Quinazolin-4-one α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic Acid (AMPA) Receptor Antagonists: Structure−Activity Relationship of the C-2 Side Chain Tether

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Received December 7, 2000

A series of 6-fluoro-3-(2-chlorophenyl)quinazolin-4-ones has been prepared, which contains a 2-fluorophenyl ring attached to C-2 by a variety of two-atom tethers. These compounds were used to probe the structure−activity relationship (SAR) for AMPA receptor inhibition. The relative potencies of the new compounds ranged from 11 nM to greater than 10 μM. The differential activity of the compounds was rationalized on the basis of alterations of the 2-fluorophenyl positioning (planar and radial) relative to the quinazolin-4-one ring based on computational methods. From this effort, new AMPA receptor antagonists, containing the methylamino tether group, have been identified.

Introduction

Hyperactivity of ionotropic glutamate receptors has been implicated in the pathophysiological sequelae which contributes to the cell death observed in many neurodegenerative processes including ischemic stroke, brain injury, and epilepsy.[1] Thus, an intense effort has been focused on the discovery of compounds that block glutamate receptor function as a potential therapeutic remedy for these ailments. Initially, the *N*-methyl-D-aspartate (NMDA) receptor was targeted. However, many issues of early drug candidates, relating to both safety and physical properties, have made development very difficult.[2] More recently, attention has been directed toward a second class of ionotropic glutamate receptors, the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, because prototype antagonists have been efficacious in many in vivo neurodegenerative models.[3]

In the course of our studies on the modulation of glutamate receptor function, we identified potent noncompetitive AMPA receptor antagonists based on the quinazolin-4-one template.[4] Initial structure−activity relationship (SAR) development taught that halogen substitution at C-6 was well tolerated and a 2-substituted phenyl ring at N-3 was essential for good activity. At C-2, a phenyl or pyridyl ring connected by a two-carbon tether was also necessary for AMPA receptor blockade because the parent structure, methaqualone (C-2 methyl group), was inactive. On the basis of the two-carbon tether, two potent series were identified containing either the vinyl or hydroxyvinyl (enol) units.[5]

To better understand the SAR in this region of these molecules, we prepared compounds that varied only in the nature of the tether unit. For this investigation, 3-(2-chlorophenyl)-6-fluoroquinazolin-4-one was used as the template and a 2-fluorophenyl ring was connected to C-2 through the various tethering groups. We report here the results of this study, which identified the methylamino spacer as an optimal tether. It should be noted that these quinazolin-4-ones exist as a stable isolable pair of atropisomers.[6] Previously, we showed that all the AMPA receptor antagonist activity resides in a single atropisomer. For this SAR evaluation, we worked exclusively with racemic materials.

Chemistry

Most of the new compounds were prepared from the readily available intermediate 3-(2-chlorophenyl)-6-fluoro-2-methylquinazolin-4-one (**17**).[4] Condensation with 2-fluorobenzaldehyde in hot acetic acid and acetic anhydride produced the vinyl-tethered derivative **1** (Scheme 1). Hydrogenation of the double bond afforded the ethyl-linked derivative **2**. Deprotonation of **17** with LiHMDS or LDA and reaction with 2-fluorobenzaldehyde or ethyl 2-fluorobenzoate provided the corresponding hydroxyethyl (**3**) and hydroxyvinyl (**4**) analogues, respectively. Compound **3** was obtained as a separable mixture of diastereomers (**3a**, **3b**) due to the atropisomeric motif resident in these structures (see below and Experimental Section). We have not determined the relative stereochemistry of the isomers of **3**. They are identified on the basis of their elution sequence during silica gel chromatographic purification, **3a** eluting first. DBU-induced elimination of the triflate derived from **4** yielded the acetylene-linked structure **5**.

To access the methylamino analogue, the C-2 methyl group of **17** was oxidized to the aldehyde (**18**) using the two-step procedure of Vetilino and Coe.[7] Reductive amination with 2-fluoroaniline, 2-fluorobenzylamine, and related anilines afforded the desired methyleneamino and three-atom C−N−C-linked compounds **6** and **7**, respectively (Scheme 2). The reductive amination procedure with aniline analogues was somewhat sluggish (**6**, **12**−**16**). Thus, it was often advantageous to preform the intermediate imine under dehydrative conditions with magnesium sulfate or with azeotropic

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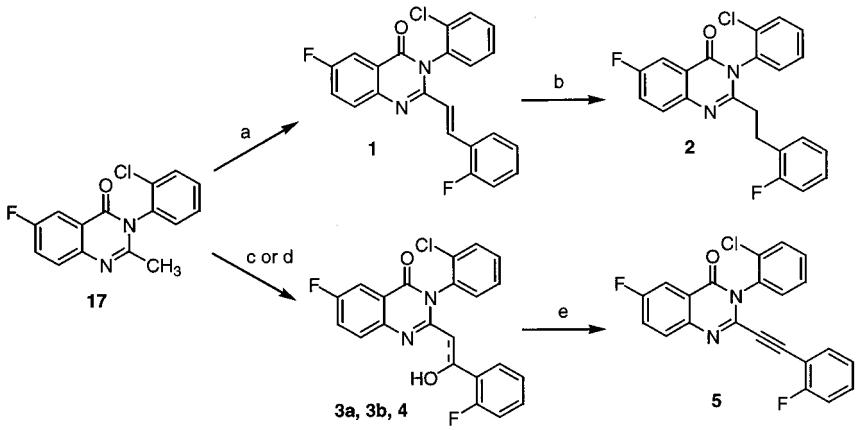
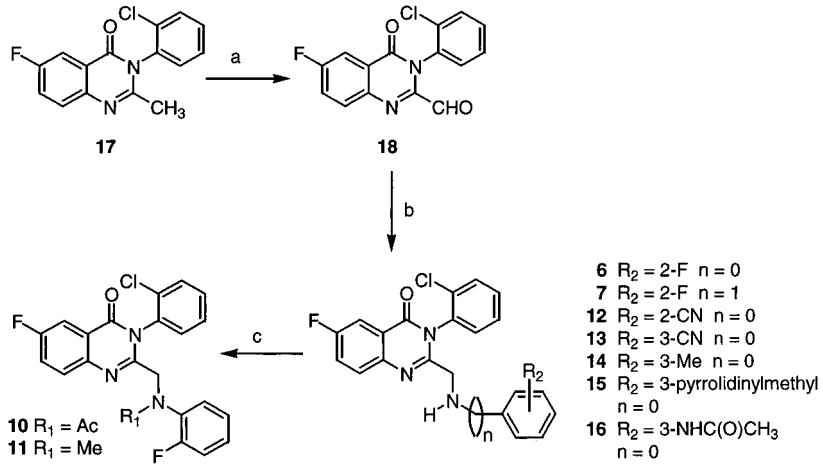
10.1021/jm000522p CCC: $20.00
Published on Web 04/25/2001

Scheme 1[a]



[a] (a) 2-Fluorobenzaldehyde, HOAc, NaOAc, Ac_2O, reflux (57%). (b) H_2, 10% Pd/C, EtOAc (66%). (c) LiHMDS, THF, 2-fluorobenzaldehyde, −78 °C to room temperature [two diastereomers formed, **3a** (19%), **3b** (61%)]. (d) LDA, THF, ethyl 2-fluorobenzoate, −78 °C (40% of **4**). (e) 2,6-lutidine, CH_2Cl_2, Tf_2O, −78 °C to room temperature; DBU, THF, −78 to −10 °C (93%).

Scheme 2[a]



[a] (a) DMFDMA, DMF, 140 °C (90%); $NaIO_4$, THF, aqueous pH 7 buffer (97%). (b) Various reductive amination procedures (see Experimental Section). (c) HOAc, Ac_2O, reflux (37% of **10**); HCOOH, Ac_2O, THF (95%, R = formyl); BH_3−THF, THF (30% of **11**).

removal of water. Reduction of the imine could also be problematic. In several instances, we found that a combination of sodium cyanoborohydride and sodium triacetoxyborohydride was more effective than either reducing agent alone (see Experimental Section). This was an empirical observation; we have no satisfactory explanation to rationalize the experimental results.

