), 2.22 (s, 6 H, CH_3); ^{13}C NMR δ 153.5 (s), 150.4 (d), 147.0 (s), 142.0 (s), 141.3 (s), 133.8 (s), 130.2 (d), 124.8 (s), 123.0 (d), 121.3 (d), 119.8 (d), 105.3 (s), 104.4 (s), 101.6 (d), 56.9 (t), 45.2 (q), 41.1 (t); HREIMS found $M^{\bullet+}$ 434.06100/436.0598/438.0577, $C_{18}H_{20}BrClN_6$ requires 434.0621/436.0592/438.05714. Anal. ($C_{18}H_{20}BrClN_6$) C, H, N, Cl.

Reaction of **43c** with formic acid as above gave 8-[(3-bromophenyl)amino]-9-chloro-3-[2-(dimethylamino)ethyl]-3*H*-imidazo[4,5-*g*]quinazoline (**14**): mp (EtOH) 182−183 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.80 (br s, 1 H, NH), 8.63 (s, 1 H), 8.56 (s, 1 H), 8.22 (br s, 1 H, H-2′), 8.07 (s, 1 H), 7.82 (br d, J = 7.8 Hz, 1 H, H-6′), 7.37 (t, J = 7.9 Hz, 1 H, H-5′), 7.33 (br d, J = 8.0 Hz, 1 H, H-4′), 4.47 (t, J = 5.9 Hz, 2 H, CH_2), 2.70 (t, J = 5.9 Hz, 2 H, CH_2), 2.19 (s, 3 H, CH_3); ^{13}C NMR δ 156.9 (s), 151.9 (d), 150.0 (d), 147.1 (s), 141.1 (s), 140.3 (s), 137.8 (s), 130.4 (d), 126.2 (d), 124.1 (d), 121.3 (s), 120.8 (d), 117.3 (s, C-9), 108.4 (s), 106.5 (d), 57.7 (t), 45.0 (q), 42.5 (t). Anal. ($C_{19}H_{18}BrClN_6$) C, H, N.

9-[(3-Bromophenyl)amino]-1*H*-imidazo[4,5-*f*]quinazoline (15): Scheme 4. A solution of 1*H*-imidazo[4,5-*f*]quinazoline-9(8*H*)-thione[16] (**44**) (1.01 g, 5 mmol) and KOH (0.36 g, 6.5 mmol) in 50% MeOH/water (50 mL) was treated with MeI (0.34 mL), and the mixture was stirred overnight at room temperature. Solvent was removed under reduced pressure to give a precipitate of 9-(methylthio)-1*H*-imidazo[4,5-*f*]quinazoline (**45**) (0.61 g, 57%): mp (EtOAc) 235−237 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 13.23 (m, 1 H, NH), 9.05 (s, 1 H), 8.60 (s, 1 H), 8.24 (d, J = 8.7 Hz, 1 H), 7.81 (d, J = 8.9 Hz, 1 H), 2.71 (s, 3 H, SCH_3). Anal. ($C_{10}H_8N_4S$) C, H, N.

A solution of **45** (0.43 g, 2 mmol), 3-bromoaniline (0.5 g, 3 mmol), and 3-bromoaniline hydrochloride (0.63 g, 3 mmol) in 2-propanol was heated under reflux for 16 h, and the resulting precipitate was treated with aqueous NH_3 to give 9-[(3-bromophenyl)amino]-1*H*-imidazo[4,5-*f*]quinazoline (**15**) (0.52 g, 77%): mp (EtOH) 335−337 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.53 (s, 1 H, NH), 8.79 (s, 1 H), 8.68 (s, 1 H), 8.53 (dd, J = 1.8, 1.9 Hz, 1 H, H-2′), 8.15 (d, J = 8.8 Hz, 1 H), 7.81 (br d, J = 8.6 Hz, 1 H, H-6′), 7.71 (d, J = 8.9 Hz, 1 H), 7.41 (t, J = 8.0 Hz, H-5′), 7.32 (br d, J = 7.8 Hz, 1 H, H-4′). Anal. ($C_{15}H_{10}BrN_5$) C, H, N.

6-[(3-Bromophenyl)amino]-1*H*-imidazo[4,5-*h*]quinazoline (16): Scheme 5. 6-Bromo-7-chloroquinazolin-4(3*H*)-one[17] (**46**) (7.17 g, 27.6 mmol) was added to a mixture of concentrated H_2SO_4 (10 mL) and fuming HNO_3 (10 mL), and the solution was heated at 100 °C for 3 h, before being cooled and poured onto ice−water. The precipitate was collected and recrystallized from AcOH to give 6-bromo-7-chloro-8-nitroquinazolin-4(3*H*)-one (**47**) (4.87 g, 58%): mp (AcOH) 295.5−296.5 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 12.90 (br s, 1 H, NH), 8.54 (s, 1 H, H-5), 8.31 (s, 1 H, H-2); ^{13}C NMR δ 157.9 (s), 149.9 (d), 145.7 (s), 140.5 (s), 131.8 (d), 129.5 (s), 123.7 (s), 119.4 (s). Anal. ($C_8H_3BrClN_3O_3$) C, H, N.

A suspension of **47** (4.0 g, 13 mmol) in *n*-BuOH (100 mL) was saturated with anhydrous ammonia gas, the the mixture

was heated at 175 °C in a sealed pressure vessel for 36 h. After cooling the product was collected and recrystallized from EtOH to give 7-amino-6-bromo-8-nitroquinazolin-4(3*H*)-one (**48**) (2.5 g, 67%): mp 290 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 12.38 (br s, 1 H, NH), 8.19 (s, 1 H), 8.11 (s, 1 H), 6.82 (s, 2 H, NH_2); ^{13}C NMR δ 158.2 (s), 148.2 (d), 142.1 (s), 141.9 (s), 130.8 (d), 130.7 (s), 111.6 (s), 198.5 (s); HREIMS found $M^{\bullet+}$ 283.9545/285.9541, $C_8H_5BrN_4O_3$ requires 283.9545/285.9525. Anal. ($C_8H_5BrN_4O_3$) C, H, N, Br.

A solution of **48** (2.28 g, 8 mmol) in MeOH and aqueous KOH was hydrogenated over 5% Pd on charcoal to give, after neutralization with formic acid, 7,8-diaminoquinazolin-4(3*H*)-one (**49**) which was used directly: ^{1}H NMR [$(CD_3)_2SO$] δ 7.96 (s, 1 H), 7.61 (s, 2 H, NH_2), 7.41 (d, J = 8.6 Hz, 1 H), 7.36 (s, 1 H), 7.11 (s, 2 H, NH_2), 6.84 (d, J = 8.6 Hz, 1 H). The crude diamine (**49**) was dissolved in HCO_2H and heated under reflux for 3 h. The solution was then evaporated to dryness, and the residue was dissolved in dilute HCl. After treatment with charcoal and filtration through Celite, the solution was neutralized with concentrated ammonia to give 1*H*-imidazo-[4,5-*h*]quinazolin-6(7*H*)-one[16] (**50**) (0.97 g, 65% yield): mp 384−389 °C dec (lit.[16] mp >320 °C); ^{1}H NMR [$(CD_3)_2SO$] δ 13.56 (br s, 1 H, NH), 12.34 (br s, 1 H, NH), 8.42 (s, 1 H), 8.24 (s, 1 H), 7.93 (d, J = 8.5 Hz, 1 H), 7.74 (d, J = 8.3 Hz, 1 H).

Thiation of **50** with P_2S_5/pyridine gave 1*H*-imidazo[4,5-*h*]-quinazoline-6(7*H*)-thione[16] (**51**), which was treated with MeI/KOH as above, to give 6-(methylthio)-1*H*-imidazo[4,5-*h*]-quinazoline (**52**) (80%): mp (EtOH) 307−311 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 13.80 (m, 1 H, NH), 9.09 (s, 1 H), 8.49 (s, 1 H), 7.98 (d, J = 8.8 Hz, 1 H), 7.85 (d, J = 8.8 Hz, 1 H), 2.72 (s, 3 H, SCH_3). Anal. ($C_{10}H_8N_4S$) C, H, N.