Two analogues of **6** were prepared with substitution on the nitrogen atom of the tether group (Scheme 2). The acetamide **10** was synthesized by acylation of **6** with acetic anhydride. The N-methylated derivative **11** was prepared by the two-step procedure of formylation with in situ generated acetylformyl anhydride followed by reduction with BH_3−THF.

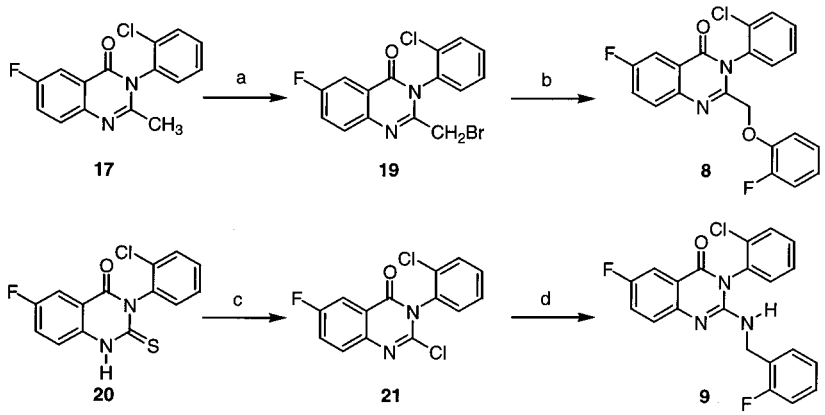
In an attempt to examine the activity of analogues with a simple amide tether, aldehyde **18** was further oxidized to its corresponding acid with sodium chlorite.[8] Unfortunately, while the oxidation proceeded in the desired manner, the product acid was unstable and decarboxylated rapidly at ambient temperature in our hands. A methoxy tether (**8**) was prepared by NBS bromination of **17** to give **19** followed by nucleophilic displacement with 2-fluorophenol (Scheme 3). Finally, the aminomethyl linking group was prepared from the readily available 3-(2-chlorophenyl)-6-fluoro-2-thioxo-2,3-dihydro-1H-quinzaolin-4-one **20**. Reaction of **20** with $POCl_3$ produced 2-chloro-2-(2-chlorophenyl)-6-fluoro-quinazolin-4-one (**21**). Nucleophilic substitution with 2-fluorobenzylamine yielded the aminomethyl-tethered analogue **9**.

Biological Results

Compounds were evaluated for their ability to block kainate-induced $^{45}Ca^{2+}$ influx into cultured rat cerebellar granule cells, a process shown to be mediated by AMPA receptors.[9] This functional assay is sensitive to both competitive and noncompetitive antagonists. Results are summarized in Table 1. The modifications to the tether group had a profound effect on the AMPA receptor antagonist activity, producing compounds with more than a 1000-fold potency range. Among the nine tethers examined, the vinyl, ethyl, acetylenyl, and aminomethyl groups (**1**, **2**, **5**, **9**) inhibited AMPA receptor function within a 4-fold range (IC_{50}s from 0.096 to 0.347 μM). It was somewhat surprising to observe negligible activity with the hydroxyvinyl tether (**4**) in light of potent activity previously observed with related compounds.[10]

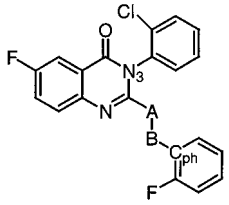
As a consequence of the chiral center introduced with the hydroxyethyl tether (**3**) and the inherent thermal

Scheme 3[a]



[a] (a) NBS, CCl_4, $(BzO)_2$, reflux, light (35%). (b) 2-Fluorophenol, NaH, DMF (88%). (c) See Experimental Section for **20**; $POCl_3$, PCl_5, reflux (42%). (d) 2-Fluorobenzylamine, EtOH, reflux (45%).

Table 1. Inhibition of Ca^{2+} Influx, Observed and Calculated Energy Differences Relative to **6**, and Selected Torsion Angles as a Function of the Tether Group in Quinazolin-4-ones



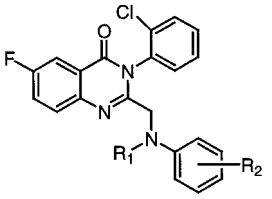
entry	A−B tether	IC_{50}, μM	$\Delta\Delta G_{rel}$,[a] kcal/mol	ΔE_{rot},[b] kcal/mol	torsion angles, deg		
					$N_3-C-A-B$[c]	$C-A-B-C_{ph}$[c]	$A-B-C_{ph}-C_F$[c]
1	−CH=CH−	0.096 ± 0.022	1.18	1.47	168.4	178.5	160.3
2	$-CH_2CH_2-$	0.160 ± 0.002	1.49	2.35	178.6	178.9	75.9
3a[f]	$-CH_2CH(OH)-$	0.240 ± 0.010					
3b[f]	$-CH_2CH(OH)-$	>3.0[d]					
4	−C=CH(OH)−	>30[d]					
5	−C≡C−	0.282 ± 0.047	1.82	0.140	177.9	8.8	178.3
6	$-CH_2NH-$	0.013 ± 0.001	0.0		171.5	164.5	−161.8
7	$-CH_2NHCH_2-$	>0.30[d]					
8	$-CH_2O-$	>10[d]	3.94	3.96	71.1	170.2	73.0
9	$-NHCH_2-$	0.347 ± 0.128	1.95	2.42	172.9	−81.9	−68.0
	NBQX[e]	2.4 ± 0.7					
	GYKI 52466[e]	22 ± 3					

[a] $-RT\ln(IC_{50}\text{compound}/IC_{50}\text{compound }\mathbf{6})$. See text for explanation. [b] ΔE_{rot} is the energy required for the 2-fluorophenyl group to adopt a conformation similar to the lowest energy conformation of **6**. [c] Torsion angles measured in degrees for the lowest energy conformer. [d] Value represents the highest concentration tested at the stage of the program. [e] Reference standards provided to add perspective. [f] **3a** and **3b** are diastereomers.

stability of the atropisomers in this series due to restricted rotation of the N-3 (2-chlorophenyl) group, a separable pair of diastereomers exist. These diastereomers were found to have differential activity (IC_{50} is 0.24 and >3.0 μM for **3a** and **3b**, respectively). It was also interesting to note the loss of activity for the methoxy-tethered analogue **8**. The methylamino tether (**6**) stood out among this survey with low nanomolar inhibitory potency (IC_{50} = 0.013 μM). The related one-carbon-extended (C−N−C) analogue **7** was essentially inactive.

We further extended the SAR of the methylamino series by alkylating or acylating the linking group nitrogen and through replacement of the 2-fluorophenyl group with other substituted benzenes (Table 2). Entries **10** and **11** (*N*-acetyl, *N*-methyl) teach that the unsubstituted nitrogen is essential to the enhancement of potency in **6**. The short list of phenyl analogues (**12**−**16**) demonstrates that the methylamino tether permits modest substitution in this region while generally maintaining good potency. The pyrrolidinylmethyl analogue **15** is particularly attractive because both good potency and solubility are achieved.[11]

Table 2. Inhibition of Ca^{2+} Influx with Analogues of **6**



entry	R_1	R_2	IC_{50}, μM
6	H	2-F	0.013 ± 0.001
10	acetyl	2-F	>3[a]
11	CH_3	2-F	2.00 ± 0.03
12	H	2-CN	0.042 ± 0.018
13	H	3-CN	0.011 ± 0.004
14	H	3-CH_3	0.213 ± 0.013
15	H	3-pyrrolidinylmethyl	0.013 ± 0.001
16	H	3-$NHC(O)CH_3$	0.26[b]

[a] Value represents the highest concentration tested at the stage of the program. [b] Single triplicate determination.