Reaction of **52** (0.216 g, 1 mmol), 3-bromoaniline (0.25 g, 1.5 mmol), and 3-bromoaniline hydrochloride (0.31 g, 1.5 mmol) in *N*-methylpyrrolidone (50 mL) at 120 °C for 2 h, followed by removal of the solvent under reduced pressure, gave 6-[(3-bromophenyl)amino]-1*H*-imidazo[4,5-*h*]quinazoline (**16**) as the hydrochloride salt (0.23 g, 61%): mp (MeOH) 327−331 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.11 (br s, 1 H, NH), 8.93 (s, 2 H, H-2,8), 8.66 (d, J = 9.0 Hz, 1 H), 8.11 (br s, 1 H, H-2′), 8.07 (d, J = 9.0 Hz, 1 H), 7.83 (br d, J = 6.8 Hz, 1 H, H-6′), 7.50−7.40 (m, 2 H, H-4′,5′). Anal. ($C_{15}H_{12}BrN_5$·HCl) C, H, N, Cl.

8-[(3-Bromophenyl)amino]-1*H*-1,2,3-triazolo[4,5-*g*]-quinazoline (17). Method A (Scheme 6). A solution of 6,7-diaminoquinazolin-4(3*H*)-one[11] (**53**) (0.91 g, 5.7 mmol) in 0.1 M HCl (250 mL) was cooled to below 10 °C, and a solution of $NaNO_2$ (0.41 g, 6 mmol) in water (10 mL) was added over 2 min. After 15 min the solution was neutralized with 0.1 M KOH solution to give a precipitate of 1*H*-1,2,3-triazolo[4,5-quinazolin-8(7*H*)-one (**54**) (1.01 g, 94%): mp (EtOH) >350 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 12.22 (m, 2 H, NH), 8.76 (s, 1 H), 8.12 (s, 1 H), 8.07 (s, 1 H); ^{13}C NMR δ 161.4 (s), 145.5 (s), 144.7 (d), 139.9 (s), 139.1 (s), 120.5 (s), 115.1 (d), 109.3 (d). Anal. ($C_8H_5N_5O$) C, H, N.

Treatment of **54** (0.56 g, 3 mmol) with P_2S_5 in pyridine under reflux for 2 h as above gave crude 1*H*-1,3,4-triazolo[4,5-*g*]-quinazoline-8(7*H*)-thione (**55**) (0.26 g, 43%), which was used directly: ^{1}H NMR [$(CD_3)_2SO$] δ 9.20 (s, 1 H), 8.15 (s, 1 H), 8.14 (s, 1 H). Treatment of **55** with MeI/KOH in 50% aqueous MeOH as above gave crude 8-(methylthio)-1*H*-1,2,3-triazolo-[4,5-*g*]quinazoline (**56**) (55%), which was used directly: ^{1}H NMR [$(CD_3)_2SO$] δ 8.96 (s, 1 H), 8.79, (s, 1 H), 8.40 (s, 1 H), 2.74 (s, 3 H, SCH_3). Reaction of **56** with 3-bromoaniline as above gave 8-[(3-bromophenyl)amino]-1*H*-1,2,3-triazolo[4,5-*g*]-quinazoline (**17**) as the hydrochloride salt (63%): mp (EtOH) >390 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 12.01 (m, 1 H, NH), 9.86 (s, 1 H), 9.02 (s, 1 H), 8.39 (s, 1 H), 8.13 (dd, J = 1.9, 1.5 Hz, 1 H, H-2′), 7.85 (ddd, J = 7.7, 1.9, 1.5 Hz, 1 H, H-6′), 7.56 (ddd, J = 8.0, 1.7, 1.5 Hz, 1 H, H-4′), 7.49 (dd, J = 7.9, 7.7 Hz, 1 H, H-5′). Anal. ($C_{14}H_9BrN_6$·HCl) C, H, N, Cl.

Method B (Scheme 1). A stirred suspension of **2** (0.20 g, 6 mmol) in 1 M HCl (100 mL) was cooled to 0 °C and treated slowly with an aqueous solution of $NaNO_2$ (0.046 g, 0.66 mmol). The mixture was allowed to warm to room temperature over 30 min before being diluted with an equal volume of MeOH and basified with concentrated ammonia. The resulting clear solution was then neutralized with AcOH to give a precipitate of 8-[(3-bromophenyl)amino]-1*H*-1,2,3-triazolo[4,5-*g*]quinazoline (**17**) as the free base (0.17 g, 82%): mp (MeOH) 300−305 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 15.90 (br m, 1 H, NH), 10.09 (br s, 1 H, NH), 9.38 (s, 1 H), 8.61 (s, 1 H), 8.30 (s, 1 H), 8.14 (s, 1 H), 7.96 (d, J = 7.7 Hz, 1 H, H-6′), 7.36 (t, J = 8.0 Hz, 1 H, H-5′), 7.31 (d, J = 8.1 Hz, 1 H, H-4′); ^{13}C NMR δ 158.7 (s), 153.8 (d), 146.3 (s), 141.23 (s), 140.8 (s), 137.4 (s), 130.3 (d), 126.3 (d), 124.3 (d), 121.2 (s), 120.8 (d), 113.3 (s), 112.1 (br d), 108.2 (br d).

8-[(3-Bromophenyl)amino]thiazolo[5,4-*g*]quinazoline (18): Scheme 7. A solution of NaSH in aqueous MeOH[25] was added dropwise with stirring to a solution of **33** (5.00 g, 0.020 mmol) in a mixture of THF/MeOH (1:1, 200 mL) until no further reaction was observed by TLC. The solution was then diluted with water and washed with CH_2Cl_2. The aqueous portion was acidified with concentrated HCl and extracted with EtOAc, and the extract was worked up to give an oily solid which was stirred vigorously with MeOH for 3 h. The resultant precipitate was removed by filtration to give 5,5′-dithiobis(4-amino-2-nitrobenzamide) (**57**) (3.11 g, 64%), mp 220−230 °C dec, which was used directly: ^{1}H NMR [$(CD_3)_2$-SO] δ 8.88, 8.33, (2 s, 2 H, $CONH_2$), 7.99, 7.94 (2 s, 2 H, H-3, 6), 3.3.6 (br 2 H, NH_2); ^{13}C NMR δ 164.95 (s), 145.25 (s), 144.81 (s), 139.72 (s), 136.86 (s), 127.06 (d), 122.76 (d).

$NaBH_4$ (0.50 g, 0.013 mmol) was added to a vigorously stirred suspension of **57** (3.00 g, 7.13 mmol) in MeOH (60 mL). After 10 min the solution was acidified with concentrated HCl, extracted with EtOAc, and worked up rapidly to give 4-amino-5-mercapto-2-nitrobenzamide (**58**) as an unstable solid which was used directly. The crude material was dissolved in formic acid (50 mL), heated under gentle reflux for 2 h, and then concentrated to dryness. The residue was triturated with MeOH/EtOAc (1:19), and contaminating **57** (1.41 g) was recovered by filtration. The filtrate was concentrated and chromatographed on silica gel. Elution with EtOAc/petroleum ether (4:1) gave foreruns, while EtOAc gave 5-nitrobenzothiazole-6-carboxamide (**59**) (1.31 g, 41%): mp (EtOAc) 271−272 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.70 (s, 1 H, H-2), 8.71, 8.52 (2 s, 2 H, H-4,7), 8.25, 7.78 (2 br, 2 H, $CONH_2$); ^{13}C NMR δ 166.93 (s), 161.93 (d), 152.55 (s), 146.39 (s), 138.18 (s), 129.22 (s), 123.25 (d), 118.66 (d). Anal. ($C_8H_5N_3O_3S$) C, H; N: found, 18.1; required, 18.8.

A solution of **59** (0.30 g, 1.34 mmol) in MeOH/EtOAc (1:1, 25 mL) was hydrogenated over 5% Pd/C at 60 psi and filtered. The solvent was evaporated under reduced pressure, and the crude residue was immediately dissolved in triethyl orthoformate (30 mL) and heated under gentle reflux for 18 h. An equal volume of petroleum ether was added to the cooled solution, precipitating thiazolo[5,4-*g*]quinazolin-8(7*H*)-one (**60**) (0.17 g, 57%): mp >330 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 12.30 (br, 1 H, NH), 9.67 (s, 1 H, H-2), 9.00 (s, 1 H, H-6), 8.31, 8.14 (2 s, 2 H, H-4,9); ^{13}C NMR δ 161.94 (d), 160.65 (s), 157.02 (s), 146.50 (s), 145.01 (d), 132.56 (s), 121.11 (d), 120.56 (s), 120.19 (d); HREIMS found $M^{\bullet+}$ 203.0146, $C_9H_5ON_3S$ requires 203.0153.