Figure 1. Two views of the overlap of **6** (orange, methylamino tether), **8** (magenta, methoxy tether), and **9** (green, aminomethyl tether). Hydrogens attached to nonheteroatoms have have been omitted for clarity. The figure was generated via the Sybyl program (SYBYL, version 6.6. Tripos Associates, Inc., 1699 S. Hanley Rd., Suite 303, St. Louis, MO 63144).

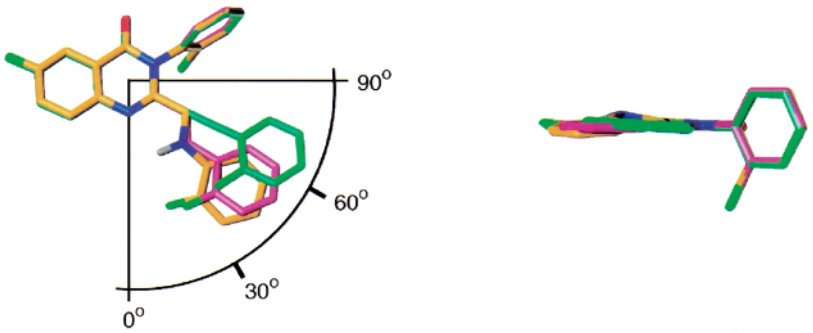


Figure 2. Two views of the overlap of **6** (orange methylamino tether), **1** (magenta, vinyl tether), and **5** (green, acetylene tether). Hydrogens attached to nonheteroatoms have have been omitted for clarity. Bound conformations are depicted.

Molecular Modeling

To better understand the influence of the tethers on AMPA receptor blockade for this series, we examined overlays of computationally minimized structures. For each of the compounds in the study, we located the lowest energy conformation (in the gas-phase, Figure 1. To facilitate interpretation of the figures, relevant torsion angles are provided in Table 1). Given the potency of **6** (0.013 μM) relative to the other compounds in the series (Table 1), we hypothesized that a nearly planar conformation of the C-2 side chain attached to the quinazolin-4-one ring afforded the best activity. Our goal in carrying out the ab initio calculations was to investigate the extent to which the SAR (Table 1) could be explained by changes in the conformational energy upon adopting the "active" conformation of **6**. Accordingly, for each of the compounds in the study, we located constrained minima corresponding to a nearly planar arrangement of pharmacophore groups, similar to the lowest energy conformation of **6**. These rotational conformation energy differences (ΔE_{rot}) were compared to the relative free energy difference between the IC_{50} for each compound compared to that of **6**. This value was obtained via $\Delta\Delta G_{rel} = -RT \ln(K_1/K_6)$, where K_1 corresponds to the measured IC_{50} of compound **1**. For example, from Table 1 the relative free energy difference calculated from the biological activities between **1** and **6** is found to be ca. 1.18 kcal/mol. In comparison, the energetic cost of **1** adopting a planar conformation is computed to be 1.47 kcal/mol (ΔE_{rot}, Table 1). Similarly, we find the experimental vs computed results for **2** to be 1.49 vs 2.35 kcal/mol. Finally, for **8** and **9**, the experimental vs computed results are found to be 3.94 vs 3.96 kcal/mol and 1.95 vs 2.42 kcal/mol, respectively.

The agreement between the computed and measured results suggests that conformational energy changes play a large role in determining the potency of each compound and that a nearly planar orientation of the C-2 substituent is the preferred bioactive conformation. Although the data set is small, the correlation between biological and conformational energy differences is good [$R^2 = 0.94$ (least-squares analysis of measured $\Delta\Delta G_{rel}$ vs ΔE_{rot}, compound **5** omitted)]. One striking difference between the observed and calculated values was found for compound **5**. We rationalized this difference on the basis of the radial positioning of the 2-fluorophenyl ring within the plane defined by the quinazolin-4-one. In the case of the acetylene tether, the 2-fluorophenyl ring maps to a unique position on a radius from the centroid of the pyrimidin-4-one ring (Figure 2). As a result, even though the 2-fluorophenyl ring of **5** adopts a conformation that is nearly coplanar with the quinazolin-4-one ring in its lowest energy conformation ($\Delta E_{rot} = 0.14$ kcal/mol), the linear nature of the acetylene tether prevents the aryl substituent from achieving the radial position that is optimal for AMPA receptor interaction. This results in a substantial difference between $\Delta\Delta G_{rel}$ and ΔE_{rot}.

Taken in concert, the radial and planar positioning of this ring are likely to account for most of the observed differences in biological activity for the molecules of this series. The most dramatic example illustrating this point compares **6** and **8**. In this instance, the unfavorable interactions between the lone pairs of electrons on the oxygen atom of the tether with N-1 of the quinazolin-4-one contribute to a relatively high energy requirement to bring the 2-fluorophenyl ring into planar alignment. However, once done, the radial positioning of this ring is nearly superimposable with the structure of **6**. Thus, nearly all of the potency difference ($\Delta\Delta G_{rel}$) between **8** and **6** can be captured in the calculated ΔE_{rot} value.

Conclusions

The pharmacophore for the quinazolin-4-one class of noncompetitive AMPA receptor antagonists may be viewed as consisting of three elements: the quinazolin-4-one ring with its small C-6 substituent, the orthogonal N-3 phenyl ring, which must contain a single ortho substituent, and the aryl ring attached to C-2 through a two-atom spacer. In this study, we have examined the consequences of modifying the tether unit while retaining a two-atom connector. As the identity of the three pharmacophoric elements was retained throughout the series, we have been able to isolate the impact of tether changes on biological activity. AMPA receptor blockade was found to vary more than 1000-fold and the methylamino tether was identified as the linking unit that conferred the greatest potency.

To rationalize the differences in potency among these relatively similar compounds, we conducted molecular modeling experiments. Inspection of minimized structures revealed first that **6** likely exists as a nearly planar array of the quinazolin-4-one and 2-fluorophenyl rings, assisted in adopting this conformation by a hydrogen bond between the tether NH and N-1 of the quinazolin-4-one. The facility with which the other compounds in the series could adopt this same planar arrangement was found to directly correlate with antagonist activity at the AMPA receptor. Thus, rotational positioning of the 2-fluorophenyl ring relative to the quinazolin-4-one ring could account for most of the difference in potency between **6** and the other compounds which we compared.

This correlation was generally good but could not completely account for the activity differences. We hypothesize that radial positioning of the 2-fluorophenyl ring likely accounts for much of the remaining difference. This is most dramatically illustrated with the acetylene-tethered compound **5** where the 2-fluorophenyl ring is nearly coincident with the quinazolin-4-one plane, but the activity remained 10-fold weaker than **6**.

Modulation of AMPA receptor activity remains an important target for neuroprotective therapy, and new compounds with increased potency and improved physicochemical properties are desired. The observations relating the positioning of the three elements of the quinazolin-4-one noncompetitive AMPA receptor pharmacophore should be of considerable assistance in the design of related structures with favorable affinity for the AMPA receptor.

Experimental Section

Computational Methods. Restricted Hartree−Fock calculations were carried out for compounds **1**, **2**, **5**, **6**, **8**, and **9**. The geometries for these series of molecules were fully optimized by means of analytical energy gradients[12] with the 6-31G(d) basis set[13] in the gas phase. The ab initio molecular orbital calculations were carried out with the Gaussian 94 series of programs on a Silicon Graphics computer.[14] For each molecule a variety of conformations were generated corresponding to ca. 60° torsions about each rotatable bond not involving a terminal hydrogen.

General Procedures. All nonaqueous reactions were run under an atmosphere of dry nitrogen and stirred with a magnetic stir bar unless otherwise stated. All melting points are uncorrected. All ^{1}H NMR spectra were recorded at 250, 300, or 400 MHz and are reported in ppm (δ) calibrated to the deuterium lock signal for the solvent deuteriochloroform unless otherwise indicated. Chromatography refers to flash chromatography on silica gel unless otherwise indicated. Solvent evaporation (or concentration or removal) implies concentration at reduced pressure with the use of a rotary evaporator.

***E*-3-(2-Chlorophenyl)-6-fluoro-2-[2-(2-fluorophenyl)vinyl]-3H-quinazolin-4-one (1).** A solution of 3-(2-chlorophenyl)-6-fluoro-2-methyl-3H-quinazolin-4-one (**17**, 0.432 g, 1.50 mmol) of 2-fluorobenzaldehyde (0.248 g, 0.22 mL, 2.00 mmol) and sodium acetate (0.20 g) were dissolved in a mixture of 5 mL of glacial acetic acid and 1.0 mL of acetic anhydride, and the mixture was heated at reflux overnight. A second aliquot of 2-fluorobenzaldehyde (0.11 mL, 1.0 mmol) was added, and reflux was continued for 6 h. The acetic acid solvent was then removed at reduced pressure, and the residues were partitioned between aqueous $NaHCO_3$ and $CHCl_3$. The aqueous layer was extracted with $CHCl_3$, and the combined organic extracts were washed with brine, dried over $MgSO_4$, treated with decolorizing carbon, and concentrated to a solid. This solid was taken up in 1:1 ethyl ether/pentane, filtered, and air-dried to give 0.338 g (57%) of **1**; mp 199−200 °C. ^{1}H NMR: δ 8.04 (d, J = 15 Hz, 1H), 7.91 (m, 1H), 7.80 (dd, J = 12, 2.0 Hz, 1H), 7.62 (m, 1H), 7.46−7.53 (m, 3H), 7.35−7.39 (m, 1H), 7.23−7.28 (m, overlapping $CHCl_3$, 2H), 6.98−7.07 (m, 2H), 6.40 (d, J = 16 Hz, 1H). Anal. ($C_{22}H_{13}ON_2ClF_2$) C, H, N.

3-(2-Chlorophenyl)-6-fluoro-2-[2-(2-fluorophenyl)-ethyl]-3H-quinazolin-4-one (2). To a solution of **1** (98 mg, 0.25 mmol) dissolved in 15 mL of ethyl acetate was added 50 mg of 10% Pd/C. The mixture was hydrogenated at 1 atm for 6 h, at which time the reaction was shown to be complete by the disappearance of the starting material peak in the MS of the mixture. The catalyst was filtered off, and the solvent was evaporated. The residues were dissolved in ethyl ether, and excess of a solution of HCl gas in ethyl ether was added. Crystallization occurred from a clear solution. After the mixture was stirred for 90 min, the crystals were filtered and washed with dry ethyl ether and air-dried to give 65 mg (66%) of **2**; mp 166−169 °C. ^{1}H NMR: δ 7.88 (dd, J = 8.3, 2.9 Hz, 1H), 7.74 (dd, J = 8.7, 4.5 Hz, 1H), 7.57 (d, J = 8.2 Hz, 1H), 7.39−7.51 (m, 3H), 7.08−7.20 (m, 3H), 6.90−6.99 (m, 2H), 3.10 (t, J = 7.9 Hz, 2H), 2.62 (m, 2H). Anal. ($C_{22}H_{15}ON_2ClF_2$) C, H, N.

Diastereomers of 3-(2-Chlorophenyl)-6-fluoro-2-[2-(2-fluorophenyl)-2-hydroxy-ethyl]-3H-quinazolin-4-one (3a and 3b). A solution of **17** (0.50 g, 1.73 mmol) in THF (50 mL) was cooled to −78° C, and 1.0 M lithium bis(trimethylsilyl)-amide (1.90 mL, 1.90 mmol) was added to give a dark-burgundy mixture. The anion solution was stirred at 0 °C for 1 h and then returned to −78 °C, and 2-fluorobenzaldehyde (0.21 mL, 1.99 mmol) in THF (10 mL) was added dropwise over 1 min. The resulting orange solution was stirred at room temperature for 30 min, saturated aqueous NH_4Cl solution was added, and the mixture was extracted with ethyl acetate (50 mL). The extract was washed with dilute sodium bisulfite solution and brine, dried over $MgSO_4$, and concentrated to an orange foam (0.72 g). The foam was chromatographed, eluting with 10% ethyl acetate/hexanes to give 0.134 g (19%) of the first diastereomeric isomer of 3-(2-chlorophenyl)-6-fluoro-2-[2-(2-fluorophenyl)-2-hydroxy-ethyl]-3H-quinazolin-4-one (**3a**) as a colorless oil. Dissolution of this oil in ethyl ether/hexanes (∼1:2) and concentration gave a white crystalline solid; mp 148−149 °C. ^{1}H NMR: δ 7.93 (dd, J = 8.3, 2.9 Hz, 1H), 7.78 (dd, J = 9.1, 4.8 Hz, 1H), 7.63−7.52 (m, 3H), 7.49−7.43 (m, 2H), 7.36−7.31 (m, 1H), 7.25−7.19 (sym mult, 1H), 7.14 (dt, J = 7.5, 1.1 Hz, 1H), 6.95 (ddd, J = 10.4, 8.1, 1.2 Hz, 1H), 5.57 (br dd, J = 9.1, 2.1 Hz, 2H), 2.72 (dd, J = 17.4, 2.5 Hz, 1H), 2.63 (dd, J = 17.4, 9.1 Hz, 1H). Anal. ($C_{22}H_{15}ClF_2N_2O_2 \cdot 0.25\ H_2O$) C, H, N.

Continued elution with 10% ethyl acetate/hexanes gave 0.435 g (61%) of the second diastereomeric isomer **3b** as a yellow oil. Repeated dissolution of the oil in ethyl ether/hexanes (∼1:2) and concentration gave a yellow solid; mp 137−138 °C. ^{1}H NMR: δ 7.93 (dd, J = 7.9, 3.1 Hz, 1H), 7.78 (dd, J = 9.1, 4.8 Hz, 1H), 7.60 (dd, J = 7.9, 1.7 Hz, 1H), 7.57−7.51

(m, 2H), 7.46 (dt, J = 7.7, 1.9 Hz, 1H), 7.40 (dt, J = 7.7, 1.5 Hz, 1H), 7.26−7.20 (m, partially overlapping $CHCl_3$, 1H), 7.14−7.10 (m, 2H), 6.96 (ddd, J = 10.8, 8.3, 1.0 Hz, 1H), 5.65 (br s, 1H), 5.59 (dd, J = 7.5, 3.7 Hz, 1H), 2.71 (dd, J = 17.0, 2.9 Hz, 1H), 2.66 (dd, J = 17.0, 7.6 Hz, 1H). Anal. ($C_{22}H_{15}ClF_2N_2O_2$) C, H, N.