A suspension of **60** (0.25 g, 1.23 mmol) in $POCl_3$ (20 mL) was heated under reflux for 3 h and then concentrated to dryness. The residue was partitioned between saturated aqueous $NaHCO_3$ and EtOAc, and the organic portion was worked up to give 8-chlorothiazolo[5,4-*g*]quinazoline (**61**) (0.21 g, 0.95 mmol) as a yellow solid which was used directly. This was heated under reflux for 45 min in THF/*i*-PrOH (1:1, 20 mL) containing 3-bromoaniline (0.21 mL, 1.90 mmol) and a trace of concentrated HCl and then concentrated to dryness. After trituration with EtOAc, the residue was partitioned between saturated aqueous $NaHCO_3$ and EtOAc and the organic portion was worked up to give 8-[(3-bromophenyl)-amino]thiazolo[5,4-*g*]quinazoline (**18**) (0.19 g, 49%): mp 302−304 °C (trituration with MeOH); ^{1}H NMR [$(CD_3)_2SO$] δ 10.05 (br, 1 H, NH), 9.74 (s, 1 H, H-2), 9.38 (s, 1 H, H-6), 8.71, 8.48 (2 s, 2 H, H-4,9), 8.31 (br s, 1 H, H-2′), 7.96 (d, J = 7.7 Hz, 1 H, H-6′), 7.39 (dd, J = 7.7, 7.7 Hz, 1 H, H-5), 7.33 (dd, J = 7.7 Hz, 1 H, H-4′); ^{13}C NMR δ 161.68 (d), 157.21 (s), 156.06 (s), 153.90 (d), 147.37 (s), 140.80 (s), 132.38 (s), 130.38 (d), 126.06 (d), 124.03 (d), 121.15 (s), 120.53 (d), 120.33 (d), 117.09 (d), 113.48 (s). Anal. ($C_{15}H_9BrN_4S$), C, H, N, S.

8-[(3-Bromophenyl)amino]-1*H*-pyrazolo[3,4-*g*]quinazoline (19) and 5-[(3-Bromophenyl)amino]-1*H*-pyrazolo[4,3-*g*]quinazoline (20): (Scheme 8). A suspension of 1*H*-pyrazolo[3,4-*g*]quinazolin-8(7*H*)-one[18] (**62**) (0.21 g, 1.13 mmol) in $POCl_3$ (20 mL) was refluxed under an atmosphere of nitrogen for 18 h and then concentrated to dryness under reduced pressure. The residue was partitioned between saturated aqueous $NaHCO_3$ and EtOAc, and the organic solution was worked up to give crude 8-chloro-1*H*-pyrazolo-[3,4-*g*]quinazoline (66 mg, 28%). A mixture of the entire sample and 3-bromoaniline (0.70 mL, 0.645 mmol) in propan-2-ol (20 mL) containing concentrated HCl (1 drop) was heated under reflux for 30 min and then concentrated to dryness. The residue was extracted into EtOAc, washed with water, and worked up to give an oil which was chromatographed on silica gel. Elution with EtOAc/petroleum ether (1:5) gave foreruns containing 3-bromoaniline, while EtOAc eluted 8-[(3-bromophenyl)amino]-1*H*-pyrazolo[3,4-*g*]quinazoline (**19**) (28 mg, 26%): mp (MeOH) 328−330 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 13.75 (s, 1 H, NH), 10.11 (s, 1 H, NH), 8.89 (s, 1 H, H-6), 8.63, 8.50 (2 s, 2 H, H-3,4), 8.38 (br s, 2 H, H-9, 2′), 8.05 (ddd, J = 8.0, 1.9, 1.9 Hz, 1 H, H-6′), 7.44 (dd, J = 8.1, 8.0 Hz, 1 H, H-5′), 7.37 (ddd, J = 8.1, 1.9, 1.9 Hz, 1 H, H-4′); ^{13}C NMR δ 158.10 (s), 151.38 (d), 142.29 (s), 141.14 (s), 137.90 (s), 134.07 (d), 130.29 (d), 127.37 (s), 125.84 (d), 124.14 (d), 121.10 (s), 120.71 (d), 118.50 (d), 114.70 (s), 102.19 (d). Anal. ($C_{15}H_{10}BrN_5$) C, H, N.