***Z*-3-(2-Chlorophenyl)-6-fluoro-2-[2-(2-fluorophenyl)-2-hydroxyvinyl]-3H-quinazolin-4-one (4).** A solution of diisopropylamine (0.183 mL, 1.39 mmol) in THF (10 mL) was chilled to −78 °C, and butyllithium (0.405 mL, 1.01 mmol, 2.5 N) was added. The solution was stirred for 10 min, then **17** (0.309 g, 1.07 mmol) dissolved in THF (3 mL) was added via syringe. The reaction turned deep-red and was stirred for 45 min at −78 °C. In a separate vessel, ethyl 2-fluorobenzoate (1.70 g, 10.1 mmol) was dissolved in THF (30 mL) and chilled to −78 °C. The red anion solution was rapidly transferred via cannula into the cold ester solution (less than 1 min). The reaction was stirred at −78 °C for 30 min, then it was quenched with saturated aqueous $NaHCO_3$ and allowed to warm to room temperature. The solvent was removed at reduced pressure, and the residue was partitioned between ethyl acetate and water. The phases were separated, and the aqueous phase was extracted with ethyl acetate. The combined organic phase was washed with brine, dried over $MgSO_4$, and concentrated. The residue was triturated with ethyl ether, and a yellow solid was collected to afford 0.176 g, (40%) of **4**; mp 218−219 °C. ^{1}H NMR: δ 7.85 (dd, J = 2, 8 Hz, 1 H), 7.76 (dt, J = 2, 8 Hz, 1 H), 7.63 (dd, J = 2, 7 Hz, 1 H), 7.54−7.46 (m, 2 H), 7.43 (dd, J = 3, 7 Hz, 1 H), 7.42−7.30 (m, 3 H), 7.15 (t, J = 8 Hz, 1 H), 6.95 (dd, J = 8, 11 Hz, 1 H), 5.18 (s, 1 H). Anal. ($C_{22}H_{13}ClF_2N_2O_2$) C, H, N.

3-(2-Chlorophenyl)-6-fluoro-2-[(2-fluorophenyl)-ethynyl]-3H-quinazolin-4-one (5). A solution of **4** (0.050 g, 0.12 mmol) and 2,6-lutidine (0.020 g, 0.18 mmol) in CH_2Cl_2 (15 mL) was chilled to −78 °C. Triflic anhydride (0.021 mL, 0.12 mmol) in CH_2Cl_2 (5 mL) was added via syringe. The reaction was stirred for 2.5 h at −78 °C, then warmed to ambient temperature and stirred for 1 h. The dark-yellow solution was poured onto saturated aqueous Na_2CO_3 and vigorously stirred for 30 min. The organic layer was separated and washed with brine, dried over $MgSO_4$ and concentrated to a brown oil (crude triflate). This oil was dissolved in THF (10 mL) and chilled to −78 °C. DBU (0.037 mL, 0.24 mmol) was dissolved in THF (5 mL) and added dropwise via syringe. The mixture was stirred 1.5 h at −78 °C and then 1 h at 10 °C. The reaction was poured into an ice cold mixture of 1 N HCl (10 mL) and ethyl acetate (50 mL). Phases were separated and the organic layer was washed with water, saturated aqueous Na_2CO_3, and brine. The organic layer was further dried over $MgSO_4$ and concentrated to a brown oil. The oil was chromatographed, eluting with 10% ethyl acetate/hexane to give a solid that was triturated with hexane to afford 0.045 g (93%) of **5** as a tan solid; mp 200−205 °C. ^{1}H NMR: δ 7.97 (dd, J = 3, 8 Hz, 1 H), 7.86 (dd, J = 5, 9 Hz, 1 H), 7.62 (dd, J = 2, 9 Hz, 1 H), 7.56−7.44 (m, 4 H), 7.34 (dq, J = 2, 8 Hz, 1 H), 7.20 (t, J = 7 Hz, 1 H), 7.05 (t, J = 8 Hz, 1 H), 6.98 (t, J = 9 Hz, 1 H). Anal. ($C_{22}H_{11}ClF_2N_2O\cdot H_2O$) C, N; H: calcd, 3.19; found, 2.77.

3-(2-Chlorophenyl)-6-fluoro-3,4-dihydroquinazolin-4-one-2-carboxaldehyde (18). A mixture of **17** (1.0 g, 3.46 mmol) and dimethylformamide dimethyl acetal (0.92 mL, 6.92 mmol) in dimethylformamide (4 mL) was heated to 140 °C for 24 h. The reaction was cooled to ambient temperature and concentrated at reduced pressure. The dark residue was triturated with methanol, and the bright-yellow crystalline solid that formed was collected and dried to give 1.075 g (90%) of 3-(2-chlorophenyl)-6-fluoro-2-(2-(dimethylamino)vinyl)-3,4-dihydroquinazolin-4-one; mp 210−211 °C. ^{1}H NMR: δ 7.86 (d, J = 12.3 Hz, 1 H), 7.79 (dd, J = 3, 8.5 Hz, 1 H), 7.61−7.54 (m, 1 H), 7.51−7.29 (m, 5 H), 4.06 (d, J = 12.3 Hz, 1 H), 2.80 (br s, 6 H). Anal. ($C_{18}H_{15}ClFN_3O$) C, H, N.

To a well-stirred mixture of sodium periodate (2.24 g, 10.47 mmol) in aqueous pH 7 buffer (10 mL) and tetrahydrofuran (10 mL) was added 3-(2-chlorophenyl)-6-fluoro-2-(2-(dimethylamino)vinyl)-3,4-dihydro-quinazolin-4-one (0.90 g, 2.62 mmol) all at once. The mixture warmed slightly to the touch and was stirred for 1 h at ambient temperature. The reaction was filtered through Celite, and the pad was rinsed with ethyl acetate. The phases were separated from the filtrate, and the aqueous layer was extracted with ethyl acetate. The combined organic phase was washed with brine, dried over $MgSO_4$, and concentrated to afford 0.802 g (97%) of 3-(2-chlorophenyl)-6-fluoro-3,4-dihydroquinazolin-4-one-2-carboxaldehyde (**18**) as a 1:2 mixture of free aldehyde and hydrate. ^{1}H NMR: δ 9.52 (s) [CHO], 8.20−7.45 (m, 7 H), 6.75 (d, J = 7.4 Hz) [hydrate OH] and 6.49 (d, J = 8 Hz) [hydrate OH], 5.14 (t, J = 7.5 Hz) [hydrate methine CH]. This partially hydrated aldehyde was used without further purification.

3-(2-Chlorophenyl)-6-fluoro-2-[(2-fluorophenylamino)-methyl]-3H-quinazolin-4-one (6). A mixture of **18** (0.40 g, 1.32 mmol), *o*-fluoroaniline (0.130 mL, 0.134 mmol), and anhydrous $MgSO_4$ (2 g) in methanol (20 mL) was stirred at ambient temperature for 18 h, then refluxed for 3 h to give a pink-red slurry of the imine intermediate. To this crude imine was added sodium cyanoborohydride (0.40 g, 6.36 mmol) and sodium triacetoxyborohydride (0.56 g, 2.64 mmol), and stirring was continued for an additional 18 h. The reaction was concentrated and partitioned between ethyl acetate and saturated aqueous $NaHCO_3$ solution. The organic phase was dried over $MgSO_4$ and concentrated to a light-pink oil. The oil was chromatographed, eluting with a 10−20% ethyl acetate/hexanes gradient to give 0.363 g (69%) of **6** as a white solid; mp 179−180 °C. ^{1}H NMR: δ 7.91 (dd, J = 8.3, 2.9 Hz, 1H), 7.84 (dd, J = 9.1, 4.8 Hz, 1H), 7.65 (dd, J = 7.5, 1.9 Hz, 1H), 7.56−7.49 (m, 3H), 7.37 (dd, J = 7.5, 1.7 Hz, 1H), 6.97 (ddd, J = 12.0, 8.1, 1.4 Hz, 1H), 6.89 (br t, J = 7.4 Hz, 1H), 6.63 (ddt, J = 7.9, 4.8, 1.6 Hz, 1H), 6.42 (sym mult, 1H), 3.90 (ABq, $\Delta\nu_{1-3}$ = 35.3 Hz, J = 17.2 Hz, 2H). Anal. ($C_{21}H_{14}ClF_2N_3O\cdot 0.25 H_2O$) C, H, N.