Similar reaction of 1*H*-pyrazolo[4,3-*g*]quinazolin-5(6*H*)-one[19] (**63**) with $POCl_3$, followed by coupling with 3-bromoaniline, gave 5-[(3-bromophenyl)amino]-1*H*-pyrazolo[4,3-*g*]quinazoline (**20**) (21% overall yield): mp (MeOH) 305−306 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 13.41 (s, 1 H, NH), 10.05 (s, 1 H, NH), 9.18 (s, 1 H, H-7), 8.61, 8.54 (2s, 2 H, H-3,9), 8.33 (br s, 1 H, H-2′), 7.98 (d, J = 9.1 Hz, 1 H, H-6′), 7.87 (br s, 1 H, H-4), 7.39 (dd, J = 9.1, 9.1 Hz, 1 H, H-5′), 7.32 (d, J = 9.1 Hz, 1 H, H-4′); ^{13}C NMR δ 158.71 (s), 153.64 (d), 146.54 (s), 141.56 (s), 141.07 (s), 135.18 (d), 130.30 (d), 125.85 (d), 124.13 (d), 123.27 (s), 121.13 (s), 120.63 (d), 116.24 (d), 110.54 (s), 104.68 (d). Anal. ($C_{15}H_{10}BrN_5 \cdot H_2O$) C, H, N.

5-[(3-Bromophenyl)amino]-1*H*-pyrrolo[3,2-*g*]quinazoline (21). A suspension of 1*H*-pyrrolo[3,2-*g*]quinazolin-5(6*H*)-one (**64**), prepared by a reported[21] method (60 mg; 90% pure by NMR) and $POCl_3$ (1.2 mL) in *p*-dioxane (2.8 mL) was heated at 105 °C for 4 h. Volatiles were removed under reduced pressure (finally at 2 mmHg for 2 h), and the resulting orange solid was cooled in an Me_2CO/CO_2 bath and treated successively with solid Na_2CO_3 followed by MeOH. The resulting suspension was sonicated for 5 min at 25 °C and filtered, and the filtrate was subjected to flash chromatography on silica gel in Me_2CO to give crude 5-chloro-1*H*-pyrrolo[3,2-*g*]quinazoline (60 mg, 100%) which was used directly. A suspension of the above chloro compound (60 mg, 0.29 mmol) and 3-bromoaniline (50 mg, 0.29 mmole) in propan-2-ol (2.5 mL) was heated under reflux for 30 min and then filtered warm and the solvent removed under reduced pressure. The residue was triturated with cold propan-2-ol to give 5-[(3-bromophenyl)amino]-1*H*-pyrrolo[3,2-*g*]quinazoline (**21**) as the hydrochloride salt (50 mg, 42%): mp >198 °C dec; ^{1}H NMR [$(CD_3)_2SO$] δ 15.10 (br s, exchanges with D_2O, 1 H), 12.07 (s, exchanges with D_2O, 1 H), 11.42 (s, exchanges with D_2O, 1 H), 9.17 (s, 1 H), 8.95 (s, 1 H), 8.12 (t, J = 1.7 Hz, 1 H), 8.01 (s, 1 H), 7.93−7.86 (m, 1 H), 7.84−7.78 (m, 1 H), 7.55−7.42 (m, 2 H), 6.89 (d, J = 3.1 Hz, 1 H); CIMS m/z 342 (10), 341 (64), 340 (61), 339 (100), 338 (49), 337 (39). Anal. (free base, mp 273 °C) ($C_{16}H_{11}N_4Br$) C, H, N.

9-[(3-Bromophenyl)amino]-1*H*-pyrrolo[2,3-*f*]quinazoline (22): Scheme 8. A suspension of 1*H*-pyrrolo[2,3-*f*]-quinazolin-9-(8*H*)-one[21] (**65**) (600 mg, 0.16 mmol) in $POCl_3$ (12 mL) was heated at 60 °C for 5 h and then concentrated under reduced pressure. The resulting residue was diluted with ice-cold 2-propanol and washed successively with propan-2-ol and ether to give 1.0 g of crude 9-chloro-1*H*-pyrrolo[2,3-*f*]quinazoline (1.0 g) which was used without further characterization. A mixture of the entire crude 9-chloro compound and excess 3-bromoaniline (1.7 g) in propan-2-ol (10 mL) was heated under reflux for 2 h and then cooled to room temperature. The resulting precipitate was collected, dissolved in a minimum volume of DMF, and purified by flash chromatography on silica gel. Elution with CH_2Cl_2/MeOH (9:1) gave 9-[(3-bromophenyl)-amino]-1*H*-pyrrolo[2,3-*f*]quinazoline (**22**) (525 mg, 48% from **65**): mp (EtOAc/hexane) 130−134 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.9 (s, br, exchangeable, 1 H), 7.92 (d, J = 8.3 Hz, 1 H), 7.68 (s, br, 1 H), 7.37 (d, J = 2.9 Hz, 1 H), 7.30 (d, J = 8.3 Hz, 1 H), 7.22 (s, 1 H), 7.16 (m, 2 H), 6.96 (m, 1 H), 6.67 (d, J = 2.9 Hz, 1 H); CIMS m/z 338 (80), 339 (100), 340 (87), and 341 (76). Anal. ($C_{16}H_{11}N_4Br$) C, H, N.

4-[(3-Bromophenyl)amino]benzo[*g*]quinazoline (23): (Scheme 8). A suspension of benzo[*g*]quinazolin-4(3*H*)-one[20] (**66**) (3.49 g, 18 mmol) in $POCl_3$ (40 mL) was heated under reflux under N_2 for 3 h. The volatiles were removed under reduced pressure, and the residue was partitioned between $CHCl_3$ (200 mL) and dilute aqueous Na_2HPO_4 solution (1 M, 50 mL). The organic phase was filtered through a silica gel plug (50 g), and the plug was then eluted with 20% EtOAc in $CHCl_3$ (500 mL). The combined eluants were concentrated under reduced pressure to give crude 4-chlorobenzo[*g*]quinazoline[20] (1.20 g, 31%), which was used directly: ^{1}H NMR [$(CD_3)_2SO$)] δ 9.04 (s, 1 H), 8.91 (s, 1 H), 8.65 (s, 1 H), 8.20−8.09 (m, 2 H), 7.75−7.60 (m, 2 H). A mixture of the above crude 4-chloro compound (214 mg, 1.0 mmol), 3-bromoaniline (213 mg, 1.25 mmol), and Et_3N (202 mg, 2.0 mmol) in methoxyethanol (5 mL) was stirred and heated under N_2 at 95 °C for 6 h. The volatiles were moved under reduced pressure, and the residual solid was triturated with MeOH and then recrystallized at 0 °C from EtOH/dilute HCl (1:1) to give 4-[(3-bromophenyl)amino]benzo[*g*]quinazoline (**23**) as the hydrochloride salt (71 mg, 18%): mp 233 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 14.0 (br s, 1 H, NH), 9.65 (s, 1 H), 9.01 (s, 1 H), 8.47 (s, 1 H, H-2), 8.29 (d, J = 8.4 Hz, 1 H), 8.24 (d, J = 8.4 Hz, 1 H), 8.18 (br s, 1 H, H-2′), 7.9−7.82 (m, 2 H), 7.78 (t, J = 7.5 Hz, 1 H), 7.58 (d, J = 8 Hz, 1 H, H-4′), 7.51 (t, J = 8 Hz, 1 H, H-5′). Anal. (free base) ($C_{18}H_{12}BrN_3 \cdot 0.25H_2O$) C, H, N.