3-(2-Chlorophenyl)-6-fluoro-2-[(2-fluorobenzylamino)-methyl]-3H-quinazolin-4-one (7). A mixture of **18** (0.20 g, 0.66 mmol), *o*-fluorobenzylamine (0.075 mL, 0.66 mmol), and sodium triacetoxyborohydride (0.20 g, 0.94 mmol) in 1,2-dichloroethane was stirred at room temperature for 18 h. The mixture was concentrated, and the residue was partitioned between ethyl acetate and saturated aqueous $NaHCO_3$. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated to a yellow oil (0.277 g). The oil was chromatographed, eluting with 20−30% ethyl acetate/hexanes to give 0.209 g (77%) of **7** as a colorless oil. Crystallization was induced by addition of a few drops of ethyl ether and scratching, resulting in a white solid product; mp 98−100 °C. ^{1}H NMR: δ 7.89 (dd, J = 8.3, 2.9 Hz, 1H), 7.75 (dd, J = 9.2, 5.0 Hz, 1H), 7.57 (dd, J = 7.9, 1.7 Hz, 1H), 7.51−7.40 (m, 3H), 7.32−7.26 (m, 2H), 7.23−7.16 (m, 1H), 7.05 (dt, J = 7.5, 1.0 Hz, 1H), 6.97 (ddd, J = 10.0, 8.1, 1.3 Hz, 1H), 3.81 (ABq, $\Delta\nu_{1-3}$ = 25.7 Hz, J = 13.5 Hz, 2H), 3.40 (ABq, $\Delta\nu_{1-3}$ = 19.5 Hz, J = 16.6 Hz, 2H). Anal. ($C_{22}H_{16}ClF_2N_3O$) C, H, N.

2-Bromomethyl-3-(2-chlorophenyl)-6-fluoro-3H-quinazolin-4-one (19). A solution of 3-(2-chlorophenyl)-6-fluoro-2-methyl-3H-quinazolin-4-one (1.00 g, 3.46 mmol) in 15 mL of CCl_4 was treated with recrystallized *N*-bromosuccinimide (0.678 g, 3.81 mmol) and a catalytic amount of benzoyl peroxide. The mixture was heated at reflux and irradiated with a 100 W floodlamp for 3 h. The mixture was then cooled in ice and filtered, and the filtrate was concentrated. The residue was chromatographed, eluting with 2:1 hexane/ethyl acetate to give 0.443 g (35%) of **19**; mp 165−167 °C. ^{1}H NMR: δ 7.89−7.92 (m, 1H), 7.74−7.78 (m, 1H), 7.59−7.61 (m, 1H), 7.49−7.55 (m, 4H), 4.06 (dd, J = 11, 167 Hz, 2H). Anal. ($C_{15}H_9ON_2$-BrClF) C, H, N.

3-(2-Chlorophenyl)-6-fluoro-2-(2-fluorophenoxymethyl)-3H-quinazolin-4-one (8). To a solution of 2-fluorophenol (0.112 mg, 1.0 mmol) in 3 mL of DMF was added oil-free NaH (40 mg, 1.0 mmol) all at once. After the foaming had subsided, **19** (60 mg, 0.16 mmol) dissolved in 3 mL of DMF was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate, and the resulting solution was washed three times with water

to remove the DMF. The organic solution was washed with brine, dried over $MgSO_4$, and concentrated. The residue was crystallized from 1:1 ethyl ether/pentane to give 1.028 g (88%) of **8**; mp 139−141 °C. ^{1}H NMR: δ 7.92 (d, J = 2.1 Hz, 1H), 7.78−7.81 (m, 1H), 7.38−7.56 (m, 5H), 6.83−7.02 (m, 4H), 4.77 (dd, J = 12.4, 67.6 Hz, 2H). Anal. ($C_{21}H_{13}O_2N_2ClF_2$) C, H, N.

3-(2-Chlorophenyl)-6-fluoro-2-thioxo-2,3-dihydro-1H-quinazolin-4-one (20). A solution of 5-fluoroanthranilic acid (2.159 g, 13.9 mmol) and of 2-chlorophenylisothiocyanate (1.81 mL, 2.35 g, 13.9 mmol) in 21 mL of glacial acetic acid was heated at reflux. After 1 h, a solid began to separate from the reaction mixture, and after 2.5 h, no starting 5-fluoranthranilic acid could be detected by TLC (silica, ethyl acetate). The reaction mixture was cooled, and the acetic acid was evaporated to give a yellow crystalline solid. This solid was taken up in ethyl ether, filtered, and washed twice with ethyl ether and air-dried to give 3.68 g (86%) of **20**; mp 295−297 °C. ^{1}H NMR: δ 7.13−7.15 (m, 1H), 7.31−733 (m, 1H), 7.39−7.67 (m, 4H), 7.80−7.82 (m, 1H). Anal. ($C_{14}H_8ON_2SClF$) C, H, N, S.

2-Chloro-3-(2-chlorophenyl)-6-fluoro-3H-quinazolin-4-one (21). A solution of **20** (1.50 g, 4.90 mmol) in 11.0 mL of $POCl_3$ was treated with PCl_5 (1.70 g, 8.17 mmol), and the mixture was refluxed for 2.5 h. The reaction was concentrated, and the residues were taken up in ethyl acetate and extracted with water and brine. The organic phase was dried over $MgSO_4$ and concentrated to leave a crystalline solid. This solid was taken up in ethyl ether, filtered, washed with ethyl ether, and air-dried to give 0.640 g (42%) of **21**; mp 160−161 °C. ^{1}H NMR: δ 7.92−7.90 (m, 1H), 7.77−7.72 (m, 1H), 7.63−7.61 (m, 1H), 7.58−7.45 (m, 3H), 7.40−7.36 (m, 1H). Anal. ($C_{14}H_7ON_2Cl_2F$) C, H, N.

3-(2-Chlorophenyl)-6-fluoro-2-(2-fluorobenzylamino)-3H-quinazolin-4-one (9). To a solution of **21** (0.267 g, 0.87 mmol) in 5 mL of absolute ethanol was added 2-fluorobenzylamine (0.2 mL, 0.216 g., 1.73 mmol). The reaction was refluxed overnight, then the mixture was cooled and concentrated. The residues were partitioned between ethyl acetate and 1 N HCl. The aqueous layer was extracted one time with ethyl acetate, and the combined organic extracts were washed with brine, dried over $MgSO_4$, and evaporated. The residue was crystallized from ethyl ether to give 157 mg (45%) of **9**; mp 163−165 °C. ^{1}H NMR: δ 7.77−7.73 (m, 1H), 7.60−7.64 (m, 1H), 7.42−7.52 (m, 3H), 7.32−7.40 (m, 3H), 7.18−7.26 (m, 1H), 7.04−7.08 (m, 1H), 6.96−7.01 (m, 1H). Anal. ($C_{21}H_{14}ON_3ClF_2$) C, H, N.

***N*-[3-(2-Chlorophenyl)-6-fluoro-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]-*N*-(2-fluorophenyl)acetamide (10)**. Acetic acid (2 mL), **6** (0.10 g, 0.25 mmol) and acetic anhydride (10 mL) were combined and refluxed overnight. The reaction was cooled and poured into saturated aqueous $NaHCO_3$ (50 mL) and ethyl acetate (50 mL) and stirred for 30 min at ambient temperature. The phases were separated, and the organic layer was washed with aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated. The residue was chromatographed, eluting with 30% ethyl acetate/hexane to afford 0.041 g (37%) of **10** as a pale-greenish solid; mp 144−147 °C. The compound exists as about a 2:1 mixture of rotomers as indicated by the ^{1}H NMR spectrum: δ 7.88 (dd, J = 3, 8 Hz, 1H), 7.74 (br s, 1 H), 7.56 (br s, 1 H), 7.52−7.47 (m, 5 H), 7.35−7.30 (m, 1 H), 7.20−7.11 (m, 2 H), [4.45 (br d, J = 270 Hz) and 4.35 (ABq, $\delta\nu_{1-3}$ = 534 Hz, J = 15 Hz) total of 2H], 1.94 S, 3 H). Anal. ($C_{23}H_{16}ClF_2N_3O_2$) C, H, N.

3-(2-Chlorophenyl)-6-fluoro-2-{[(2-fluorophenyl)-methylamino]methyl}-3H-quinazolin-4-one (11). Formic acid (0.57 mL, 15.1 mmol) and acetic anhydride (1.5 mL, 16.8 mmol) were stirred at room temperature for 30 min. A solution of **6** (0.36 g, 0.90 mmol) in THF (20 mL) was added, and the mixture was stirred at room temperature for 2 h. A second batch of acetylformyl anhydride was separately prepared (identical reagent stoichiometry as above) and added to the mixture. The reaction was stirred 18 h, then it was concentrated. The residue was taken up in ethyl acetate and washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated directly onto silica gel. The product was purified by chromatography, eluting with a 10−30% ethyl acetate/hexanes gradient to give 0.36 g (95%) of *N*-[3-(2-chlorophenyl)-6-fluoro-4-oxo-3,4-dihydro-quinazolin-2-ylmethyl]-*N*-(2-fluorophenyl)formamide as a white solid; mp 145−146.6 °C. ^{1}H NMR: δ 8.38 (d, J = 2.1 Hz, 1H), 7.87 (dd, J = 8.3, 2.9 Hz, 1H), 7.68 (dd, J = 8.7, 4.8 Hz, 1H), 7.64−7.62 (m, 1H), 7.58 (dt, J = 7.7, 1.9 Hz, 1H), 7.54−7.42 (m, 4H), 7.33−7.25 (m, 1H), 7.21−7.12 (m, 2H), 4.50 (ABq, $\Delta\nu_{1-3}$ = 209.1 Hz, J = 17.2 Hz, 2H). Anal. ($C_{22}H_{14}ClF_2N_3O_2$) C, H, N.

The formamide (0.10 g, 0.235 mmol) was dissolved in THF (5 mL), and borane−THF (1.25 mL, 1.25 mmol, 1 N in THF) was added. The resulting mixture was stirred at room temperature for 18 h. Methanol was added to quench the excess borane, and the mixture was concentrated onto silica gel. The product was purified by chromatography, eluting with 10% ethyl acetate/hexanes to give 29 mg (30%) of **11** as a colorless oil. Crystallization was induced by warming with hexanes (∼2 mL) to afford white needles; mp 126−127 °C. ^{1}H NMR: δ 7.89 (dd, J = 8.7, 2.9 Hz, 1H), 7.73 (dd, J = 8.7, 5.0 Hz, 1H), 7.54−7.44 (m, 2H), 7.38−7.29 (m, 3H), 6.97−6.85 (m, 3H), 6.81−6.75 (m, 1H), 4.06 (ABq, $\Delta\nu_{1-3}$ = 40.7 Hz, J = 16.4 Hz, 2H), 2.93 (s, 3H). Anal. ($C_{22}H_{16}ClF_2N_3O$) C, H, N.

2-{[3-(2-Chlorophenyl)-6-fluoro-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]amino}benzonitrile (12). A mixture of **18** (0.20 g, 0.66 mmol), *o*-cyanoaniline (0.083 g, 0.70 mmol), and *p*-toluenesulfonic acid (0.012 g, 0.063 mmol) in toluene (20 mL) was refluxed for 18 h with azeotropic removal of water (Dean−Stark trap). The reaction mixture was concentrated to afford the crude imine as a red oil. The crude imine was dissolved in anhydrous methanol (10 mL), and sodium cyanoborohydride (0.20 g, 3.18 mmol), sodium triacetoxyborohydride (0.28 g, 1.32 mmol), and anhydrous $MgSO_4$ (1 g) were added. This mixture was stirred at ambient temperature for 6 days, then concentrated and partitioned between ethyl acetate and saturated aqueous $NaHCO_3$. The organic phase was dried over $MgSO_4$ and concentrated to an orange-red oil. The oil was chromatographed, eluting with a 15−25% ethyl acetate/hexanes gradient to give 0.145 g (54%) of **12** as a red oil. Dissolution and concentration from ethyl ether gave a red solid; mp 169−170 °C (melt which solidified to a material that further melted at 178−180 °C). ^{1}H NMR: δ 7.92 (dd, J = 8.3, 2.9 Hz, 1H), 7.87 (dd, J = 9.1, 4.8 Hz, 1H), 7.68 (dd, J = 7.9, 1.9 Hz, 1H), 7.59−7.50 (m, 3H), 7.43−7.38 (m, 2H), 7.33−7.28 (sym mult, 1H), 6.70 (dt, J = 7.5, 0.8 Hz, 1H), 6.40 (d, J = 8.7 Hz, 1H), 3.93 (ABq, $\Delta\nu_{1-3}$ = 33.2 Hz, J = 17.0 Hz, 2H). Anal. ($C_{22}H_{14}ClFN_4O$) C, H, N.

3-{[3-(2-Chlorophenyl)-6-fluoro-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]amino}benzonitrile (13). A mixture of **18** (0.150 g, 0.50 mmol), glacial acetic acid (10 mL), 3-aminobenzonitrile (0.050 g, 0.42 mmol), and anhydrous Na_2SO_4 (0.71 g, 5 mmol) was stirred at ambient temperature overnight. TLC indicated that the imine had formed (R_f = 0.43, silica, 30% ethyl acetate/hexane, UV detection). Sodium triacetoxyborohydride (0.267 g, 1.26 mmol) was added, and the reaction was allowed to stir over the weekend (72 h). The mixture was poured into saturated aqueous $NaHCO_3$ and repeatedly extracted with ethyl acetate. The combined organic layer was dried over $MgSO_4$ and concentrated to afford a yellow solid. This solid was triturated with 50% ethyl ether/isopropyl ether to give 0.133 g (78%) of **13** as an off-white solid; mp 225−228 °C. ^{1}H NMR: δ 7.93 (dd, J = 3, 8 Hz, 1 H), 7.87 (dd, J = 4.5, 8.5 Hz, 1 H), 7.70 (dd, J = 1.5, 7.5 Hz, 1 H), 7.62−7.52 (m, 4 H), 7.40 (dd, J = 1.5, 7.5 Hz, 1 H), 7.20 (t, J = 8 Hz, 1 H), 6.97 (d, J = 7.5 Hz, 1 H), 6.80 (dd, J = 2, 8 Hz, 1 H), 6.66 (s, 1 H), 3.88 (ABq, $\Delta\nu_{1-3}$ = 39.5 Hz, J = 17 Hz, 2 H). Anal. ($C_{22}H_{14}ClFN_4O{\cdot}0.5\ H_2O$) C, H, N.

3-(2-Chlorophenyl)-6-fluoro-2-(*m*-tolylaminomethyl)-3H-quinazolin-4-one (14). A mixture of **18** (0.20 g, 0.66 mmol), *m*-toluidine (0.075 mL, 0.70 mmol), and anhydrous $MgSO_4$ (1 g) in methanol (10 mL) were stirred at room temperature for 1 h to give a pink-orange slurry. To this crude imine was added sodium cyanoborohydride (0.20 g, 3.18 mmol)

and sodium triacetoxyborohydride (0.28 g, 1.32 mmol), and stirring was continued for an additional 15 min. The reaction was concentrated, and the residue was partitioned between ethyl acetate and saturated aqueous $NaHCO_3$. The organic phase was dried over $MgSO_4$ and concentrated to a light-brown oil (0.27 g) that was chromatographed, eluting with a 10−20% ethyl acetate/hexanes gradient to give 0.176 g (68%) of **14** as a tan solid; mp 167−168 °C. ^{1}H NMR: δ 7.91 (dd, J = 8.3, 2.9 Hz, 1H), 7.80 (dd, J = 9.1, 4.8 Hz, 1H), 7.65 (dd, J = 7.9, 1.7 Hz, 1H), 7.56−7.47 (m, 3H), 7.36 (dd, J = 7.5, 1.7 Hz, 1H), 7.02 (t, J = 7.7 Hz, 1H), 6.54 (d, J = 7.5 Hz, 1H), 6.40 (s, 1H), 6.34 (dd, J = 7.9, 2.1 Hz, 1H), 3.84 (ABq, $\Delta\nu_{1-3}$ = 47.3 Hz, J = 17.2 Hz, 2H). Anal. ($C_{22}H_{17}ClFN_3O\cdot 0.125\ H_2O$) C, H, N.