4-[(3-Bromophenyl)amino]pyrazino[2,3-*g*]quinazoline (24): Scheme 1. A mixture of **2** (90 mg, 0.27 mmol) and 1,4-dioxane-2,3-diol[13] (0.2 g, 1.6 mmol) in MeOH (20 mL) was stirred at room temperature overnight to give a precipitate of 4-[(3-bromophenyl)amino]pyrazino[2,3-*g*]quinazoline (**24**) (80 mg, 83%): mp (MeOH) 244.5−245.5 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.45 (br s, 1 H, NH), 9.52 (s, 1 H), 9.09 and 9.06 (2 d, J = 1.6 Hz, 2 H, H-7 and H-8), 8.71 (s, 1 H), 8.44 (s, 1 H), 8.32 (br s, 1 H, H-2′), 7.99 (br d, 1 H, H-6′), 7.45−7.34 (m, 2 H, H-4′ and H-5′). Anal. ($C_{16}H_{10}BrN_5$) C, H, N.

Enzyme Assay. Epidermal growth factor receptor was isolated from human A431 carcinoma cell shed membrane vesicles by immunoaffinity chromatography as previously described,[26] and the assays were carried out as previously reported.[1] The substrate used was based on a portion of phospholipase Cγ1 having the sequence Lys-His-Lys-Lys-Leu-Ala-Glu-Gly-Ser-Ala-Tyr^{472}-Glu-Glu-Val. The reaction was allowed to proceed for 10 min at room temperature and stopped by the addition of 2 mL of 75 mM phosphoric acid. The solution was then passed through a 2.5 cm phosphocellulose disk which bound the peptide. This filter was washed with 75 mM phosphoric acid (5×), and incorporated label was assessed by scintillation counting in an aqueous fluor. Control activity (no drug) gave a count of approximately 100 000 cpm. At least two independent dose−response curves were done and the IC_{50} values computed. The reported values are averages; variation was generally ±15%.

EGF Receptor Autophosphorylation in A431 Human Epidermoid Carcinoma Cells. Cells were grown to confluency in six-well plates (35 mm diameter) and exposed to serum-free medium for 18 h. They were then treated with **8** for 2 h and with EGF (100 ng/mL) for 5 min. The monolayers were lysed in 0.2 mL of boiling Laemlli buffer (2% sodium dodecyl sulfate, 5% β-mercaptoethanol, 10% glycerol, and 50 mM Tris, pH 6.8), and the lysates were heated to 100 °C for 5 min. Proteins in the lysate were separated by polyacrylamide gel electrophoresis and electrophoretically transferred to nitrocellulose. The membrane was washed once in 10 mM Tris, pH 7.2, 150 mM NaCl, 0.01% azide (TNA) and blocked overnight in TNA containing 5% bovine serum albumin and

1% ovalbumin. The membrane was blotted for 2 h with antiphosphotyrosine antibody (UBI, 1 mg/mL in blocking buffer) and then washed twice in TNA, once in TNA containing 0.05% Tween-20 and 0.05% nonidet P-40, and twice in TNA. The membranes were then incubated for 2 h in blocking buffer containing 0.1 mCi/mL of [^{125}I]protein A and then washed again as above. After the blots were dry they were loaded into a film cassette and exposed to X-AR X-ray film for 1−7 days. Band intensities were determined with a Molecular Dynamics laser densitometer.

Growth Factor Mediated Mitogenesis. Swiss 3T3 fibroblasts were grown to 90−100% confluency in 24-well plates (1.7 × 1.6 cm, flat bottom) and growth arrested in serum-free media for 18 h. Compound **8** was added to specified wells 2 h prior to growth factors, and then the cells were exposed to either 20 ng/mL EGF, PDGF, or bFGF or 10% serum for 24 h. Two μCi of [*methyl*-^{3}H]thymidine was added to each well and incubated for 2 h at 37 °C. The cells were trypsinized and injected into 2 mL of ice-cold 15% trichloroacetic acid (TCA). The resulting precipitate was collected on glass fiber filters, washed five times with 2 mL aliquots of ice-cold 15% TCA, dried, and placed in scintillation vials along with 10 mL of Ready gel (Beckman, Irvine, CA). Radioactivity was determined in a Beckman LS 6800 scintillation counter.

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