3-(2-Chlorophenyl)-6-fluoro-2-[(3-pyrrolidin-1-ylmethylphenylamino)methyl]-3H-quinazolin-4-one (15). A mixture of **18** (0.50 g, 1.65 mmol), 3-pyrrolidin-1-ylmethylaniline (0.291 g, 1.65 mmol), and anhydrous Na_2SO_4 (2.3 g, 16.5 mmol) in CH_2Cl_2 (20 mL) was refluxed for 24 h. The mixture was diluted with water and stirred for 20 min. The phases were separated, and the organic phase was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated to afford 0.61 g of crude imine. The imine was dissolved in ethanol (20 mL), and 10% Pd/C (0.61 g) and formic acid (2.6 mL, 69.7 mmol) were added. The reaction was stirred at ambient temperature for 3 h, and then saturated aqueous $NaHCO_3$ was added. The mixture was filtered through Celite, and the filtrate was concentrated to remove most of the ethanol. The milky aqueous residue was extracted with ethyl acetate. The organic phase was washed with water and brine, dried over $MgSO_4$, and concentrated. The residue was chromatographed, eluting with 10% methanol/0.5% ammonium hydroxide/$CHCl_3$ to give 0.322 g (53%) of **15** as an off-white foam; mp 105−110 °C. ^{1}H NMR: δ 7.92 (dd, J = 3, 8 Hz, 1 H), 7.80 (dd, J = 5, 9 Hz, 1 H), 7.66 (dd, J = 2, 7 Hz, 1 H), 7.59−7.50 (m, 3 H), 7.39 (dd, J = 2, 7 Hz, 1 H), 7.08 (t, J = 8 Hz, 1 H), 6.69 (br s, 1 H), 6.66 (d, J = 7.5 Hz, 1 H), 6.40 (d, J − 8 Hz, 1 H), 5.13 (s, 1 H), 3.94 (dd, J = 5, 17 Hz, 1 H), 3.81 (dd, J = 4.5, 17 Hz, 1 H), 3.59 (br s, 2 H), 2.58 (br s, 4 H), 1.80 (br s, 4 H). Anal. ($C_{26}H_{24}ClFN_4O\cdot H_2O$) C, N; H: calcd, 5.45; found, 5.04.

***N*-(3-{[3-(2-Chlorophenyl)-6-fluoro-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]-amino}phenyl)acetamide (16)**. This compound was prepared by following the procedure to make **7**, giving a 29% yield (after chromatographic purification eluting with a 25−50% ethyl acetate/hexanes gradient). The analytical sample was prepared by trituration with 10:1 ethyl ether/ethyl acetate to afford **16** as an off-white solid; mp 167.5−169.5 °C. ^{1}H NMR δ 7.91 (dd, J = 8.3, 3.1 Hz, 1H), 7.83 (dd, J = 9.1, 4.8 Hz, 1H), 7.65 (dd, J = 7.9, 1.9 Hz, 1H), 7.56−7.47 (m, 3H), 7.38 (dd, J = 7.1, 2.0 Hz, 1H), 7.10−7.02 (m, 3H), 6.61 (d, J = 7.9 Hz, 1H), 6.24 (d, J = 6.6 Hz, 1H), 3.86 (ABq, $\Delta\nu_{1-3}$ = 47.7 Hz, J = 17.2 Hz, 2H), 2.12 (s, 3H). Anal. ($C_{23}H_{18}ClFN_4O_2$) C, H, N.

References

(1) Greenamyrre, J. T. The role of glutamate in neurotransmission and in neurologic disease. *Arch. Neurol.* **1986**, *43*, 1058−1063. Danysz, N.; Parsons, C. G.; Bresink, I.; Quack, G. Glutamate in CNS disorders. *Drug News Perspect.* **1995**, *8*, 261−277.

(2) Muir, K. W.; Lees, K. R. Clinical experience with excitatory amino acid antagonist drugs. *Stroke* **1995**, *26*, 503−513.

(3) Bigge, C. F.; Nikam, S. S. AMPA receptor agonists, antagonists and modulators—their potential for clinical utility. *Expert Opin. Ther. Pat.* **1997**, *7*, 1099−1114.

(4) Welch, W. M.; Ewing, F. E.; Huang, J.; Menniti, F. S.; Pagnozzi, M. J.; Kelly, K.; Seymour, P. A.; Guanowsky, V.; Guhan, S.; Guinn, M. R.; Critchett, D.; Lazzaro, J.; Ganong, A. H.; DeVries, K. M.; Staigers, T. L.; Chenard, B. L. Atropisomeric quinazolin-4-one derivatives are potent noncompetitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonists. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 177−181.

(5) Chenard, B. L.; Menniti, F. S.; Pagnozzi, M. J.; Shenk, K. D.; Ewing, F. E.; Welch, W. M. Methaqualone derivatives are potent noncompetitive AMPA receptor antagonists. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1203−1205.

(6) As described in ref 4, all activity resides in the S isomer. Full details of the equilibration kinetics will be published separately. Newell, L. M.; Sekhar, V. C.; DeVries, K. M.; Staigers, T. L.; Finneman, J. I. Determination of the activation parameters for atropisomerization of (S)-3-(2-chlorophenyl)-2-[2-(6-diethylaminomethylpyridin-2-yl)-vinyl]-6-fluoro-3H-quinazolin-4-one. *J. Chem. Soc., Perkin Trans. 1*, submitted.

(7) Vetelino, M. G.; Coe, J. W. A mild method for the conversion of activated aryl methyl groups to carboxaldehydes via the uncatalyzed periodate cleavage of enamines. *Tetrahedron Lett.* **1994**, *35*, 219−222.

(8) Bal, B. S.; Childers, W. E., Jr.; Pinnick, H. W. Oxidation of α,β-unsaturated aldehydes. *Tetrahedron* **1981**, *37*, 2091−2096.

(9) Menniti, F. S.; Chenard, B. L.; Collins, M. B.; Ducat, M. F.; Elliott, M. L.; Ewing, F. E.; Huang, J. I.; Kelly, K. A.; Lazzaro, J. T.; Pagnozzi, M. J.; Weeks, J. L.; Welch, W. M.; White, W. F. Characterization of the binding site for a novel class of noncompetitive AMPA receptor antagonists. *Mol. Pharmacol.* **2000**, *58*, 1310−1317.

(10) A possible rationale for the lack of AMPA receptor antagonist activity of **4** has been proposed in ref 5.

(11) The good solubility noted for **15** was an empirical observation. Solubility was not experimentally quantified.

(12) Schlegel, H. B. Optimization of Equilibrium Geometries and Transition Structures. *J. Comput. Chem.* **1982**, *3*, 214−218.

(13) Francl, M. M.; Pietro, W. J.; Hehre, W. J.; Binkley, J. S.; Gordon, M. S.; DeFrees, D. J.; Pople, J. A. Self-Consistent Molecular Orbital Methods. XXIII. A Polarization-Type Basis Set for Second-Row Elements. *J. Chem. Phys.* **1982**, *77*, 3654−3665.

(14) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. *Gaussian 94*, revision B.3; Gaussian, Inc.: Pittsburgh, PA, 1995.

JM000522P